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Book of Abstracts

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PS1A-01

A Bayesian Power Prior Approach for Incorporating Pilot Data into Cluster Randomised Controlled Trial Design: A hypothetical redesign and simulation study

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Introduction
In Cluster Randomised Controlled Trials (CRCTs), randomisation occurs at a group level, which has methodological implications that make design, conduct and analysis more complicated. Typically, CRCTs are analysed using mixed-effects regression, which accounts for clustering in the data. The Power Prior is a class of informative prior distribution constructed using historical data, which is then discounted according to the similarity between the historical and current datasets. A Normalised Power Prior (NPP) approach has been proposed which accounts for the clustered structure of CRCT data, enabling incorporation of evidence from clustered historical data (e.g. pilot study) into analysis of definitive trial data whilst allowing for potential differences between the two datasets, where greater differences automatically result in less information borrowing. The aim of this work was to assess whether the NPP approach can facilitate more efficient CRCT design by justifying reduced sample sizes.

Methods
A hypothetical redesign of a completed CRCT, the Healthy Lifestyles Programme (HeLP; ISCTRN: 15811706), was undertaken assuming analysis using the NPP approach, to calculate the required number of clusters and compare with the typical formula-based approach to sample size determination. Subsequently, a simulation study was undertaken to explore the effect of borrowing information from historical data using the NPP on the required number of clusters, in comparison to the formula-based approach. A range of scenarios was considered, with differing target and observed treatment effects.

Results
When the treatment effect in the historical data was the same, larger or slightly smaller than the target treatment effect, the required number of clusters to achieve 80% power was reduced compared with the formula-based approach. Conversely, when the treatment effect in the historical data was substantially smaller than the target effect, an increased number of clusters was required. Type I error rates were inflated as a result of using the NPP, unless the treatment effect in the historical data was zero.

Discussion
In comparison with the traditional formula-based method, use of the NPP approach can justify smaller CRCTs when historical data provides evidence in support of the target treatment effect, but may result in greater sample size requirements if evidence from the historical data favours the null, or is smaller in magnitude than the target treatment effect. As a result, if information borrowing is to be considered during study design, this should be pre-specified before analysis of the historical data.

PS1A-02

Sample size determination in basket trials: a Bayesian approach for borrowing of information

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Basket trials are increasingly used for the simultaneous evaluation of a new treatment in various patient subgroups. Eligible patients would share a commonality (e.g., a genetic aberration or clinical symptom), on which the treatment may potentially improve outcomes. A few sophisticated analysis models, which feature borrowing of information between subgroups, have been proposed for enhanced estimation of the treatment effects. Yet development of methods to choose an appropriate sample size appears to fall behind. A widely implemented approach is to sum up the sample sizes, calculated as if the subtrials are to be carried out as separate studies.

We propose a Bayesian approach to sample size determination in basket trials, where patients are randomly assigned to the experimental treatment or a control within each subtrial. Closed-form sample size formulae are derived to enable borrowing of information between commensurate subtrials. Our approach ensures that each subtrial has a specified chance of correctly deciding whether the new treatment is superior to or not better than the control by some clinically relevant difference. Given fixed levels of pairwise (in)commensurability, the subtrial sample sizes are solved simultaneously. Our solution resembles the frequentist formulation of the problem in yielding comparable sample sizes for circumstances of no borrowing. When borrowing is permitted, a considerably smaller sample size is required. We illustrate the application using data examples based on real trials. A comprehensive simulation study further shows that the proposed approach can maintain the true positive and false positive rates at desired levels.

PS1A-03

Bayesian Adaptive Clinical Trial Design using Integrated Nested Laplace Approximations

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Background
Designing Bayesian adaptive trials requires comprehensive simulations that mimic the proposed trial. These are conducted to understand the error rates and determine appropriate values for key design parameters, such as the decision thresholds, the number of interim analyses, and the required sample size. These simulations are expensive in trials that consider regular adaptations as Bayesian modelling must be conducted at each proposed analysis and usually require Markov Chain Monte Carlo (MCMC) simulations. The Integrated Nested Laplace Approximations (INLA) algorithm is a fast approximation method for Bayesian inference, which can drastically improve the feasibility of simulations. INLA efficiently incorporates hierarchical modelling structures, allowing for complex trial designs with significantly reduced computational complexity.

Methods
We will demonstrate the use of INLA in the Corticosteroid Early and Extended (CORT-E2) Randomized Controlled Trials and the Driving Pressure-Limited Ventilation in Hypoxemic Respiratory Failure (DRIVE) trials. CORT-E2 and DRIVE are adaptive, multi-centre, randomized, open-label, Bayesian adaptive trials within a platform aimed at improving outcomes for patients with acute hypoxemic respiratory failure. These trials have no fixed sample size and will undertake a sequence of analyses every three months until a conclusion is reached. The trials consider stopping based on the probability that the tested intervention is superior to standard care. The trials can stop for superiority, equivalence, futility (the novel intervention does not offer sufficiently high benefit), and inferiority (the novel intervention is harmful compared to standard care). We evaluate all trial designs across different assumptions about the treatment effect and calibrate the trials to ensure that the error rates are well-controlled.

Results
Using INLA to fit Bayesian hierarchical models requires around five seconds. Thus, despite the complexity of the proposed designs, which includes a large number of interim analyses, each set of simulated trials requires between 6-8 hours. The expected sample size for the CORT-E2 trials was between 1563 and 2231, depending on the treatment effect assumption, and between 860 and 1539 for DRIVE. The simulations confirmed that the type 1 error rates for the trials were below 5% and the power for expected treatment effect sizes was above 80%.

Conclusion
INLA can drastically increase the feasibility of designing complex Bayesian adaptive trials and allows for the inclusion of hierarchical modelling in the design phase. Thus, it can be leveraged as a tool to improve the design of Bayesian adaptive trials.

PS1A-04

A Bayesian method for safety signal detection in ongoing blinded randomised controlled trials

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Introduction
Sponsors have a responsibility to minimize risk to participants in clinical studies through safety monitoring. This is emphasized in the FDA Final Rule legislation for IND Safety Reporting which requires routine aggregate safety analyses of ongoing, blinded studies. Blinded studies present challenges for evaluating potential safety signals. For monitoring, we are interested in estimating the probability that the true event rate in the experimental arm exceeds that of the control arm.

Methods
We developed a Bayesian approach for estimating the quantity of interest. We started by deriving an informative meta-analytic predictive (MAP) prior on the AE hazard in the control arm using safety outcomes from historical trials. Across-trial variability is estimated within the model so that historical trials with greater heterogeneity yield less informative MAP priors for the ongoing blinded trial, and vice-versa. Data is often sparse on the investigational treatment, so we assumed an uninformative prior on the AE probability in the experimental arm. We combined these priors with a mixture likelihood that considers that each patient in the ongoing blinded trial may belong to the experimental or control arm, allowing us to estimate the quantity of interest without unblinding. We programmed the models in Stan and R and evaluated our method by a simulation study, varying elements of the data generating process in scenarios. We paired scenarios that varied only in whether a safety signal was present or missing. We then appraised the ability of our model to discriminate between the two using signal detection theory framework.

Results
Our approach shows benefit. As expected, it detects safety signals more reliably the greater the sample sizes in the historical or ongoing blinded trials. Similarly, it more reliably detects signals for common rather than rare AEs. Performance does not deteriorate markedly when historical trials exhibit heterogeneous AE hazards. Performance is modestly worse when AE hazards are accelerating or decelerating rather than constant.

Discussion
Our method will allow us to monitor for potential safety signals in ongoing blinded trials with the goal of earlier identification and risk mitigation. Our method could be adapted to use informative priors on both arms or predictive covariates where pertinent data exist. We stress that ongoing safety monitoring requires involvement of a multi-disciplinary development team. Statistical methods provide a quantitative framework for evaluating potential signals but must be paired with medical judgement for signal assessment and validation.

PS1A-05

Bayesian modelling strategies for borrowing of information in randomised basket trials

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Background
Basket trials are a precision medicine trial design that evaluate a single targeted experimental treatment in different disease types that share a common characteristic such as genetic biomarker. Several Bayesian methods for the analysis of basket trials exist, which incorporate the efficiencies of borrowing information across subgroups, and whose inferences are known to be superior to stand-alone analyses of subgroups. Unlike single-arm basket trials, information sharing in a randomised basket trial design can be done in two ways, either based on i) similarity of the treatment effects or ii) the similarity of the treatment response across subgroups. The most suitable approach to borrowing in this setting is unknown but it is plausible that inferences from either borrowing strategy could lead to potentially different conclusions.

Method
We propose an alternative Bayesian approach for the analysis of randomised basket trials with a continuous endpoint. Our proposed methodology (called treatment response borrowing, TRB) considers the similarity of the mean response across the control and experimental treatment separately instead of the treatment effect. The Bayesian modelling strategy is based on the commensurate predictive prior approach. We perform a simulation study in the context of a randomised basket trial with five subtrials to evaluate our proposed methodology against the treatment effect borrowing (TEB) and the no borrowing strategy under nine different scenarios. The control treatment is assumed to be similar across all subtrials.

Results & Conclusion
Borrowing information across subgroups of a basket trial leads to increased power compared to stand-alone analyses. Our findings demonstrate that TRB outperforms when the trial sample size small, and the mean response is similar across subtrials. However, there are marginal differences when the sample size is large, although TEB has higher operating characteristics in this case. When applied to the analysis of real trial data, we show that TRB and TEB lead to different conclusions; TRB recommends a treatment should progress to a phase III trial while TEB suggests otherwise. We recommend that the design and analysis of randomised basket trials should utilise the most appropriate Bayesian modelling strategy for robust and reliable inferences.

PS1B-01

Use of SWAT methodology to investigate intervention implementation processes – Case studies of two trials

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Introduction

A study within a trial (SWAT) is a self-contained research study embedded within a host trial that typically evaluates the effectiveness of small refinements to trial processes, often relating to recruitment or retention processes. There is limited evidence of SWATs investigating intervention implementation processes. We used SWAT methodology to test novel aspects of intervention implementation relating to participant engagement or compliance with the intervention.

Methods

Mixed methods SWATs consisting of nested randomised (or cluster randomised) controlled trials (RCT) and qualitative interview studies were embedded within the intervention arms of two RCTs. The first trial (PROSPER) evaluated the effects of a personalised care planning intervention for older adults with frailty while the second trial (RECREATE) assessed the effects of a service-level intervention to reduce sedentary behaviour in stroke survivors. In both SWATs, the intervention component tested was a video animation (developed by professional animators, researchers and lay members of an intervention development group) intended to facilitate intervention delivery. The SWAT control condition was no video: in PROSPER this was a verbal explanation of the intervention accompanied with an information sheet, whilst in RECREATE the comparator was usual intervention delivery.

Results

We present the potential benefits of using SWATs to investigate intervention implementation as well as discussing methodological considerations when embedding a SWAT of this nature within a host trial. The use of SWAT methodology allows us to test the effectiveness of minor refinements to intervention implementation processes in a robust and controlled manner, with the possible outcome of increasing trial efficiency by enhancing intervention implementation processes. Our experiences have highlighted important methodological considerations surrounding the design and conduct of these SWATs such as careful selection of the intervention to be tested in the SWAT without changing the trial intervention itself, and delivery of the intervention without contamination. Statistical considerations include randomisation level, sample size, outcome choices in the SWAT, and analysis for the SWAT and host trial. Health economic considerations and considerations relating to conduct of a process evaluation and SWAT within one trial should also be taken into account.

Potential Relevance and Impact

This is a novel use of SWAT methodology to investigate intervention implementation processes on participant engagement and compliance with the intervention. These aspects of intervention implementation are crucial to explore as they can link directly to intervention effectiveness. These methods can act as a template for researchers considering how to optimise intervention implementation within trials.

PS1B-02

Using a simultaneous SWAT design to increase the recruitment and retention evidence base: two case studies

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Introduction
Randomised Controlled Trials (RCTs) are the gold standard for evaluating health and social care interventions. It is crucial for RCTs to be able to recruit and retain participants. Strategies to increase recruitment and retention are often untested but there is increasing interest in testing these strategies, often using Studies Within A Trial (SWAT), where the strategy is evaluated within the context of a host RCT. Typically it can take years to accumulate enough evidence within a range of contexts to determine effectiveness. One novel approach to speed up the accumulation of evidence is to undertake a simultaneous SWAT design, where one SWAT is embedded within several host trials at the same time.

Methods
As part of the PROMETHEUS programme, a NIHR funded body of work aiming to routinely embed SWATs in RCTs, two simultaneous SWATs were undertaken. Two case studies will be used to demonstrate the benefits and disadvantages of this design: a training intervention for surgical trials as a recruitment strategy, and the use of Christmas cards as a retention strategy

Results
The recruiter training SWAT was embedded within four host trials. The intervention demonstrated improved recruiter confidence but showed no evidence of increasing recruitment (55% intervention, 63% control). This was undertaken in a limited number of host trials; further evaluations are needed before overall effectiveness can be concluded. The Christmas Card SWAT was embedded within eight host trials. Although COVID reduced the follow up time, enough evidence was accrued to conclude that sending Christmas cards does not improve trial retention (85.3% with card, 85.4% without). Due to the wide range of host trial contexts, this one SWAT evaluation provided sufficient evidence to answer the SWAT question, demonstrating that it is possible to reach a definitive conclusion on a strategy effectiveness in a short timeframe.

Discussion
The simultaneous SWAT design is an efficient way of increasing the evidence base for recruitment and retention strategies. It allows high-quality evidence to be accrued quickly, may provide a definitive answer and has benefits in terms of cost and time. It would not be suitable for all SWATs, and without a central point of coordination would be difficult to undertake. Due to their novelty, it may prove more difficult to obtain approval for and identifying suitable host trials may prove troublesome. However, where possible, a simultaneous SWAT design should be used to generate more timely evidence about trial processes.

PS1B-03

Improving follow-up and retention to paediatric randomized controlled trials: a qualitative study

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Introduction
Retention to paediatric randomized controlled trials (RCTs) is a novel research area. No qualitative studies have investigated retention or follow-up across trials within different disease areas and settings. The aim of this qualitative study was to investigate follow-up and retention for those involved in paediatric RCTs and how it can be improved.

Methods
I conducted in-depth, semi-structured interviews with clinical trialists who had experiences of working on paediatric RCTs. Trialists were purposefully sampled across different disease areas and settings in the UK. 20 interviews were audio-recorded and analysed thematically.

Results
Burden: Parents, and participants, can find prioritising trial follow-up difficult due to other competing aspects of their life. Flexibility in timings of return needs to be inbuilt into data collection methods. It is important to give participants the choice in how they complete data collection.
Inclusivity: Trialists feel that children want to be more included in all aspects of trials. Adolescents want to be given more freedom to be involved in data collection without needing parental involvement. Electronic devices are exciting for younger children, but adolescents have more concerns about their privacy.
Relationships: The personal touch with participants in trials should not be underestimated. Incentives show appreciation to participants, but should not be prioritised at the expense of using appropriate data collection methods. Research is needed into what incentivises adolescents to respond in trials. Schools are engaged when they are partnered with individually.
Understanding: Communication with participants should be regular, and not just about collecting data. Participants like to know what is going on in the trial, what they will be doing and feeling part of a research community.

Discussion
There is intense scrutiny and pressure on trials to recruit well, but there is limited understanding of how to improve follow-up and retention. The timing and method of data collection needs to be flexible for both participants and their caregivers. Trials need to spend time carefully co-designing trials with young people so that young people can be more involved in reporting data and are given agency over their participation in trials. Trialists need to cultivate a personal relationship with their participants to improve retention. These results need to be further explored with young people and their caregivers and considered in conjunction with other sources of evidence.

PS1B-04

Effects on retention of different weight assessment approaches during trials of Behavioural Weight Management Interventions (BWMI). Nested Study within a Trial (SWAT).

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Background
Digital interventions could provide a novel way of delivering behaviour change for people living with obesity. They may enable greater access to programmes especially for underserved groups often under-represented in BWMIs and trials. However digital interventions could also diminish the interpersonal relationships which some studies have associated with improving outcomes and retention.
This SWAT aims to evaluate the effects on retention of two weight assessment approaches delivered to intervention groups only at 3 and 6 months (M) within a 3-arm (i) SMS+Incentive; ii) SMS-Only and iii) 12M Waiting List Control), assessor blind, randomised controlled trial (RCT) comparing weight change at 12M (ISRCTN91974895).

Methods
A randomised controlled SWAT (SWAT147, MRC SWAT Repository) nested within the Game of Stones RCT. Participants in the two intervention groups were randomly allocated to receive one of two protocolised weight assessments: i) Task-oriented: focus on weight verification tasks ii) Relational: focus on developing the researcher-participant relationship (alongside weight verification tasks). Participants complete the self-reported weight stigma questionnaire (WSSQ) at baseline and 12M and the Consultation and Relational Empathy (CARE) measure at 12M. Intervention participants (n=30) are interviewed after 12M and/ or 24M follow-up visits.
Researchers (n=6), involved in recruitment and data collection, completed baseline questionnaires including self-reported weight stigma (Fat Phobia Scale; Revised Anti-Fat Attitudes Scale) and empathy (Questionnaire of Cognitive and Affective Empathy (QCAE)). Researchers received a 1-hour virtual training session including instruction and demonstration of delivering the weight assessment protocols. Audio-recordings of the 3 and 6M weight assessments are submitted with researcher ratings of protocol adherence and relationship quality. Details of the researcher completing the assessments in addition to assessment duration are recorded.

Timing of Potential Results
390 intervention participants were randomised to the task-oriented group (n=196) and to the relational group (n=194) and completed baseline data. To date 188 protocolised 3-month follow-up weight assessments and 83 6-month follow-up weight assessments have been undertaken by 6 researchers across the trial centres (Belfast, Bristol and Glasgow), with all expected to be completed by November 2022. Data from the 3M evaluations will be complete in August 2022 and early findings regarding fidelity in relation to the 2 protocols will be presented.

Potential Relevance & Impact

This SWAT will provide important preliminary data regarding the participant-researcher relationship and protocol fidelity within trials. This will help inform trial methodology in relation to trial retention and the implementation of digital behavioural weight management interventions in public health.

PS1B-05

Optimising the Notification Policy to Improve Engagement with an Alcohol Reduction App: Results from a Micro-Randomised Trial

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Introduction

Behaviour change apps can help people manage many long-term or chronic conditions. However, a key challenge is developing sufficiently engaging apps to achieve better health outcomes. Push notifications can prompt engagement with the app, and an optimal notification policy would send the right support to the right person at the right moment, while avoid states of disengagement due to less helpful notifications over time.

We aim to develop such an optimal notification policy for Drink Less, a behaviour change app to help higher risk drinkers reduce their alcohol consumption. To create an optimal policy, we want to understand (i) if notifications have a marginal, near-term effect, (ii) if the notification effect changes due to time-varying states of an individual and (iii) if there are longer-term effects, as well as a near-term effect.

These aims present unique methodological and statistical challenges, due to the stochastic and longitudinally rich nature of engagement measures.

Methods

The Micro-Randomized Trial (MRT) is an experimental design in which users are repeatedly randomized to notifications many times, for the purpose of creating such policies. To target users' motivation and perceived usefulness of the app, we tested a bank of 30 new evidence-informed notifications, comparing these to the standard message "Please complete your mood and drinking diaries".

We tested if receiving a notification at 8PM, compared to receiving no notification, increased the probability of opening the app in the subsequent hour, over the first 30 days since downloading Drink Less. To understand time-to-disengagement, two additional randomised arms were added to complement the MRT, (i) the standard policy of a daily, fixed message and (ii) a policy of no-notification.

Results

We randomised 350 users to the MRT, 121 users to the standard policy and 98 users to receive no notification. Receiving a notification, compared with not, increased the probability of opening the app in the next hour 3.5-fold (95% confidence interval (CI) 2.91, 4.25). Recent states of 'already engaged' reduced the near-term effect of a new message non-significantly by 0.80 (95% CI 0.55, 1.16). Time-to-disengagement between the three polices was not significantly different.

Conclusion

Notifications are powerful tools to increase 'in-the-moment' engagement. However, to improve longer-term engagement, tailoring notifications to an individual's recent history of engagement may help. Sending a notification to encourage engagement, only when users are at a greater risk of disengagement, may reduce burden, and could keep users engaged for longer.

PS1C-01

Behavioural Optimisation & Operational Strategies for Trials: The BOOST Approach

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Introduction
Clinical trials are expensive and often fail to deliver on their promise due to problems with trial conduct, for example through problems with recruitment or retention. At its heart, the conduct of trials involves multiple behaviours, in other words, they rely on people (patients, clinicians, trial staff) performing, or not, an action such as approaching eligible participants or returning a questionnaire or delivering the trial intervention as prescribed. These trial related behaviours are pervasive, contextually determined, but most importantly are amenable to change. Indeed, a failure to recognise behavioural influences (and to change them where appropriate) could contribute to the trials overall success or failure. Thus, if behaviours are at the heart of clinical trial delivery, then the scientific discipline of behavioural science (that is, the study of behaviour and behaviour change) may be able to provide useful insights for the clinical trials community. This presentation will introduce the potential benefits that employing insights from behavioural science can bring to optimise trial processes using recent work as examples.

Methods/Approach
We will first introduce the area of behavioural science and how it has direct relevance to the field of clinical trials. Applications will then be exemplified through the use of case studies from recent trials that have used behavioural science to target trial staff or trial participants so as to improve recruitment or retention. Case studies will include:
1. Use of behavioural feedback (through audit and feedback) to change trial staff recruitment behaviour in a surgical trial;
2. Application of a behavioural diagnostic approach (the Theoretical Domains Framework) to develop solutions for participant retention across a number of trials;
3. Behavioural analysis (to identify behaviour change techniques) of information and strategies targeting trial participants that aim to support recruitment and retention.

Impact
This presentation will also provide an outline of some of the key strengths of this approach but also consider the threats to its viability in the clinical trial space (e.g. consideration of the ethical acceptability of applying a behavioural approach to trial conduct). Opportunities for further refinement and extension of this approach will also be discussed.

PS1C-02

Screening Log Guidelines (SLoG): A standardised model for screening data: who should be included and which data should be collected?

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Introduction
The reporting of randomised controlled trials (RCTs) often includes information on the number of individuals assessed for inclusion in the study. Such information is typically referred to as "screening data", and recorded on paper or electronically, using screening logs. The Good Clinical Practice (GCP) guide suggests screening logs can be reviewed to identify barriers to recruitment relating to inclusion and exclusion criteria. The CONSORT group recommend that, when reporting an RCT, "if available, the number of people assessed for eligibility should also be reported". GCP guidance also specifies that reporting of screening data is "a useful indicator of whether trial participants were likely to be representative of all eligible participants" and this is an important consideration, for example the NIHR Include initiative.
There is little consensus on what data should be collected on screening logs, nor who to include. There is currently a paucity of information available to guide the collection of consistent screening data. The aim of this work is to propose a standard set of rules regarding who, and what, to record on a screening log, and whether on occasions data from other sources can provide useful and equivalent information.

Methods/Approach
We conducted a literature review assessing inclusion of screening data in a selection of peer-reviewed publications of individually randomised clinical trials over a ten-year period. We also devised surveys for circulation to all UKCRC CTUs and other trials methodology professionals, as well as nurses and NHS staff. We asked about respondents' experience, and opinions of collection of screening data from RCTs, as well as inviting respondents to participate in the development of screening log guidelines if they wished. The Delphi method will be used to define and refine screening log guidelines and a template log; we aim to have representation from a broad selection of stakeholders. It is expected that Delphi rounds will begin in June 2022, 2-3 rounds are anticipated with the template and guidelines finalised in September.

Results Structure & Timelines
We will report on the findings of the literature review, summarise the survey results and present a finalised screening log template and accompanying guidelines.

Potential Relevance & Impact
The ultimate aim of this work is to produce screening log guidelines for adoption nationally. With more consistent and appropriate collection and reporting of screening data, time may be saved, barriers to recruitment may be more rapidly identified, and representativeness of participants may be assessed.

PS1C-03

The development of guidance for the use of eConsent by UKCRC Registered Clinical Trials Units

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Introduction

The expectations of the informed consent process for participants in a clinical trial are well documented in Good Clinical Practice, traditionally involving paper documents such as the participant information sheet and consent form.

Prior to the COVID-19 pandemic, some trials units were investigating the use of eConsent as an alternative process to improve efficiencies in trials. However, many questions still needed answering coupled to concerns about the suitability of electronic means of consenting and little practical guidance. During the pandemic, patient pathways changed, almost overnight, with the need for eConsent to be implemented to allow many studies to continue to recruit. As the effects of the pandemic start to subside, many questions around the practicality and regulatory issues that eConsent brings remain to be answered.

Methodology

A collaboration between the Trials Methodology Research Partnership, UK Trials Manager's Network and the UKCRC Registered Clinical Trials Units Network was setup to investigate the use of eConsent in registered Clinical Trials Units, what guidance was followed and what concerns units had. This collaboration circulated a web-based survey to all registered CTU's with data collected between April and July 2021. This was followed by a national meeting in January 2022 to disseminate these results (attended by ~180 delegates), showcase existing use cases in different types of trial and further understand what questions and guidance, surrounding the different aspects of eConsent, still remained unanswered.

Discussion

It is clear that eConsent is not a one size fits all solution however, it is a valuable tool to be used by trialists. Building on the results of the survey and outcomes from the meeting, we will present guidance, currently under development by this collaboration, aimed at addressing the issues identified by the community such as documentation, implementation, validation, and training. We will present this guidance utilising case studies from existing trials.

PS1C-04

Inviting people to a clinical trial - how do we challenge the default decline response?

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Introduction
To date, little attention has been given to the role of human behaviour in successful clinical trial recruitment. Indeed behavioural science—the study of behaviour and behaviour change—can provide critical, replicable, and generalisable insights for the clinical trials community (Gillies et al., 2021). We therefore developed a study to help determine whether behavioural science techniques can help with clinical trial recruitment, by optimising invitation letters to clinical trials with behavioural insights (also termed 'nudges').

Methods/Approach
We used existing literature in the fields of behavioural science and clinical trial recruitment to help define the nudges most likely to be effective in invitation letters. We selected five of these nudges to incorporate in letters.
A representative sample of 6000 members of the public, all living in England, were each randomly assigned to an experimental condition where they were shown one of seven letters, inviting them to participate in a form of health research involving a blood donation. These letters were:

- A standard letter with no specific behavioural science technique (the control)
- An abbreviated version of this standard letter, and
- Five further letters, each with a nudge embedded. These nudges were Active Choice, Altruism, Anticipated Regret, Low Cognitive Load and Norms.

Participants were asked to rate, on receiving such a letter, their likelihood to a) seek further information on the health research, and b) take part in the research.
We then analysed results to determine if reported likelihood was higher on the five experimental letters, compared with the control. We also compared the abbreviated version with the control.

Results and Discussion
Results showed that the Active Choice and Altruism letters performed better than the control in terms of reported likelihood to take part in the research*. The Anticipated Regret and Low Cognitive Load letters performed better than the control on both measures (likelihood to seek information and to take part in the research)**. This demonstrates that including nudges in invitation letters has potential to increase clinical trial uptake, and should be further explored. These findings are helping to inform letter content to be tested in real-world trial invites which will be sent to the general public, and we are currently partnering with institutes in order to carry this out.

*Not significantly so
**Low Cognitive Load was significantly higher than the control for the measure of likelihood to visit the website. Other comparisons not significant

PS1C-05

Optimization of the run-in stage in randomized clinical trials: an ensemble machine learning approach

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Introduction
The "run-in" is a period before randomization aimed at identifying/excluding groups of patients less likely to respond to the treatment. Even though it represents an added value to trial design and conduction, it is associated with increasing time and costs. Conversely, it would be desirable to use available a-priori data to inform the potential patients' outcome to skip such a period. The present work aims to present the application of an ensemble Machine Learning (ML) tool to optimize the run-in process in randomized clinical trials

Method/Approach
A couple of twin randomized, placebo-controlled trials (A and B) aimed at assessing the superiority of a treatment for osteoarthritis by evaluating 6-month changes on the Western Ontario and McMaster Universities (WOMAC) scale were considered (all data information about the trials not disclosed due to confidentiality reasons). A SuperLearner (SL) ML approach was employed. First, data from trial A were used to train the SL approach to predict six-month changes in the WOMAC scale. Then, data from trial B were used for validation purposes of the algorithm developed on trial A. The Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) was reported together with Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Results
Trial A included 120 patients (54 in the placebo group and 66 in the experimental group) and the trial B consisted of 137 patients (70 in the placebo group and 67 in the experimental group). The SL tool's ability to correctly predict responders and non-responders in the experimental group was about 70%. For what concerns the placebo arm, the probability of correctly classifying non-responders was slightly more than 50%.

Discussion
ML approaches within randomized clinical trials are still limited, even though they offer promising opportunities for improving trial design and management. The present work showed a good performance of the SL tool in predicting responders in the experimental group, suggesting the usefulness of this algorithm type for optimizing the run-in stage. However, it is worth pointing out that the algorithm's performance on the placebo group was suboptimal, probably due to the small sample size.

PS1D-LT01

Introducing CDISC standards for Data Sharing in Clinical Trials

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Introduction
The NIHR offers funding for CTUs to support developments in the delivery of efficient and innovative research. Employing data standards are an efficient way to exchange clinical trial data between research collaborators and to improve the way CTUs record their trials data. Clinical Data Interchange Standards Consortium (CDISC) is commonly used to refer to a set of standards primarily used in the pharmaceutical industry. CDISC provides a standardised way of presenting clinical trial data and harmonisation for data sharing. This NIHR project was funded to introduce CDISC, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets to an academic CTU audience and to help demystify the concepts used within these data standards.

Methods
Training in these standards was seen as a potential barrier to implementation within an academic setting. This project involved identifying a real trial example that could be used as a training tool. This example was converted into SDTM and demonstrated how SDTM reference materials are used in practice to derive the SDTMs and produce Annotating Case Report Forms (aCRFs).

Results
Our example of CDISC standards being applied demonstrates how the collection and presentation of clinical trial data can be standardised providing consistency across datasets. We found that there are additional benefits of applying CDISC e.g. we found data that could not be mapped to SDTM suggesting its collection was superfluous. By attempting to apply CDISC standards to clinical trial data not designed for CDISC, we identified several issues which made the process challenging. Ideally CDISCS standards should be considered in the data collection stage. Our training presentation was delivered in a Trials Methodology Research Partnership webinar.

Discussion
Using CDISC standards at the data collection stage for clinical trials in the future could mean CRFs are designed to make the process more straightforward when mapping data items to SDTM datasets. This may mean unnecessary data is no longer collected in UK trials where it cannot map to an SDTM dataset. There is also the potential to increase staff efficiency if CDISC standards were implemented, as the data would always be in the same format and standardised statistical programs could be used. Ultimately, if data were standardised across clinical trials data sharing would become much more feasible. By removing barriers such as training costs and improving understanding about the language used, CDISC standards can be implemented within an academic trials unit.

PS1D-LT03

Handling delayed toxicities in real-world oncology dose-finding trials: comparison of Continual Reassessment Method (CRM) and time-to-event CRM (TITE-CRM)

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Introduction
Novel agents, such as molecularly targeted agents (MTA) and immunotherapies (IO), can cause predictable and unpredictable delayed toxicities. Ignoring the delayed toxicities can result in biased toxicity estimates and compromise trial's performance whilst waiting until all participants are fully followed-up for dose-limiting toxicity (DLT) can lead to a prolonged dose-finding trial. Some trials circumvent recruitment suspension between cohorts by using only cycle 1 DLT information for dose-decisions but permit utilizing fully observed DLT data for final maximum tolerated dose (MTD) recommendations. Other designs, e.g., TITE-CRM, allow continual recruitment by using a weighted dose-toxicity model to account for incomplete toxicity information. This study explores the performance of the designs tailored to consider delayed toxicities using CRM, TITE-CRM and its variations.

Methods/Approach
We compare the performance of six designs under various practical scenarios based on an ongoing phase I MTA+IO combination trial where DLT can occur up to cycle 2:
Design 1-CRM: uses cycle 1 DLT data only.
Design 2-CRM: uses cycle 1 DLT data for dose escalation, but fully observed DLT up to cycle 2 for final MTD recommendation.
Design 3-CRM: allows continual accrual but only utilises participants with complete DLT information when making dose-decisions.
Design 4-CRM: requires all participants within a cohort to be fully followed-up prior to dose-decisions.
Design 5-TITE-CRM: One-stage.
Design 6-TITE-CRM: Two-stage.
Cohort size of 1 is used for all designs, except for Design 6 which uses 2 in the initial stage. Data from a published phase I trial in pancreatic cancer will also be used to assess whether different designs will yield different dose recommendations.

Results Structure and Timelines
Three indicators are used to compare the performances: accuracy of identifying MTD; participant allocation and trial duration. Initial results show ignoring delayed toxicity will result in poor participant allocation and low accuracy in MTD identification. Determining MTD when all participants are fully followed-up can improve the accuracy, but will overdose more patients due to underestimated toxicity probabilities when delayed toxicities are not considered during dose-escalation. Simulations and case studies will be completed by July 2022.

Potential Relevance and Impact
Considering delayed toxicities is an increasing demand in the era of novel agents. Our study elucidates the appropriateness of existing designs to handle expected delayed toxicities by modelling incomplete toxicity data properly for escalation and recommendation decisions. If unexpected delayed toxicities do occur, it is important to incorporate them to inform dose-decisions, to keep patients safe.

PS1D-LT04

Updating existing core outcome sets to include LMiC participants: a meta core outcome set for stillbirth

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Introduction

Two million stillbirths occur annually with most occurring in sub-Saharan Africa and South Asia. Core outcome sets (COS) have been developed for stillbirth to increase the comparability of results from stillbirth studies. These COS studies did not include parents and had limited input from other stakeholders from these low-income settings and therefore these COS may not reflect the needs of parents in these communities. Barriers for including LMiC participants in COS studies include lack of time, lack of funding and infrastructure for research. The NIHR Global Health Research Unit on Stillbirth and Neonatal Death Prevention and Management in Sub-Saharan Africa and South Asia provides a unique opportunity to overcome these obstacles. The aim of this study is to contribute to the rapid development of stillbirth COS exclusively to an LMiC setting. In combination with the previously published COS developed in a high-income setting, a recommendation will be made on a 'meta-COS' which could be seen as the first steps towards a 'global' COS for stillbirth studies across the world.

Methods/Approach

This study follows the minimum standards for COS development. A long list of outcomes will be taken from the previous COS studies and supplemented with outcomes mentioned in the extensive qualitative literature on this topic in a LMiC setting. Outcomes will be scored by multiple stakeholder groups (including parents) in a Delphi survey from six sub-Saharan African countries and two from South Asia. The results of the Delphi will be summarised and discussed at a consensus meeting with representation from all stakeholder groups.

Results Structure and Timelines

We will present the approach that we will take to rapidly update the exiting COS for stillbirth in an LMiC setting. The talk will also highlight the infrastructure, support mechanisms needed, challenges and highly variable processes encountered for obtaining ethics approvals across several countries, in a study which includes parents or family that have experience of perinatal death.

Potential Relevance and Impact

This work is potentially the first COS to be initiated from Africa and will be a step towards enhancing future research studies by ensuring that outcomes are available that are relevant to all key stakeholder groups, such that real improvements in public health outcomes in regions of the world most impacted by poor perinatal outcomes may be observed. The research will also provide guidance to COS developers on how to include LMiC participants within the COS development process.

PS1D-LT05

The key elements of the core outcome set (COS) and the application of master protocol in the development of COS

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Background
With the increasing number of core outcome sets (COSs) in recent years, several COSs with different or overlapping results have been developed in some disease areas. In addition, the scope or/and methodology of the COS for the same disease have differed, or the characteristics of specific interventions have not been reflected in existing COSs, encouraging researchers to produce duplicate COSs that results in research waste.

Methods
The Core Outcome Measures in Effectiveness Trials (COMET) database was searched on August 18th, 2021, for the first of time and on May 5th, 2022, for the second time. To identify key factors that influence COS results, research with duplicated areas of health were extracted from the top 10 disease categories in COS development. Results were analyzed by descriptive analysis. The authors, who have experience in developing COS or/and in participating in the design of master protocols, discussed methods of developing a master COS protocol and achieved consensus.

Results
The results show that different researchers defined different scopes of disease, which included overlapping or intersecting diseases and co-morbidities with other diseases. Overlapping or intersecting diseases resulted in overlapping or intersecting outcomes in COS. In addition, other key factors, such as different scopes of COS, including interventions (prevention or treatment), types of outcomes (efficacy outcomes or safety outcomes), settings, and users, also influenced the COS results. Umbrella trial designs may be used to develop a common COS and intervention-specific set for the same disease or sub-type of disease. Basket trial design may be used for developing disease-specific sets and a common outcome set after meta-analysis or a consensus process.

Discussion
Using umbrella trial design and basket trial design to develop COSs may provide new ideas for researchers, which may improve efficiency of COS research and reduce waste in the future. The methods of master protocol in the development of COS may provide new ideas for researchers, which may improve efficiency of COS research and reduce waste in the future.

PS1D-LT07

Challenges of implementing and running a study within a trial (SWAT) across multiple host trials – the SPRUCE study.

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Introduction
Within ICR-CTSU trials, we currently collect patient reported outcomes (PRO) from our trial participants on paper. With advancing technology, it has become possible to collect PRO electronically (ePRO). We designed a SWAT, SPRUCE, to assess the impact of ePRO versus paper PRO collection in our oncology trials.

Methods
The primary objective of SPRUCE is to assess differences in return rates between ePRO and paper PRO. SPRUCE has a partially randomised design comparing paper and ePRO, preventing exclusion of participants with a modality preference. The sample size for randomised patients was based on the existing response rate to PRO across ICR-CTSU studies. We implemented a SWAT to optimise recruitment and have a population representative of ICR-CTSU trials. We included a feasibility endpoint based on the number of patients choosing to be randomised after 50 participants.
We aim to sequentially activate SPRUCE in large host trials following their PRO schedule, which requires the approval of a host trial amendment. The first host trial was selected due to high recruitment, however host trial recruitment outpaced set-up meaning fewer patients entered SPRUCE than expected.
We required a new software to implement ePRO. This took considerable time to acquire as the system needed to link with existing systems and databases within the ICR-CTSU to ensure data could be shared with the host trial for their analyses.
With patient and public input, study documentation was made generic where possible for use across host trials, easing set-up and minimising workload for site and ICR-CTSU staff. To increase site engagement, non-clinicians are allowed to be principal investigator at their centre as there is no clinical intervention.
The consent process for SPRUCE and the host trials had to align. Potential participants were required to be enrolled into a host trial prior to SPRUCE but could be approached for the host trial and SPRUCE in parallel. Remote consent was permitted.

Results
Ethics approval was given on 15/10/2021. The first host trial's amendment was approved on 03/02/2022. The first participant was enrolled 12/04/2022. As of 25/05/2022, 13 participants have been enrolled, with two sites open. An amendment to open the second host trial is in progress.

Discussion
Setting up a SWAT to work efficiently across ICR-CTSU trials presents unique challenges, however we hope SPRUCE will provide robust evidence for the use of ePRO in clinical trials and the framework developed may be used for future SWATs within ICR-CTSU.

PS1D-LT08

A systematic review of the application of randomisation methodology in RCTs and association with study characteristics.

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Introduction
When conducting a randomised controlled trial, there exist many different methods to allocate participants, and a vast array of evidence-based opinions on which methods are the most effective at doing this, leading to differing use of these methods. There is also evidence that study characteristics affect the performance of these methods, but it is unknown whether the study design affects researchers' decision when selecting a method.
Our aim was to describe current randomisation method use, investigate associations between choice of method and study characteristics, and to explore changes in methodology over time.

Methods
We conducted a literature review of all randomised controlled trials published in JAMA, NEJM, The Lancet and BMJ and the NIHR HTA library in 2019. For each paper the method of randomisation and study design features were recorded. Randomisation methodology use was compared with a similar review conducted in 2014.
We used descriptive tables to informally compare study features across the different methods, and to compare method use across these two timepoints.

Results
Of the 330 trials included in the review, 49% used block stratification. A combination of simple randomisation, block randomisation, stratification and minimisation accounted for 318/330 trials, with only a small number of more novel methods (e.g. Bayesian or adaptive designs) being used, although this number has increased marginally since 2014. More complex methods such as stratification and minimisation seem to be used in larger multicentre studies, whereas simple randomisation is generally used for much smaller sample sizes.

Discussion
Within this review, most methods used can be classified using a combination of simple, block stratification and minimisation, suggesting that there is not much if any increase in the uptake of other methods since 2014. There seems to be a noticeable polarisation of method use, with an increase in the use of simple methods (simple or block randomisation), but an increase in the complexity of more complex methods including greater numbers of randomisation variables being subsequently included in the analysis , and a greater number of strata. This polarisation adds to the evidence that differing opinions on randomisation methods affects their application in clinical trials.

PS1D-LT10

RCT vs registry based observational studies in evaluating outcomes in spinal interventions

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Introduction
Lumbar spine disorders are a heterogeneous group of conditions with a lack of diagnostic clarity. Thus, in both surgical and non-surgical spinal interventions there are large variations in practice. RCTs are the considered gold-standard for assessing the impact of interventions, but especially for surgical procedures there are complications in their conduct, such as surgeon preferences, patient selection, difficulties in blinding and high cost. Well-designed observational studies with registry data can complement RCTs and deliver insights into real-world practice. Over 25 national and international registries collect spinal surgery data, but there is lack of evidence that these registries have had an impact on the quality of spine care. Analysis of large registry data sets can give more accurate estimates of percentages of rare events and details about the patient demographic. Therefore, continuous analysis, feedback and communication is recommended. In this study the potential of registries on both routine care and on clinical trials will be explored.
A more modern approach of the use of registries are registry-based randomized clinical trials (RRCTs), which use a registry for a variety of purposes throughout a trial, including the identification of eligible patients, random assignment of treatment, collection of baseline variables, and the detection and adjudication of clinical end points.

Methods/Approach
We will review both RCTs and observational studies from spinal registries, regarding spinal surgeries due to disc herniations. The focus will be on how and which outcomes were collected, how much missing data occurred, effectiveness of treatment and length of follow-up intervals. For RCTs we will assess whether any registry data was used in the design or conduct of the study.

Results Structure and Timelines
The results of this review will be presented descriptively, comparing collected outcomes, follow-up intervals, treatment effects and missing data of RCTs and registry-based observational studies of surgery for herniated discs. This is ongoing work which will be completed by early September.

Potential Relevance and Impact
The aim of this review is to compare characteristics of observational studies carried out using spinal registry data with RCTs, and to assess opportunities for incorporating spinal registry data into future RCTs. Making use of the large amount of data routinely collected in various spinal registries within RCTs could have the potential to improve the quality of evidence for spinal interventions.

PS1D-LT11

The cost-effectiveness of improving patient recruitment in RCTs: a case-study of dexamethasone from the RECOVERY trial

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Introduction
The RECOVERY trial assessed the effectiveness of medicinal treatments on preventing severe outcomes from COVID-19 disease in hospitalised patients from 176 NHS hospitals. Of the 9,355 eligible recruited COVID-19 patients, 6,425 participated in the comparison of dexamethasone plus usual care versus usual care alone. Mortality benefits of dexamethasone were observed for COVID-19 patients who received invasive mechanical ventilation and non-invasive ventilation. Despite the urgency for results the average recruitment rate across the participating hospitals was only 15%. The aim of this study was to estimate the cost-effectiveness of improving recruitment to the RECOVERY trial from 15% to 50%, related to the evaluation of dexamethasone as a COVID-19 treatment, by employing two additional research nurses to each hospital affiliated with the RECOVERY trial.

Methods
A decision tree model of 14 clinical pathways was developed, to estimate the cost-effectiveness of dexamethasone plus usual care, against usual care only. Probability, utility, and cost inputs were estimated for each clinical pathway and dexamethasone arm. A cost-utility analysis of clinical practice post-RECOVERY trial versus previous clinical practice was undertaken; this analysis aggregated at the population level and included the cost of two research nurses recruiting at each hospital, to estimate the incremental cost-effectiveness ratio of improved recruitment to the RECOVERY trial and the overall net benefit at the £20,000 cost-effectiveness threshold. Deterministic sensitivity analyses with respect to the model's inputs were also undertaken to assess the robustness of the findings.

Results
Improved recruitment to the dexamethasone arm in the RECOVERY trial could have generated an incremental net monetary benefit of £125,500,281, thus highlighting the magnitude of the foregone population health benefits due to the absence of implementing a more effective recruitment strategy. If recruiting two research nurses to each involved hospital was such an effective strategy, only £2,559 would need to be invested to generate an incremental quality-adjusted life year for COVID-19 hospitalised patients. The one-way sensitivity analyses confirm that even if a very low share of COVID-19 inpatients were treated with dexamethasone, improving recruitment to the RECOVERY trial would still generate positive incremental net benefits. Also, even if dexamethasone was not more effective than usual care, the incremental net benefit of improved recruitment would sustain positive figures, according to the two-way sensitivity analysis.

Conclusion
Poor recruitment to randomised controlled trials is not only limited to trial teams, but it can also have wider implications for national healthcare systems.

PS1D-LT12

A comparison of methods for estimating dichotomous treatment effects: a simulation study

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Introduction
The odds ratio (estimated via logistic regression) is a well-established and common approach for estimating covariate-adjusted binary treatment effects when comparing a treatment and control group with dichotomous outcomes. Its popularity is primarily because of its stability and robustness to model mis-specification. However, the situation is different for the relative risk and risk difference, which are arguably easier to interpret and better suited to specific designs such as non-inferiority studies. So far, there is no equivalent, widely acceptable approach to estimate an adjusted relative risk and risk difference when conducting clinical trials. This is partly due to the lack of a comprehensive evaluation of available candidate methods.

Methods/Approach
A simulation study is designed to evaluate the performance of a number of candidate methods used to estimate relative risks to represent conditional and marginal estimation approaches. We consider the log-binomial, generalised linear models (GLM) with iteratively weighted least-squares (IWLS) and non-robust standard errors (SE); log-binomial GLM with convex optimisation and non-robust SEs; modified-Poisson GLM IWLS and robust SEs; log-binomial generalised estimation equations (GEE) and robust SEs; marginal standardisation and delta method SEs; and marginal standardisation and permutation test SEs.
Independent and identically distributed datasets are simulated from a randomised controlled trial to evaluate these candidate methods. Simulations are replicated 10000 times for each scenario across all possible combinations of sample sizes (200, 1000, and 5000), outcomes (10%, 50% and 80%), and covariates (ranging from -0.05 to 0.7) representing weak, moderate or strong relationships. Treatment effects (ranging from 0, -0.5, 1; on the log-scale) will consider null (H0) and alternative (H1) hypotheses to evaluate coverage and power. Performance measures (bias, mean square error (MSE), relative efficiency and convergence rates) are evaluated across scenarios covering a range of sample sizes, event rates, covariate prognostic strength and model mis-specifications.

Timing of Potential Results and Potential Relevance & Impact
Overall, there are several methods for estimating unadjusted and adjusted relative risks. However, it is unclear which method(s) preserves type-I error rate, is robust to model mis-specification or is the most powerful when adjusting for non-prognostic and prognostic covariates. GEE estimations may be biased when the outcome distributions are not from marginal binary data. Also, it seems that marginal standardisation and convex optimisation may perform better than GLM IWLS log-binomial.
Findings from this work will comprehensively summarise estimation algorithm convergence rates, absolute mean bias, MSE, relative efficiency, nominal coverage and power.

PS1D-LT13

Identification of causal mediation effects with non-adherence and missing data

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Many clinical trials suffer from participant non-adherence and missing data. Non-adherence is a post-randomisation event that affects the interpretation of the outcome. A standard intention-to-treat (ITT) analysis will estimate the causal effect of treatment offer without bias, though ignores the impact of non-adherence. Alternatively, a complier-average causal effect (CACE) analysis provides an estimate of the average causal effect of treatment receipt in the subgroup of participants who comply with their randomisation. Still, the reliability and interpretability of results obtained from either approach is affected by missing data. Clinical trials in mental health often evaluate complex, non-pharmacological interventions, such as psychotherapy. Evaluating how a complex intervention has led to changes in the outcome (the mechanism) is key for the development of more effective interventions. A mediation analysis aims to decompose a total treatment effect into a mediated effect, one that operates via changing the mediator, and a direct effect. However, current methods for mediation analysis in trials usually decompose the ITT effect, and the corresponding direct and mediated effects ignore the impact of participant non-adherence. As well, there is limited guidance on how to estimate mediation effects with missing data.

This work will summarise the literature on methods that combine each pairwise combination of non-adherence, mediation, and missing data. To our knowledge, there is no guidance on how to consider all three in a unified causal analysis.

We found six papers that identify mediation effects with non-adherence; though only four identify both direct and mediated effects, and three of these decompose a randomisation preserving estimand (CACE). We show that the CACE can be decomposed into two estimands: a complier average natural direct effect (CANDE) and a complier average causal mediated effect (CACME), and these can be estimated using linear structural equation models under a given set of assumptions. To combine missing data, we will review the missing data assumptions for mediation analysis applied to the ITT and CACE approaches.

Clinical trials in mental health are particularly susceptible to issues related to non-adherence and missing data. As well, clinical trials in mental health often evaluate complex interventions where mediational research questions are of interest. Non-adherence, missing data, and mediation are all independent areas of active research, though there is no guidance on how to consider all these issues in a unified causal analysis. Trials should consider a unified analysis of non-adherence, mediation, and missing data, to accurately explore treatment mechanisms without bias.

PS1D-LT14

Ascertaining patient and clinician views on the severity of post-operative complications after cardiac surgery: design, conduct and analysis of a survey.

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Introduction
A composite objective outcome measure is being developed incorporating the impact of post-operative complications following cardiac surgery as judged by patients and clinicians. Typically trials record the occurrence of complications and their effect on post-operative hospital stay but this does not necessarily reflect patient or clinician views on the impact of complications on recovery.

Methods
Twenty complications commonly reported in the literature were identified. A survey, using a balanced incomplete block design, was developed. Respondents (past cardiac surgery patients and cardiac surgeons) were asked to rank groups of four complications according to severity. Surgeons were asked to provide two sets of rankings, one based on immediate threat to life (TTL) and the other on impact on length-of-stay (LoS). Responses were analysed using the Plackett-Luce (PL) model (implemented using PlacettLuce in R). Consistency across (external) and within (internal) respondents was assessed by converting rankings into paired comparisons.

Results
Seventy-eight patients and fifteen surgeons completed the survey in full. Stroke, heart attack and septic shock were the most serious complications from the patient perspective, with atrial fibrillation (AF) and leg wound infections being least serious. Stroke was also rated as having the greatest impact on LoS by surgeons, followed by wound dehiscence and gastrointestinal complications; deep vein thrombosis and AF had the least impact. Gastrointestinal complications were ranked as having the highest TTL, followed by septic shock and stroke; leg wound infections and AF had the lowest TTL. Differences between rankings for LoS and TTL support the inclusion of two ranking criteria when assessing surgeon views. There was good external and internal consistency.
Coefficients derived from the PL models were rescaled and combined to produce a single coefficient for each complication as illustrated, which were summed to give an overall complication score.
AF_coeff_combined=(0.5×AF_coeff_patient_survey)+(0.25×AF_coeff_surgeon_LOS_survey)+(0.25×AF_coeff_surgeon_TTL_survey)

Discussion
This score can be applied to any cardiac surgery dataset recording the component complications. It requires data on the occurrence of complications with no further assessment of severity by a member of the clinical team, unlike existing complication scores. This is particularly important for trials where blinding may not be possible and objective outcome assessment is of high importance.
This work forms part of a PhD project; this score will be combined with a second complication score (coefficients guided by analyses of trial data to ascertain the impact of complications on LoS) and a score representing the early recovery period in the Intensive Care Unit.

PS1D-LT15

Enhancing the transparency and reporting of randomised trials: update of the SPIRIT 2013 and CONSORT 2010 Statements

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Introduction

Well-designed and properly executed randomised trials provide the most reliable evidence on the efficacy of healthcare interventions. However, there is overwhelming evidence that the completeness of trial reporting is often poor. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (CONsolidated Standards Of Reporting Trials) Statements are widely adopted standards for reporting protocols and results of randomised trials; endorsed of by hundreds of medical journals and organisations worldwide. It is important SPIRIT and CONSORT are kept up-to-date and relevant to end users, reflecting new evidence, methodological advancements and emerging perspectives. It has been over 10 years since CONSORT was last updated in 2010 and eight since publication of SPIRIT in 2013.

Aim

We are conducting a programme of research to concurrently update SPIRIT 2013 and CONSORT 2010 Statements, including integrating key extensions, and by developing implementation strategies to promote adherence. The aim is to provide researchers with consistent guidance in considering how key aspects of the trial design, conduct, and analysis are reported from protocol to final publication.

Methods

Using established methods for development of health research reporting guidelines we plan to:

1. Conduct a scoping review of the literature to identify new evidence relevant to reporting of randomised trials [completed].
2. Conduct a Delphi survey to identify changes needed to existing SPIRIT and CONSORT checklist items and seeking views on new items identified from the scoping review or suggested by Delphi panellists.
3. Organise a meeting of key stakeholders to establish consensus on items to be included in the updated SPIRIT and CONSORT checklists.
4. Develop the SPIRIT and CONSORT Statements and accompanying Explanation and Elaboration documents, which explain and illustrate the principles underlying the updated Statements.
5. Disseminate and implement the updated Statements, including a new joint SPIRIT-CONSORT website, online training modules and new patient-facing trial portal.

Relevance and Impacts

To ensure implementation and adherence of the updated SPIRIT and CONSORT guidance it is essential we include the views of a broad range of stakeholders as part of this process. This includes views from experienced clinical trial researchers, clinicians, representatives from funding bodies, ethics committees,

medical journals, regulatory agencies and patient and public involvement groups. We want to invite interested stakeholders to register their interest in taking part in the Delphi survey process via the SPIRIT-CONSORT project website and find out more about this project. Funded by MRC-NIHR Better Methods, Better Research [MR/W020483/1].

PS1D-LT16

Review of reporting of time to event analyses and the proportional hazards assumption in Randomised Controlled Trials

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Introduction
The most commonly used approaches for the analysis of time-to-event (TTE) outcomes impose an assumption of proportional hazards (PH), such that the hazard ratio (HR) is assumed to be constant over time. Methods are available for assessing the validity of the PH assumption, however, the assumption is not always checked or reported for validity. The objectives were to (i) assess the frequency and approaches used for exploring the PH assumption within individual Randomised Controlled Trials (RCTs), and (ii) assess which methods of analysis are used in current practice by undertaking a survey of current practice targeted at the UK Clinical Research Collaboration (UKCRC) network of registered Clinical Trials Units (CTUs).

Methods
Eligible studies included RCTs of TTE outcomes which were included as a primary and/or secondary outcome, where RCTs including phase II/III studies were analysed using a PH model. To conduct the survey all 51 UKCRC registered CTUs in the UK were contacted. This work was carried out to supplement the review of RCTs, which could be prone to selective reporting of the information about the PH assumption.

Results
106 RCTs, all of which were phase III, were eligible for inclusion in our review. Testing of the PH assumption was only reported in 12 out of 106 (11%) RCTs that conducted a survival analysis using Cox PH model and log-rank test. In total, 31 out of 51 (61%) CTUs completed the survey. The majority of the CTUs said that they used methods dependent on the PH assumption to analyse TTE data and 100% of CTUs said that they assess the PH assumption. However, when asked about what approach would be used if the PH assumption was invalid, three CTUs did say they would still continue to use the method assuming PH.

Discussion
Findings of this review demonstrate the poor reporting of the investigation of the PH assumption in published RCTs of TTE outcomes and inadequate description of methods and results of appropriate approaches to assess the validity of the PH assumption. However, these inadequacies may only reflect a reporting issue as the survey of CTUs suggest that the assumptions are routinely explored in practice. Further work is needed to improve reporting.

PS1D-LT17

Public Perceptions of Clinical Research

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Introduction
Issues of attitudes towards clinical research and concepts of trust in research are important if we are to better understand how to include, engage and communicate with the public on health research. Lack of trust in research is one of the main obstacles to research participation. We undertook an online survey to examine respondents' attitudes, trust and understanding of clinical research and their willingness to participate as an enroled patient or an adivising lay member. Additionally, we explored whether COVID-19 has had an impact on the public's interest and views on clinical research.

Methods
Participants completed an online survey via Jisc online surveys consisting of 21 questions, taking around 20 minutes to complete. The survey was co-designed by authors with PPI input. Participants were members of the public aged 18+, residing in the United Kingdom.

Results
There were 101 responses however two were excluded as they were outside the UK. Therefore, a sample of 99 was reached. Most respondents (>80%) felt that clinical research benefits our society, is important to improving our nation's health and for the advancement of science. However, 28% felt that clinical research can harm society.
Many stated that the most important reasons clinical research is undertaken is for the advancement of science (47%) and patient benefit (59%). Trust in publication of results varied with some respondents (33%) disagreeing that results of clinical trials are made available to the public. Over a third (37%) agreed that funding bodies may manipulate research data and results. Many respondents (74%) agreed that clinicians would still provide best quality care if you decided not to participate in a trial, however some disagreed with this (15%).
When asked if they would participate in a trial, 47% said it was somewhat likely, 32% very likely, 5% wouldn't and 10% were not sure. 40% expressed they previously contributed to clinical research as a member of the public. Over 60% stated that their awareness, interest and trust in clinical research has increased following the COVID-19 pandemic.

Discussion
Much of the sample appeared to have some trust in clinical research, however, there were notably responses that contradicted this view.
Educating the public on clinical trials with a focus on increasing trust should be a priority for those working in this area to increase participation in trials either as a lay member or participant. Research into how this could be best carried out should be prioritised.

PS1D-LT18

Inclusion of stakeholders from low- and middle-income countries in core outcome set development and use

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Introduction
Only a fifth of core outcome sets (COS) have included low- and middle-income countries (LMIC) stakeholders in their development. We explored views on inclusion of LMIC stakeholders in COS development and use.

Methods
We conducted two online surveys, the first targeted researchers from high income countries (HIC) who had led COS work that included LMIC stakeholders (identified from the COMET database) while the second targeted LMIC stakeholders (through a newsletter invitation to Global Health Network members). Questions included asking for views on how to improve the use of COS in LMICs. In the second survey, three existing COS (Pre-eclampsia, COVID-19 and Palliative care) were presented as case scenarios, and respondents asked to state [with reason(s)] if they would/would not use the COS if they were working in that area.
Both surveys were delivered using JISC Online Surveys® software.

Results
We received 37 (49%) responses from 75 researchers in the first survey. Of the 81 respondents to the second survey, 26 had COS experience, 9 of whom had been involved in COS development.
Common findings across both surveys were that personal research interests are a key driver for initiation/participation in a given a COS, and determination of 'what to measure' was the most common stage of COS development process where LMIC stakeholders were involved.
From the second survey, a majority of respondents would use the COS for pre-eclampsia (18/26) and COVID 19 (19/26) since the development process included key stakeholders. More than half of the respondents were not sure or would not use the palliative care COS as they felt stakeholders engagement was limited and it was developed for a different setting.
Common issues that can impact on the use of COS in LMICs: (i) feasibility of measuring the outcomes in the COS, (ii) knowledge on the usefulness and availability of COS and (iii) wide stakeholder engagement in the COS development process including having patients and carers in the development process.
Endorsements of COS use by professional associations or by funders and regulatory agencies was not a major enabler for usage of a COS by LMIC stakeholders despite it being highlighted by HIC researchers as a potential enabler.

Discussion
There is need to provide guidance on how outcomes will be measured and how to involve key stakeholders in the development process. Sensitization of LMIC stakeholders on COS utility is needed, with professional associations being a potential influential route for this.

PS1D-LT19

Applying the Estimand Framework to the microbiological outcome

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Introduction

In 2017, the International Council for Harmonisation (ICH) released an addendum R1 to ICH E9 "Estimands and Sensitivity Analysis in Clinical Trials". This addendum aims to improve the study design, planning and performing primary and sensitivity analyses by having clarities about trial design, data collection and statistical analysis when describing the treatment effect of interest at the planning stage. Using this addendum could help to facilitate dialogue on the effects of microbiological outcomes that a clinical trial seeks to estimate.

In clinical research, data generated from laboratory sample analyses (blood, faeces, urine etc) are called microbiological data. This generally includes the types of organisms detected and their level of growth, plus susceptibility to tested antibiotics (R, S, I). A previous systematic review found that the outcomes comprised from the microbiological data, such as the number of detected organisms (counted variable) and resistance to at least one antibiotic (binary variable), have been oversimplified. Moreover, the analyses of the microbiological outcome were questionable due to poor reporting quality.

Methods/Approach

We have explored a list of issues related to microbiological outcomes identified from the systematic review and perspectives from stakeholder groups, including challenges of working with microbiological data. We are currently working through the Estimand framework on how to define appropriate microbiological estimands. Considerations include the study population selection, methods of handling missing data and intercurrent events, and the estimand of interest.

Results Structure and Timelines

The systematic review work and the stakeholder group work have been completed. We are currently working through the estimand framework and writing up the critical elements to consider when defining microbiological outcomes in clinical trials. All works will be completed by the end of July.

A summary of issues and challenges of using microbiological data will be presented followed by considerations when defining microbiological outcomes using the five estimand attributes.

Potential Relevance and Impact

Our results will help to standardise the format and the quality of microbiological outcomes in clinical trials. This could reduce the problem of data wastage (oversimplifying the complex data) and provide insight into handling and analysing microbiological data more appropriately. These analyses are conducted as part of my PhD.

PS1D-LT20

Survey findings of the UK researchers about the challenges and barriers to blinding in complex intervention randomised controlled trials (RCTs)

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Objective:
This survey aims to explore the current practice and views about outcome blinding in complex intervention randomised controlled trials (RCTs) among researchers and experts affiliated with UK Clinical Research Collaborative (UKCRC) registered Clinical Trials Units (CTUs), and Trial Methodology Research Partnership (TMRP) executives.

Background
The current research quality standards emphasise blinding as a vital criterion to maintain the credibility of estimating the effect of an intervention in an RCT. However, conventional blinding is difficult or impossible to apply in complex intervention RCTs. Many researchers perceive blinding as a genuine hurdle in these trials. However, there is little information about the actual views of research teams in the UK towards such challenges. This survey of TMRP members and staff affiliated with UKCRC registered CTUs offers an opportunity to better understand issues of blinding in complex intervention RCTs.

Methods
We developed a 30 item questionnaire, including questions about the respondent's job role and experience of complex intervention RCTs, and questions on their views regarding blinding in such RCTs. The survey questionnaire was made available through Microsoft Forms. Eligible participants were invited to participate by email, with a reminder after four weeks. Results were reported descriptively for each question using percentages for each response option.

Conclusions
Our survey provides data on the attitudes and views of researchers about the challenges of outcome blinding in complex intervention RCTs within the UK clinical trial community.

PS1D-LT21

AlcoChange: Lessons for Stepped Wedge Trials after the Pandemic

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Introduction

Alcohol-related liver disease (ArLD) is now the second commonest cause of preventable death in the UK. The numbers requiring care are rising, putting increasing pressure on Alcohol Care Teams (ACTs).
Reducing ongoing alcohol use is the single most important determinant of survival in ArLD, but there are no effective pharmacological therapies to maintain abstinence. Behaviour change interventions (BCIs) are effective tools for reducing alcohol consumption, but only ~6% of individuals with harmful drinking receive a BCI, usually face-to-face, which is difficult to scale.
AlcoChange is a digital therapeutic (smartphone app and breathalyser) that can deliver BCIs remotely and are easily scalable. AlcoChange allows self-monitoring of craving, alcohol use/abstinence and breath alcohol. In response to cravings, users are sent motivational messages (pre-designed by the user).

Methods

The Phase III study to evaluate the effectiveness of AlcoChange in reducing alcohol use in patients with ArLD was originally designed as a cluster-randomised stepped wedge trial (SWT), involving 18 hospitals divided into 6 clusters. A SWT is like a crossover design as the clusters experience both the control and intervention conditions, but at different times. All clusters start in the control condition, introducing the intervention randomly at regular intervals to one cluster at a time, until all clusters are delivering the intervention. The SWT design was chosen due to the complex nature of the behaviour change intervention, and the potential of contamination between the two arms if both control and intervention were delivered in the same hospital.
The main logistical challenge of a SWT is that all hospitals have to start recruiting together on day 1.

Results

The Covid-19 pandemic put considerable strain on trial sites and staff to deliver trials, with a backlog of 'non-Covid' studies. Consequently, we were unable to align all trial sites to open simultaneously. The Trial Management Group redesigned the study as an individually randomised trial.

Discussion

The SWT design has several advantages for complex interventions, but with considerable logistic challenges in delivery. For this study, the risk of contamination between groups was mitigated by the research team delivering the intervention rather than the ACT (who build a relationship with the patient). Access to the app is restricted via 2-factor authentication, further decreasing the risk of contamination. Other studies of complex interventions may need to take similar mitigating steps, while pressures on delivery of SWTs remain.

PS1D-LT22

How COVID-19 policy changes during the Com-COV3 trial in adolescents impacted trial design and results

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Introduction
On 13th September 2021 the Joint Committee on Vaccination and Immunisation (JCVI) recommended all 12-17 year olds in the UK receive a first COVID-19 vaccination of BNT162b2 (Pfizer/BioNTech, BNT), deferring decisions about timing and nature of a second dose. Rare side effects had been recorded after a second dose of BNT, including myocarditis and pericarditis, especially in young men. The Com-COV3 trial was designed to investigate options for the second dose.

Methods
Com-COV3 is a participant-blind, randomised, phase II multi-centre clinical trial evaluating reactogenicity and immunogenicity of COVID-19 vaccine schedules in 12-16 year olds. The first dose of BNT was given either in the community or the study. Participants were randomised at the time of second dose (1:1:1) to receive BNT full dose, or BNT 1/3rd dose, or NVX-CoV2373 (Novavax), 8 weeks after first dose.
On 29th November, following the wave of infections in UK adoloscents, the JCVI recommended a second vaccination of BNT full dose for adolescents. After urgent consultation with the Trial Steering Committee, the study was adapted, to provide information most relevant to policy makers. Participants enrolled before 29th November 2021, but not yet randomised, were henceforth randomised (1:1) to BNT full dose or BNT 1/3rd dose. Following further consultation with study oversight committees, recruitment was discontinued.

Results
The study recruited 148 participants, instead of the planned 270. Sixteen withdrew from the study before their second dose (most to accept newly-offered community vaccination). Despite curtailed recruitment, the study demonstrated mixed COVID-19 vaccination schedules in adolescents elicited strong immune responses with a favourable reactogenicity profile and no safety concerns.

Discussion
Rapidly changing infection rates in the UK required the JCVI to respond promptly based on available evidence, which in turn had a significant impact on study recruitment. Com-COV3 has established trial infrastructure in place, and the study has now been extended to recruit another cohort, addressing a new research question, comparing third COVID-19 vaccination options in UK adolescents.
Designing a trial to answer new policy questions, particularly during a pandemic, can be challenging, as vaccine policy changes in response to epidemiological circumstances. Prompt responses from study oversight committees are necessary to enable swift study amendments. Com-COV3 exemplifies the necessity for flexibility and adaptability of clinical trial design during a global pandemic, thereby ensuring the delivery of high-quality, policy informing clinical trials.

PS1D-LT23

Conducting clinical trials during the COVID-19 pandemic: experiences from a dengue trial in Ho Chi Minh City, Vietnam.

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The Oxford University Clinical Research Unit (OUCRU) in Vietnam has a dynamic dengue research group conducting several clinical trials on both dengue prophylaxis as well as therapeutics. Obesity is a growing problem among young people in Vietnam and is increasingly recognised as an important risk factor for severe dengue, likely due to alterations in host immune and inflammatory pathways. An open label clinical trial assessing the safety and tolerability of Metformin as an adjunctive therapy for dengue patients with obesity – the MeDo trial- was initiated in July 2020.The first patient was enrolled on 26 July 2020 at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City, with the aim of recruiting 120 obese/overweight dengue patients within two dengue seasons. Due to the COVID-19 pandemic overwhelming most hospitals in Vietnam, and causing many difficulties for clinical research conduct, the dengue team experienced significant challenges in the conduct of the MeDo trial.

Vietnam was one of the few countries that initially succeeded in controlling COVID-19 well in 2020 due to strict border controls and contact tracing. However, the few cases that were identified in the city were hospitalized at HTD. The fear and stigma of the disease resulted in patients with other diseases like dengue seeking healthcare elsewhere or not at all. In June-September 2021 during a large delta wave, HTD transferred all their services for COVID-19 patients and all non-COVID studies conducted at this hospital were suspended. The strict city lockdown strategy prevented patients with other illnesses, from accessing health care systems and the many strict pandemic control policies, including the requirement of COVID-19 screening in all patients, also led to hesitancy of presenting to hospitals. In early 2022, a large omicron wave occurred which resulted in less hospitalization but was associated with healthcare staff shortages due to illness or isolation policies. This led to ongoing disruption to clinical research and, despite dengue still circulating in the city, recruitment rates, retention and follow-up of our trial have been badly affected. The team adapted to these challenges by initiating new collaborations with different hospitals, diversifying study sites, reinforcing public and community engagement and communication with local healthcare staff.

During the pandemic, conducting clinical research has been challenging due to strict lockdowns, fear of accessing healthcare services and staff shortages. Adapting to rapidly changing pandemic policies, engagement and renewed collaborations allowed us to continue research despite the challenges of the pandemic.

PS1D-LT24

Delivering COVID-19 Vaccine Trials at Speed: The ComFluCOV Experience

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Background

In February 2021, the Department Health and Social Care (DHSC), sought evidence to inform autumn 2021 Covid-19/influenza vaccine policy. Co-administration of these vaccines would potentially increase uptake and reduce healthcare appointments, but safety data on co-administration was lacking. ComFluCOV (ISRCTN14391248) was designed to provide the necessary evidence to inform policy.

Methods

ComFluCOV, run by the Bristol Trials Centre (BTC), was an urgent public health study, facilitating fast-track regulatory approval and prioritisation at study sites. Healthy volunteers due their second Covid-19 vaccine were eligible. The target sample size was 756 participants. Participants were followed-up for 6 weeks. The study was advertised via social media, TV, radio and newspapers, and local Clinical Research Networks supported sites with volunteer screening. Electronic trial management and data capture systems were used. Participant data were reviewed daily. Weekly virtual meetings were held with stakeholders.

Results

ComFluCOV was completed within six months, from conception to publication. Set-up was achieved in three weeks. Collaboration with Oxford Clinical Trials Unit (CTU), who had delivered Covid-19 trials, enabled efficient development of IT systems and study materials. Recruitment took place at 12 sites. Over 380 site staff were trained. Partway through recruitment the study was adapted to incorporate an additional influenza vaccine at the request of the DHSC. Media coverage was facilitated by the Sponsor communication team. 679 (90%) participants were recruited over 2 months. The target sample size was not reached due vaccine expiry and a decreasing pool of eligible volunteers. The final report to the DHSC was submitted in September 2021, following a preliminary safety report in May 2021. Trial results are available (Lazarus R et al. Lancet. 2021;398(10318):2277-87).

The study was delivered by 11 BTC staff (Senior leadership, five trial managers, two statisticians, three IT staff) plus others who supported the screening of volunteers. Over busy periods staff worked >70 hours/week.

Discussion

It is feasible to rapidly deliver vaccine trials in a pandemic situation. Study milestones to inform Government policy were met. Working with a CTU enabled immediate mobilisation of a team of experienced researchers. Altruism and media publicity were critical to successful recruitment. Use of wholly electronic data capture methods is not without challenges.

Elements of the trial could be adopted to increase efficiency of future trials; 1) greater sharing of resources between CTUs; 2) use of electronic trial management systems and materials, virtual meetings; 3) expedited regulatory reviews, with feedback ahead of submission.

PS2A-01

Priority setting the opportunities for routinely collected data and trials: COMORANT-UK

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Introduction

Researchers are increasingly seeking to use routinely-collected data to support data collection in clinical trials. This approach has potential to transform the way clinical trials are conducted in the future. The availability of routine data for research, whether healthcare or administrative, has increased and infrastructure funding has enabled much of this. However, challenges remain at all stages of a trial life cycle. The COMORANT-UK study aimed to systematically identify, with key stakeholders across the UK, the ongoing challenges related to trials that seek to use routinely-collected data.

Methods

This 3-step Delphi method consisted of two rounds of anonymous web-based surveys (steps 1 and 2), and a virtual consensus meeting (step 3). Stakeholders included trialists, Health Relevant Data infrastructures (i.e. HDRUK), funders of trials, regulators (HRA, MHRA), data providers and the public. Stakeholders provided research questions/uncertainties that they believed are of particular importance (step 1), and then selected their top 10 in the second survey (step 2). The ranked questions were taken forward to the consensus meeting (step 3) for discussion with representatives of the stakeholder groups.

Results

A total of 66 respondents yielded over 260 questions or challenges. These were thematically grouped and merged into a list of 40 unique questions, 88 stakeholders then selected their top ten from the list in the second survey. The top 14 questions were brought to the virtual consensus meeting in which stakeholders agreed a top list of seven questions. This presentation will report these seven questions which are within the following domains: data access, efficiency of use, regulatory approvals, data quality, communication with participants and the public. These questions address both evidence gaps (requiring further methodological research) and implementation gaps (requiring training and/or service re-organisation). Funding from HDRUK has been secured to take forward two of these questions as part of the PRIMORANT-UK study.

Discussion

This prioritised list of seven questions can inform the direction of future research in this area and direct efforts to ensure that the benefits in major infrastructure for routinely collected data are achieved and translated into methodology and efficiency. Without this and future work to address these questions, the potential societal benefits of using routinely collected data to help answer important clinical questions will not be realised.

PS2A-02

Demonstrating the data integrity of routinely collected healthcare systems data for clinical trials

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Introduction

Regulatory issues are a major roadblock to widespread use of routinely collected healthcare systems data in clinical trials. Trialists must demonstrate to regulatory authorities that all data used in a clinical trial, including healthcare systems data, have integrity and are reliable and complete. Data integrity is defined as the extent to which all data are complete, consistent, accurate, and reliable throughout the data lifecycle. There was little guidance on how to assess and document the integrity of centrally curated healthcare systems data, so in 2021 we co-developed a process. Three key stages of the lifecycle were evaluated: (i) collection and transfer from healthcare systems, (ii) centralised processing and curation, and (iii) linkage and extraction for trialists. Two NHS Digital data assets were assessed using this process as being "equivalent to a transcribed copy of the original source data" and therefore suitable for use in trials: (a) the Admitted Patient Care dataset of Hospital Episode Statistics (HES APC), and (b) the Civil Registration of Deaths (CRD).

Methods/Approach

As an extension and implementation of our previous work, we aimed to explore the use and further development a metadata cataloguing tool (Collibra) to record the integrity and provenance of datasets within NHS Digital's data platform. Our initial method was automated to ensure more assets can be evaluated for integrity, and to avail this evaluation to trialists. NHS Digital holds over 200 data assets; therefore, automation is necessary. We further developed Collibra to report integrity information on HES APC and CRD datasets. Using information from our initial published assessment, we checked that the data lifecycles were fully captured and reported in Collibra, including pertinent information on collection and transfer from healthcare systems, centralised processing and curation within NHS Digital, and linkage and extraction. We then scaled-up Collibra to report on the integrity of other NHS Digital data assets.

Results

The Collibra reports of the two datasets will be reviewed for accuracy and completeness by Sep 2022, and a narrative analysis of the reports will be presented.

Relevance/Impact

This puts aside a key roadblock to using healthcare systems data: Trialists can access accurate documentation on the integrity of NHS Digital datasets. Datasets considered integral and equivalent to a transcription of source data are more likely to support trials. We urge data providers to assess and document their datasets in a similar manner. This will make data collection in Academic and Industry trials more efficient.

PS2A-03

Big drug data for big drug trials – validation and data-driven implementation of routinely-collected, nationwide English prescribing and dispensing datasets in the RECOVERY trial

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Introduction
Routinely-collected data (RCD) may help reduce the cost and complexity of randomised trials, and improve data completeness – but it requires validation and development of source-specific analytic approaches.

Methods
We describe the first use within a trial of two novel nationwide datasets on medications in England: 1) the General Practice Extraction Service Data for Pandemic Planning and Research (GP) dataset (a focused extract used for commissioning and surveillance) and 2) the Medicines Dispensed in the Community (Dispensing) dataset (pharmacy claims). Using a subset of 36,454 participants in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial - which had no other sources on outpatient drug exposure - we explored: 1) linkage coverage; 2) capture of different drugs using broad (British National Formulary [BNF] chapters) and specific drugs groups (of interest to RECOVERY); and 3) timeliness and stability (by comparing discrepancies in overlapping periods across consecutive data extracts). Finally, we developed data-driven analytic approaches, namely 4) establishing a lookback period to define current use at randomisation; 5) handling of temporal data for incident events in the Dispensing dataset (which provides dates as months only); and 6) quantifying the value of using one or both sources.

Results
90% of participants recruited in England were captured in both datasets. Those not linked in either dataset (3%) were younger, spread nationally, and more ethnically diverse. Dispensing data is more complete across BNF chapters, while GP data focuses mostly on cardiovascular, respiratory, and diabetes drugs. Dispensing data captures more individuals in most drug groups, but GP data identifies additional exposures for some drugs like immunosuppressants and vaccinations. Dispensing data is more stable across consecutive extracts, but using either source involves a two-month lag. Based on average intervals between consecutive prescription/dispensing events, a 3-month lookback period before randomisation identifies >85% participants on most chronic medications, and was used for baseline assessments in the trial. Inputting day 15 as date for Dispensing records (and ignoring those in the month of randomisation) closely approximates GP records for initiation of the same drugs – but different date handling rules did not substantially alter either baseline or incident drug exposure estimates.

Discussion
Our experience lays the groundwork for expanded use of large-scale drug data in trials and observational studies in England. For most studies, Dispensing data provides comprehensive drug exposure information on its own. This data utility assessment approach may be repurposed by studies working with other novel RCD sources.

PS2A-04

Lack of standardised recording of inflammatory bowel disease outcomes in electronic health records in the UK: mind the data gap between clinical trials and practice

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Introduction
There is growing interest in utilising routine electronic health records (EHR) for pragmatic clinical trials in inflammatory bowel disease (IBD). However, standardised recording of clinical outcomes for IBD in routine practice in the UK is limited. We aimed to describe and quantify variation in the coverage of the main symptoms of IBD and disease activity recorded by practitioners in hospital-based routine EHR.

Methods
We analysed EHR generated by 127 clinicians (94 doctors and 33 nurses) for 909 consultations with 102 patients in face to face IBD clinics in 2009-2019 at six hospitals across the North West region of England. We studied the coverage of symptom items and physician rating of disease activity required for the common disease activity indices used in clinical trials (Crohn's Disease Activity Index, Mayo Clinic Score [MCS]) and clinical practice (Harvey-Bradshaw Index and Simple Clinical Colitis Activity Index). We compiled a lexicon of descriptors used to define severity and frequency of symptom items form disease activity indices.

Results
IBD symptoms were captured as individualised clinical narratives using a wide range of terms and descriptors. Capture of indices was rare (9% [81/909] of EHR) and quantification of symptoms did not adhere closely to standardised descriptors. Although coverage of symptoms was not uncommon in EHR (from 28% for urgency of stool to 68% for stool frequency), standardised quantification was infrequent (18-52% of EHR where symptoms from indices were captured). Mean 19 (11-25) alternative descriptors were recorded in EHR for each symptom item (e.g. sharp, intense, remarkable abdominal pain instead of mild, moderate, severe). Recording of symptoms during a standardised time frame was scarce (e.g. 4% [22/534] of EHR where stool frequency was captured). Grading of disease severity as defined by the physician rating from the MCS (mild, moderate, severe) was used in only 8% (20/250) of EHR where assessment of disease severity was recorded.

Conclusions
There was little evidence for standardised recording of IBD symptoms and disease activity in routine EHR. This presents challenges for leveraging clinician-recorded outcomes from routine data sources. Utilising real world EHR for research may require computational methods to interrogate varied terminologies and unstructured data. Our work provides a starting point for building a lexicon of terms and phrases to support natural language processing approaches to extract clinical outcomes from routine IBD records in a secondary care setting.

PS2A-05

A more efficient approach to randomised controlled trials in primary care using routinely collected practice-level data

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Introduction

Conducting randomised controlled trials (RCTs) in primary care is challenging; recruiting patients during time-limited or remote consultations can increase selection bias and physical access to patients' notes is costly and time-consuming. A more light-touch approach, with practice-level intervention adoption, which avoids recruiting individuals, is possible. The CHICO (CHIldren's COugh) cluster RCT aimed to reduce antibiotic prescribing in children presenting with respiratory tract infection and cough, using a clinician-focused intervention that was integrated into primary care practice computer systems. By using routinely collected data, aggregated at the practice level for the primary outcomes, we removed the need to recruit individual participants.

The change from a traditional patient-level research design in our previous feasibility CHICO RCT to a light touch practice-level design used in the full RCT, provided an opportunity to look at the barriers and facilitators to a more efficient trial design and the impact on practice recruitment, engagement, understanding of research and data collection.

Methods/Approach

We collected data on practice level characteristics, at baseline and follow up, as well as intervention usage and acceptability during follow up. Primary outcomes were collected using routinely collected data from Clinical Commissioning Groups (CCG) (hospitalisations) and the NHSBSA ePACT2 dashboard (dispensing). Feedback on the roles of Clinical Research Networks (CRNs) and CCGs in recruiting practices were obtained from a short questionnaire sent to all CRNs and semi-structured interviews with a convenience sample of 5 key individuals in CRNs and CCGs.

Results

We recruited 294 of the intended 310 practices (95%) representing 336,496 registered 0-9 year-olds (5% of all 0-9 year-old children). Practices included in the trial were slightly larger, had slightly lower baseline prescribing rates and were located in more deprived areas than the English average and reflecting the national distribution. Engagement with CCGs and their understanding of their role in this research was variable. Engagement with CRNs and installation of the intervention was straight-forward although the impact of updates to practice IT systems and lack of familiarity required extended support in some practices. Data on the co-primary outcomes was almost 100%.

Discussion

The infrastructure for efficiently designed trials within primary care in England is viable and should be promoted where appropriate, particularly where routinely collected electronic health records are available for primary outcomes.

PS2B-01

Shining a light into the 'black box of horrendousness': a qualitative study exploring barriers and facilitators to conducting trials involving adults lacking capacity to consent

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Introduction
Improving the inclusion of under-served groups has received growing attention across the international trials community. Adults who lack capacity to consent are often excluded from research due to the complex methodological and ethical issues involved. However, there is little evidence regarding the nature and extent of the challenges researchers face when conducting trials including adults with impaired capacity, nor strategies to improve the design and conduct of such trials. Our qualitative study explored researchers' and healthcare professionals' experiences of the barriers and facilitators to conducting trials involving adults lacking capacity to consent.

Methods
We conducted semi-structured interviews with 26 researchers and healthcare professionals in the UK with experience in a range of roles, trial populations and settings. Participants included trial managers, chief investigators, and research nurses, and they were involved in trials in emergency conditions such as cardiac arrest, surgical and trauma-related trials, as well in dementia and care home settings. Interviews were conducted remotely via a teleconference platform or phone and were audio-recorded and transcribed verbatim. Data were analysed thematically.

Results
Multiple barriers and facilitators were identified which mapped against key stages in the design and conduct of a trial including when making trial design decisions, navigating ethical approval, assessing capacity, identifying and involving alternative decision-makers, and revisiting consent. Three themes were identified: 1) the complexity of trials involving adults lacking capacity, 2) importance of having access to appropriate support and resources, and 3) need for building greater knowledge and expertise to support future trials. Barriers included the complexity of the legal frameworks and ethical approval processes and the resource-intensive nature of these trials. Facilitators included having prior relevant experience, use of effective communication, and public involvement to inform the trial. Participants highlighted the need to 'design in' flexibility and called for further training and support.

Discussion
Researchers encountered both generic and context-specific challenges when conducting trials with adults lacking capacity, which were often reinforced by factors such as resource limitations and knowledge deficits. In order to facilitate the delivery of trials involving this under-served population, a system-wide approach to addressing these challenges is needed. We make a series of recommendations for funders, researchers designing and delivering trials, and organisations at both policy and research governance level. Recommendations include the development of methodological tools and interventions, providing training and support across the wider trial community, building research capacity, and ensuring that adequate resources are available to support inclusion.

PS2B-02

Beyond “must speak English”: Systematic review of language-related eligibility criteria in patient recruitment to trials

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Introduction

Trial teams often select participants based on specific inclusion and exclusion criteria. One common non-clinical eligibility criterion is that patients must speak English in order to participate. Excluding patients who are perhaps unfairly or inaccurately judged as ineligible to participate due to language means that participants who could usefully contribute may be excluded and their perspectives ignored. This could limit external validity and potentially exacerbate health inequalities. Conversely, participants may be included when they are unable to sufficiently understand the conditions of research participation and, hence, cannot provide truly informed consent. This study aims to better understand how trial teams make language-related eligibility decisions, as described in full-length research monographs, which are likely to have the most comprehensive descriptions of any publication type.

Methods

We conducted a systematic review of NIHR research reports published since 2010. We focused on UK-based randomised controlled trials (RCTs) recruiting adult patients with either of two conditions (clinical depression or type 2 diabetes) that disproportionately affect ethnic minorities. Two reviewers independently conducted title/abstract screening. Data extraction was subjected to dual coding and verified by a third researcher. We assessed the communication demands of the interventions and language-based primary outcome measures in relation to how language screening was reported, including any procedures/instruments that could be used as a proxy for language-related gatekeeping.

Results

32/185 identified monographs (24/99 depression, 8/86 diabetes) met the inclusion criteria. Ethnic diversity of recruited patients was limited, particularly in depression RCTs (92% White on average). Over half (18/32) of included RCTs explicitly specified a language-based eligibility criterion, including over 70% of both talking therapy for depression trials (12/17) and lifestyle (behavioural/educational) intervention studies (3/4), compared to less than 30% (3/11) of trials assessing medication treatments. Just one depression RCT mentioned offering translation; no trial provided interpretation. Explicit and implicit language-related gatekeeping measures included the ability to complete baseline/screening questionnaires, provide informed consent, and engage in the intervention as judged by recruiters, with one study stating that recruiters excluded participants they deemed “inappropriate to invite.”

Discussion

RCTs in this study aimed to mirror clinical practice. However, in clinical settings, language-based exclusions would not be anticipated. This review exposes methodological elements of RCTs that could preclude the participation of ethnically and linguistically diverse patients. “Linguistic demandingness” of interventions/outcomes needs to be considered in justifying language-related screening and

accommodations. A screening tool that offsets recruiters' reliance on gut feeling could lead to fairer assessments.

PS2B-03

Increasing diversity and inclusion in clinical trials with underserved populations at risk for hepatitis C in Ho Chi Minh City, Viet Nam

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Introduction
Increasing the inclusion of underserved groups in clinical trials is essential to improve the therapeutic possibilities for all patients. Based on enrollment data from two recent trials exploring strategic treatment options with direct acting antivirals for people with HCV in southern Vietnam, as well as survey research, we found that people who inject drugs, and other groups at risk for HCV were under-represented, although these factors are associated with high rates of HCV in Viet Nam.

Methods
In order to identify the underserved groups and increase engagement with them, we worked with community partners to explore the range of people at risk of HCV who are not currently accessing care. We formed two stakeholder groups to advise on the project. Based on their input we developed three community-based participatory research (CBPR) groups comprised of individuals from underserved populations. CBPR is a research approach that is community-led, relies on the strengths of the communities, and seeks to identify and solve locally defined problems.

Results
The groups, with internal leadership and support from the project team, have met regularly over 12 months to identify barriers to access and other community-prioritized health issues. The CBPR groups identified several issues and solutions surrounding HCV and recruitment into the trial. In response to the groups' requests, the trial coordinator and study physicians visited with each group to provide information about HCV and the trial in more detail. We created an animation to help explain the clinical trial process, as well as general information about HCV in lay terms, as current explanations were too complex. The project team discussed particular issues around recruitment into clinical trials on an ongoing basis with the groups and fed the information back to the OUCRU HCV trial team. By mid-2022, referrals from the underserved communities increased and while some were enrolled in the trial, others were excluded for not meeting inclusion criteria.

Discussion
The benefits and challenges of increasing trial participation with underserved groups should be explored prior to trial start. Recruitment strategies should avoid relying solely on institutionally-based populations as the potential for unintentionally excluding underserved groups is high and for these populations, the trial results are often of particular relevance. CBPR approaches can provide linkages to increase enrollment of these groups while also forming partnerships within the communities.

PS2B-04

Comparing trial communication between patients from the most and least socio-economically disadvantaged backgrounds: qualitative findings from three studies embedded in cancer-related trials

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Introduction
Patients from socio-economically disadvantaged areas are under-represented in cancer research, yet cancer incidence and mortality are highest among patients from such backgrounds. It is crucial to address this inequality to ensure that data from trials is representative of, and generalisable to, the target population. Improving how trials are verbally communicated is an unexplored strategy to make trials more inclusive. This study aimed to establish if and how trial communication differs by patient socio-economic status.

Methods
Secondary analysis of data from three qualitative studies embedded in their respective cancer-related trials. We analysed 51 trial consultations from 41 patients, purposively sampled to reflect patients from the most (n=18) and least (n=23) socio-economically disadvantaged areas (determined using English Indices of Multiple Deprivation scores). Analysis drew on thematic and content approaches.

Results
Initially, recruiters uniformly introduced most trial concepts, such as voluntariness and standard of care. However, they provided patients from disadvantaged backgrounds with less information regarding confidentiality. Recruiters provided patients from disadvantaged backgrounds with less detail about the risks and side effects of intervention arms compared with patients from advantaged backgrounds. Patients from advantaged backgrounds asked more questions, expressed more opinions, and engaged in more talk generally. Patients from disadvantaged backgrounds expressed concerns that they were imposing on recruiters and taking up too much of their time.

Conclusion
Patients require sufficient information to make an informed decision about participating in a trial. Our findings suggest that recruiters adapt trial communication in response to how active the patient is in trial discussions, which we found to differ between patients from the least and most socio-economically disadvantaged backgrounds. This resulted in patients from disadvantaged backgrounds having less in-depth discussions about the trials than patients from advantaged backgrounds. Future research with patients and recruiters should explore the underlying reasons for the identified differences in trial communication by socio-economic status. The findings can be used to inform future strategies to enhance trial communication with patients from socio-economically disadvantaged backgrounds, to help recruiters to conduct research that better reflects the populations they serve.

PS2B-05

How can we effectively engage diverse communities into clinical research? Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE and PANORAMIC Trials)

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Introduction

COVID-19 has disproportionately affected people living in areas of high socio-economic deprivation and Black, Asian and ethnic minority communities, and who are also generally under-represented in clinical trials.

Our study aims to ensure recruitment to the PRINCIPLE Trial (national Urgent Public Health trial for treating COVID-19 in the community) is representative and inclusive of the wider population and of those most vulnerable.

Methods

Enhanced recruitment strategies included: appointing a national pharmacist expert working with ethnic minority communities; a community outreach strategy to develop UK-wide relationships with community and religious organisations (including places of worship); collaborating with universities (targeting university towns and cities with a high proportion of ethnic minority communities); engaging with national and regional healthcare institutions and organisations including pharmacy; and gathering nationwide support from ethnic minority leaders, health professionals, and their organisations.

The trial was promoted in multiple languages via local and national and social media channels. User-friendly, culturally acceptable information leaflets and videos were developed to help reach audiences across all four nations.

Results

PRINCIPLE was visible in over 7,500 community pharmacies UK-wide. Places of worship e.g. Europe's most influential Hindu temple, BAPS Neasden, also announced encouraging people to join PRINCIPLE. This was associated with a three-fold increase in the 61-day average number of visits to the trial website which remained elevated – for six weeks.

Our recruitment strategy contributed to the inclusion of 55 (4·0%) South Asian and seven (0·5%) Black participants in our azithromycin analysis for treating suspected COVID-19, which was comparable to 3·7% Asian ethnicity and 1·6% Black ethnicity among people older than 50 years (PRINCIPLE's target age group) in England and Wales.

The proportions of participants in Index of Multiple Deprivation (IMD) quintiles were (from most to least socioeconomically deprived): 352 (26%) of 1375 in IMD1; 267 (19%) of 1375 in IMD2; 270 (20%) of 1375 in IMD3; 241 (18%) of 1375 in IMD4, and 245 (17%) of 1375 in IMD5, reflecting good recruitment from socioeconomically deprived and ethnic minority communities, all helping to building the evidence of how antibiotics should play no role in the primary treatment of COVID-19.

Discussion

There was no dedicated funding for this work, yet the learning now influences recruitment in major national trials. For future clinical trials to be equitable, inclusive and diverse in their recruitment, strategies like these must have targeted investment, initiatives, collaboration, and institutional support in place from the beginning.

PS2C-01

Designing devolved international databases in a UK-run international randomised trial platform in colorectal cancer (The FOxTROT Platform)

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Introduction
The FOxTROT platform consists of multiple large-scale confirmatory trials in colorectal cancer, testing a variety of neo-adjuvant treatment options in both frail and fit populations. FOxTROT is funded in the UK and intends to recruit across numerous international collaborators. However, funder and sponsor restrictions mean that the platform must devolve data collection and management to a coordinating centre in each collaborating country. This poses some significant challenges in trial database design and setup which have required creative solutions and, we believe, makes the FOxTROT platform a valuable case study for designing the data collection of multinational trial platforms.

Approach
1) We are required by the funder and sponsor to separate the UK and international data while also holding the international data in a structure directly comparable to the UK data. However, the UK funder is reluctant to fund development of bespoke international databases. Working with our IT team we created a duplicate of the UK database for use internationally, making only the minimum changes required to adapt the database to the international data.
2) Recruiting countries are legally obliged to provide differing combinations of participant identifiers. Thus, we needed to develop a registration/randomisation system which would accept only those identifiers valid for each specific country, while not duplicating data management or IT workload.
3) Certain participating countries requested that certain data items be added to the trial database, in order to meet national requirements. Incorporating this data collection without putting undue burden on sites across the trial required that careful compromises be made.
4) Participating countries also have their own preferred or required ways of working with an eRDC database. In some countries sites will enter data directly, in others paper CRFs will be used at sites and national centres will enter data, and some countries require that they host their own duplicate database within the country and provide data downloads to us. Establishing both the data collection architecture and contractual agreements to accommodate these different approaches required flexibility and careful communication with collaborators in multiple countries.
5) Some participating countries intend to take part in only some trials within the overall FOxTROT platform, or to participate in FOxTROT as a pilot study for running similar trials of their own in future. Thus, all elements had to be designed in order to allow maximum flexibility in terms of international participation.

PS2C-02

Evaluating the effect of regular symptom monitoring on trial outcomes: using electronic patient-reported outcome measures in an online eczema randomised controlled trial

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Introduction
Eczema is a chronic, inflammatory skin condition causing itchiness, sleep disturbance and affecting quality of life. Electronic patient-reported outcome measures (PROMs) in the form of online questionnaires, are often used in eczema clinical trials. However, completing PROMs regularly in clinical trials, i.e. monitoring symptoms, may prompt patients to enhance the self-management of eczema and increase standard topical treatment use that can lead to improvements in outcomes over time. This is concerning since regular monitoring may constitute an unplanned intervention, instead of being a data collection tool, which can cause erroneous estimation of the treatment effect. We conducted the Eczema Monitoring Online (EMO) randomised controlled trial (RCT) to assess the effect of regular patient-reported symptom monitoring on eczema severity, using PROMs.

Methods
The EMO study is a prospectively registered online, parallel group RCT (ISRCTN45167024). Parents/carers of children with eczema and young people and adults with eczema were recruited, mainly through social media. Potential participants who clicked on the study link displayed in the advert were directed to the study website for enrolment. All trial processes were automated, including: eligibility screening, consenting, randomisation and data collection. In this methodological trial we compared weekly online eczema questionnaires (intervention) with questionnaires sent only at the primary outcome timepoint of 8 weeks (control). Randomised participants received questionnaires via a weblink. If the follow-up questionnaires were overdue, email and text reminders were sent to participants.

Timing of Potential Results
A total of 296 participants from a range of ethnicities were recruited into the study, including: white (78%), Asian (11.8%), mixed background (4.7%), Black (4%) and another ethnic group (1.3%). Participants joined the study from 16 different countries, resulting in a geographically diverse population. Most participants had moderate (43%) or severe (44%) eczema, followed by mild eczema (13%). Primary outcome data was available for 81.1% of randomised participants. Statistical analyses are ongoing and results will be available in September 2022.

Potential Relevance & Impact
The results of this study will inform the design of future eczema RCTs on the impact of regular PROM collection on trial outcomes. If a considerable effect size is found, eczema clinical trials may benefit from reducing the frequency of patient-reported measurements in a balanced way, ensuring adequate contact with participants is still maintained to limit attrition.

PS2C-03

Using two-way text messaging to collect daily pain outcome data in participants with Hidradenitis Suppurativa

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Introduction
Hidradenitis suppurativa (HS) is a long term, inflammatory skin disease affecting 1% of UK adults. Pain and reduced quality of life are amongst the debilitating outcomes experienced by HS patients. Ameliorating the condition to reduce pain is a top clinical priority. However, quantifying HS-associated pain can be problematic. Pain can vary from nil to severe within 24 hours due to the nature of acute flares, so measuring current levels may not accurately reflect the patient's pain experience. Similarly, asking patients to report on past pain experience is subject to recall bias, and therefore prone to error.

Aims
To better understand the natural history of HS-related pain the THESEUS study (a prospective observational cohort study) imbedded a sub-study to explore the feasibility of using two-way SMS messages to record participants' pain score daily for up to twelve weeks after treatment initiation. The aims were to 1) to test the feasibility of this data collection method in a research context; and 2) to check if the method and frequency of data collection was acceptable to participants.

Methods
Text messages were sent using an SMS provider (Esendex) once they had commenced treatment. The THESEUS data collection database was programmed to initiate outbound messages. Outbound messages were delivered every day at 6pm for up to twelve weeks. The message asked participants to provide their current level of pain using a numeric rating scale between 0 (no pain) and 10 (maximum pain). Inbound data were held on Esendex servers during data collection and were retrieved via the API after the receipt of the last message.

Results
Of the 149 THESEUS participants, 146 consented to receive daily text messages about their pain. 130 participants met the criteria to receive messages, but 20 participants didn't receive messages due to logistical issues. Text messages were initiated in 110 participants, with 99 participants providing at least one response indicating their pain level. 18 participants chose to opt-out of receiving further messages. A total of 5212 messages containing pain data were retrieved. After removing the duplicates per patient in a daily message of 84 days, 4902 messages were retained for further analysis.

Discussion
The THESEUS study has shown that two-way daily text messaging to collect pain data is achievable and acceptable to participants. However, the outbound-message implementation process requires review and improvement if it is to be operationalised to measure pain outcomes in a randomised controlled trial.

PS2C-04

Development of a risk-based validation framework for central monitoring and statistical analysis scripts

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Introduction
The regulatory authorities support risk-based management of trial activities (e.g. monitoring, system validation, vendor management), including script validation. As there are large differences between programming activities for central monitoring versus statistical programming, it may not be feasible to have the same validation approach. Central monitoring checks are run throughout the trial, and are more likely to need updates after initial validation. Moreover, for trials with long electronic Case Report Forms (eCRFs), there can easily be more than 50 central monitoring scripts that would require a lot of time spent on validation if a full validation approach is used.

Methods/Approach
We have developed different processes for risk-based validation for central monitoring scripts compared to scripts for statistical analysis. One difference is that we base the risk assessment of central monitoring scripts on different risk parameters than for statistical analysis scripts. A second difference is that the validation process for central monitoring scripts allows for more flexibility regarding minor changes after their initial validation. This should allow trial teams to focus resource on higher risk scripts and changes, and allow for quick implementation of minor changes to central monitoring scripts.

Results Structure and Timelines
The developed risk-based validation approaches have been implemented for a phase 1 clinical trial which has just started and is due to finish in September 2022. Information about feasibility of the approaches and lessons learned will be available in September 2022. We will present both validation processes, their feasibility, and pros and cons.

Potential relevance and impact
The results may guide organizations that run clinical trials in developing their own risk-based script validation processes. We will provide helpful insights from the validation activities performed during our trial and elicit a meaningful discussion about how best to support programming activities in clinical trials.

PS2C-05

Textnums: A tool to streamline the use of analysis results in manuscripts

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Introduction
Journal manuscripts and other clinical trial reports often include large volumes of statistical analysis results, in the form of single numbers, dates, tables, and figures. During the authoring process, the outputs of these analyses may change, and keeping the document up to date is a challenge. Workflows which involve copying and pasting into a Microsoft Word document are time-consuming and error-prone.
A number of tools exist for authoring 'reproducible documents' or 'executable manuscripts', in which analysis code and narrative text are intertwined, and to update the output, one re-runs the code. Examples include R Markdown, Observable, Jupyter Book, and StatTag. However, most existing tools in this arena are geared towards authors who are comfortable working with code. Though the text can be rendered in more visual formats such as DOCX or PDF, this is usually a one-way process: edits made in the rendered file cannot easily be translated back into the source file. For authors whose work does not normally involve code, who are more likely to be accustomed to working with Microsoft Word (including many clinical trial PIs), this can present a significant barrier to uptake.

Methods/Approach
We produced a tool (titled 'Textnums') which manages statistical analysis results within a Microsoft Word document. The tool is simple for non-technical authors to use, and allows the main writing process to take place within Word. It enables a two-way workflow, allowing results to be updated even when the document text has changed. In this talk, we discuss the design and implementation of Textnums as a Word add-in using TypeScript; it leverages native Word features such as content controls and custom XML parts.

Results
Using Textnums, analysis results can be embedded within a Word document. Authors can use the add-in to format and insert analysis results from the embedded results dataset into the document. When the data or the analysis code changes, the results dataset is replaced and any inserted results are automatically updated.

Discussion
Textnums streamlines the writing workflow by simplifying and automating the use of analysis results in manuscripts. Its approach differs from other similar tools, by using analysis outputs rather than directly requiring the code to be re-run. Its use is being trialled for a major forthcoming paper.

PS2D-01

Investigating SMART analysis methods in late phase Myeloma trials: a simulation study

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Introduction
In oncology trials, different treatments are often given at different stages of a patient's therapy. In the Myeloma XI trial, patients are given induction, consolidation and maintenance therapy, with choice of treatment at each stage dependent on response to previous treatment. However in this trial and many others like it, the treatment course as a whole is rarely considered with comparisons being made on a stage-wise basis.
Sequential, multiple-assignment, randomised trials (SMARTs) compare the performance of dynamic treatment regimes (DTRs) which consider patients' full treatment experiences. Pre-specified decision rules are set that determine an individual patient's course of treatment based on their intermediate responses. Comparisons are then made to find the best DTRs overall, allowing personalised routes of treatment based on individual patient experiences to be recommended.
Myeloma XI was set up in a style that could be considered a SMART, with overall survival as the primary outcome, but was not analysed as such meaning no recommendations were made as to the best overall treatment strategy for patients.

Methods/Approach
In this investigation, a simulation study is conducted to explore SMART analyses using the design of part of the Myeloma XI trial with individual patient covariates being simulated from the distributions of those observed within the trial. A range of scenarios are specified such that the optimal DTRs differed. The SMART analysis then uses Q-learning techniques to estimate the DTR with the highest expected survival time.

Results structure and timelines
For each simulated scenario, the true optimal DTR is compared against the recommended DTRs from the original trial methods and the SMART analysis. For the original trial method, a breakdown will be given of the hazard ratios at each stage for the different assessed DTRs to illustrate the potential drawbacks of failing to consider the whole course of treatment.

Potential relevance and impact
SMARTs have the potential to allow better consideration of the beginning-to-end treatment of patients than standard oncology trials. As biomarkers and surrogate endpoints are becoming increasingly prevalent in oncology, there can be more assurance in the information used at decision points when deciding future treatments for patients. This means we could start to see more oncology SMARTs in future as we seek to further personalise patients' treatment regimes.

PS2D-02

The UK Myeloma Research Alliance OPTIMUM trial: a synthetically-controlled phase II trial in a rare sub-population

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Introduction
Multiple myeloma (MM) is a cancer of bone marrow plasma cells with approximately 4500 new cases each year in the UK. Approximately 25% of patients can be characterized as having ultra-high risk (UHiR) disease representing a rare cancer or sub-population. Conventional approaches to trial design incorporating randomization are prohibitive in this setting, not only with respect to feasibility due to their relative rarity, but also ethically, with known poor outcomes with standard of care therapy for this population. Utilising a Bayesian design incorporating a prospective synthetic control can overcome these hurdles. OPTIMUM is a single-arm phase II trial for patients with UHiR MM to determine if a novel treatment strategy is sufficiently active to take forward to phase III.

Methods
A Bayesian framework was used to determine if the experimental arm had sufficient evidence of improvement in progression-free survival at 18months against a control prior, incorporating pre-planned interim analyses. The availability of individual patient data from a large near-concurrent phase III trial from patients treated within the same healthcare system and geography enabled the use of a synthetic control arm for final analysis. Purposefully similar, permissive entry criteria and the same central laboratory screening allowed for a case-matched approach. At the time of design, these data were not available, therefore a control prior from recent historical data was used, with a sample size re-estimation incorporated to update the prior as synthetic data became available

Results
The planned re-estimation of the prior data increased the required sample size from 95 to 105. The trial recruited a year ahead of target and was not stopped early at interim analysis. Synthetic control patients were selected from 590/2507 patients with available risk status data with a stratified, clinically representative sample of 302/590 patients screened for additional UHiR features. At final analysis data from 120 synthetic control patients were utilized to achieve a comparative PFS primary endpoint result. Sensitivity analyses were conducted around the composition of the synthetic control. The positive results of OPTIMUM have already informed the design of current phase III trials.

Discussion
Our results provide a framework for patient-centric synthetic, external control trials for UHiR MM and other cancers where individual patient data are available . We present the successful case study of the OPTIMUM trial, from design through final analysis. The design spared patients the uncertainty of randomization to standard of care therapy, with known unsatisfactory outcomes for this population.

PS2D-03

Overcoming the Challenges of Delivering a National Randomised Controlled Trial in Organ Donation

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Introduction

SIGNET is a single-blind, randomised controlled trial (RCT) recruiting 2600 organ donors diagnosed dead by neurological criteria, across 76 large hospital trusts in the United Kingdom (UK). The intervention is a single dose of Simvastatin, a safe, affordable, and commonly used drug. The trial utilises the UK's unique infrastructure for organ donation and transplantation, with specialist nurses for organ donation (SNODs) seeking family consent and randomising donors. SIGNET uses UK Transplant Registry (UKTR) data for all recipient outcomes and is a pragmatic trial, assessing not only whether Simvastatin will help limit damage in donor hearts, but also whether it is feasible to deliver an interventional organ donor trial using a risk-adapted approach.

Methods

The trial team held discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority to consider risk-adapted approaches appropriate for a study in deceased patients during the organ donation process and to review applicable trial regulations in this context. There were several challenges to overcome including the volume of sites involved, applicable consent for organ donors and recipients, GCP training for SNODs, workload for site research teams and Clinical Trial of an Investigational Medicinal Product (CTIMP) status.

Result

Following these discussions, SIGNET is not considered a CTIMP, and the SIGNET team gained approvals and proceeded with site set-up. Using novel approaches developed for the pandemic for site training and a GCP proportionate approach for SNODs, over 500 people (SNODs and research teams) were trained over a 4-month period, with 67 trusts (103 hospitals) currently open to recruitment. Randomisation, which had not previously been performed by SNODs, has been trouble free and sites have reported very little burden on them.

Discussion

SIGNET will be the largest global RCT in organ donation, benefiting from the unique strengths of the UK NHS infrastructure. We have utilised the MHRA's Innovation office to set precedents for interventional organ donation trials and implement risk-adapted approaches. Using a GCP proportionate approach and methods developed during the pandemic, we trained and set up numerous teams in a short period of time whilst minimising burden on site research departments. We are utilising the SNODs' skills and knowledge of consent to reach a large recruitment target. The centralised nature of the UKTR ensures high data completeness and a low burden on site research teams. These approaches could encourage further research into organ donation and help embed organ donation research into normal practice.

PS2D-04

WILL (WHEN TO INDUCE LABOUR TO LIMIT RISK IN PREGNANCY HYPERTENSION) – A MULTICENTRE RANDOMISED CONTROLLED TRIAL; ADAPTATIONS TO DELIVER A TRIAL DURING A PANDEMIC

Mrs Katie Kirkham[1], Prof. Laura Magee[2], Mrs Sue Tohill[3], Ms Ruth Evans[1], Mrs Eleni Gkini[1], Mrs Catherine Moakes[1], Mr Clive Stubbs[1], Prof. Jim Thornton[4], Prof. Peter von Dadelszen[2]
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Introduction
As a pragmatic randomised timing-of-birth trial, WILL adapted its trial procedures in response to the COVID-19 pandemic. These are reviewed here to inform post-pandemic trial methodology.

Methods/Approach
The WILL trial paused recruitment in March 2020, re-opened in July 2020, and is currently recruiting in 37 United Kingdom NHS consultant-led maternity units. We evaluated the adaptations made to the WILL trial processes in light of the COVID-19 pandemic; remote site initiation visits (SIVS), electronic investigator site file (ISF), remote monitoring and remote consent. Sites were surveyed for their views of these changes (20 sites, videoconference).

Results
Site initiation visits (SIVs) were conducted remotely; 50% of sites preferred remote SIVs, 44% felt that it was trial-dependent, while few preferred SIVs in-person as standard procedure. The central team felt remote SIVs provided scheduling and attendance flexibility (for sites and trial staff), the option of recording discussions for missing or future staff , improved efficiency by having multiple sites attend, and time and cost-savings; the negative impact on rapport-building and interaction was partially mitigated over time with more familiarity with technology and new ways-of-working.
Despite the ISF being paper based an online repository was set up to facilitate ease of access for site staff with 88% of sites favouring this approach.
For remote data monitoring (5 sites), advantages were primarily for the monitor (e.g. flexibility, no time constraints, reduced cost), and disadvantages primarily for the sites (e.g. document and access preparation, attendance at a follow-up meeting), but 81% of sites desired having the option for remote monitoring post-pandemic.
Two methods of remote consent were developed and used by 30/37 sites and for 54/156 recruits. Most (86%) sites using remote consent felt it improved recruitment.

Discussion
COVID adaptations to WILL trial processes improved flexibility of trial delivery, for central and site staff, and participants. Flexibility to use these strategies should be retained post-pandemic.

PS2D-05

Integrating photovoice into a process evaluation: the case of the NightLife study

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Introduction
UK Government COVID-19 restrictions required researchers to adapt accordingly. While these changes felt disruptive at the time, the need to respond quickly and effectively has created space for resourceful and innovative approaches. Here we show the how the research design for a qualitative workstream of the NightLife study (ISRCTN87042063) has been adapted to include virtual photovoice, facilitated through WhatsApp.

Methods
The NightLife study is a five year, National Institute for Health and Care Research (NIHR) funded clinical trial to evaluate nocturnal haemodialysis vs standard care, activated in January 2020. The research design was agreed prior to the pandemic and includes five multi-method workstreams to ensure a holistic evaluation that covers clinical, economic and experiential factors. Workstream two, focused on here, is a qualitative process evaluation of the trial. The original research design was planned to take an ethnographic approach, including significant researcher time spent in the field (UK renal units). In response to the COVID-19 restrictions, virtual photovoice was added to this design. Photovoice is a qualitative, visual method that uses participant lead photography to capture experience. Patients are given a week to take photographs of anything and everything to show their haemodialysis experience and how this impacts on their lives. Photographs are taken using smartphones and shared to a study phone using WhatsApp. At the end of the week participants are interviewed about their photographs.

Results
14 patients have engaged in virtual photovoice so far. Virtual photovoice has allowed unintrusive access to lived experience, directed by the patients themselves, allowing the research to extend beyond the clinical setting to reflect the wide-ranging impact of haemodialysis. Participants' photographs and talk provide rich visual data, much of which would not have been captured using the original research design. The method has been well received by most patients, however, challenges such as visual impairment, age and access to technology have been encountered. Semi-structured interviews are offered as an alternative to ensure voices are not missed.

Discussion
The shared photographs have captured a wide variety of experiences and emotions so far and show the diverse impact of haemodialysis, highlighting the importance of context and circumstance to the experience of haemodialysis. Ultimately, the innovative adaptation of the research design for the NightLife trial shows how the need to respond to an unexpected pandemic has yielded insight into patient experience that would not have been captured if this change had not been made.

PS3A-01

Co-designing an adaptive clinical trials platform to slow the progression of multiple sclerosis.

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Introduction
Multiple sclerosis (MS) is characterised by a gradual accumulation of symptoms and disability. Finding drugs to treat progression is an important unmet need in MS and hence, potential treatments need to be tested in an efficient manner. Octopus is a mutli-arm, multi-stage trial platform that will test multiple drugs at once, thereby speeding up the process of testing drugs for progressive MS.

Methods
Six people affected by MS (PaMS) were involved in designing the trials platform from the start. PaMS was defined as a person who had a diagnosis of MS or had a close family member or friend who had been diagnosed with the condition. PaMS joined the Governance Group and two Strategy groups which looked at (a) Treatment Selection and (b) Trial Design and Delivery. The Trial Design and Delivery group was further split into three Working Groups (WGs); (i) Design, (ii) Outcomes, and (iii) Infrastructure. Each of these WGs had PaMS in their core membership.
To advise on the ongoing patient and public involvement (PPI), four PaMS formed a PPI Strategy Group alongside the MS Society's Public Involvement Manager and a researcher with experience in PPI. The PPI Strategy Group organised a series of workshops across the UK, which over 30 PaMS attended.

Results
Involving PaMS in the Strategy Groups, WGs, and workshops throughout the design process confirmed the need for Octopus in the field of MS. The co-design approach enabled a number of ideas to be integrated into the trial design from the beginning, creating an inclusive clinical trials platform for people who are experiencing a very complex condition. Workshop discussions focused on designing an acceptable trial for PaMS and selecting outcome measures that address key challenges of the condition. One specific example was ensuring that patients will be re-randomised to a different treatment arm if their current arm was stopped. Other topics included eligibility criteria, engagement strategies, wearable devices and improving the trial experience for participants.

Discussion
Involving PaMS at an early stage has ensured that the platform has been shaped by people with lived experience. Octopus has shown that co-designing a clinical trials platform is an effective and efficient way of developing a platform that works both for members of the public and the trials team. This collaborative approach will be continued throughout the lifetime of the trials platform.

PS3A-02

Co-producing an RCT with autistic adults: lessons on trial design and conduct for engaging perceived hard-to-reach populations

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Introduction

Few large placebo randomised controlled trials (RCTs) for autistic adults have been conducted. They are considered challenging because they rely on uncertainty and blinding of treatments, aspects that can be particularly difficult for people with autism. The NIHR funded STRATA RCT aimed to assess whether sertraline is an effective treatment for anxiety in adults with autism. Anticipating recruitment and retention issues, we co-produced, in collaboration with a long standing autistic advisory group and with support of the charity Autistica, a programme of qualitative research to explore autistic adults' views on being invited to an RCT to treat anxiety in both a hypothetical situation (APRiCoT study) and during a real RCT (STRATA study). We used results from the former to refine optimal ways to present the study and fine tune the protocol of the latter. Our research allowed us to compare the views of those considering participating in a hypothetical RCT with those based on real experiences to investigate how well views align and what we can learn from this to advance design and conduct of RCTs for an autistic population.

Methods

Thematically analysed data from in-depth interviews with 49 APRiCoT and 30 STRATA study participants. Interviews explored reasons for accepting or declining trial participation (real or hypothetical), views on the trial process, and experiences and acceptability of medication.

Results

We found a strong support for obtaining scientific evidence within the autistic community, especially for effective treatments for anxiety. We confirmed pre-trial hesitancy about taking trial medication because of experiences of autistic people developing unusual responses to commonly prescribed medications, reactions that may not be acknowledged or addressed by healthcare professionals. Design suggestions for RCTs included a bespoke safety check system to reassure individuals as well as a preference for online over face-to-face contact. Adjustments to the design of the RCT following feedback from participants in APRiCoT were recognised and appreciated by participants in STRATA. Length of blinding in the hypothetical trial produced divergent views amongst interviewees, yet retention in the real trial has been better than expected.

Discussion

Whilst hypothetical studies are useful to understand views and possible actions in healthcare scenarios, continuing co-production with research partners provide anchorage when faced with real situations. This methodology will contribute to improving the conduct of ongoing and future RCTs so that they are more appropriate and inclusive, enabling robust treatment effectiveness in this under-served population to be determined.

PS3A-03

PPIE at the heart of the design of the NHS DigiTrials service

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Introduction
Clinical trials aim to improve health outcomes for people and communities and they cannot take place without wiling volunteers. However, some people and communities face barriers to participation. They may not hear about trials, not trust them, or believe trials are not relevant to their community. Patient and public involvement is critical to reversing this pattern.
NHS DigiTrials provides safe, lawful access to patient data held by NHS Digital to help clinical trials and is able to use routine healthcare data to reach out to under-represented people and communities. The service has worked with several large trials most recently supporting the NHS-Galleri Trial to be the fastest recruiting large randomised trial.

Methods/approach
In a commitment to genuine co-production, NHS DigiTrials hosts a patient panel, made up of 10 diverse and committed people. The panel is embedded in all aspects of NHS DigiTrials and work closely with the team to shape all aspects of the service design.

Results
To date the panel has led and supported numerous projects, including the design of the new recruitment service, and in making patient-facing information more accessible. In early 2022 the panel co-produced a short animation to explain - in simple and engaging terms - how patient data is collected, stored, and shared with approved researchers. Working alongside partners from NHS Digital – including information governance, brand and design colleagues - the panel selected the creative agency, developed the script, reviewed visuals and signed off the final cut.

Discussion
Currently, working with a content designer, the panel is working to re-draft NHS DigiTrials' new web pages to feature the panel members and to their stories. This is one of the ways the panel is looking to encourage wider representation of trial participants, bust myths and kickstart a wider discussion about how trials can engage with seldom heard voices. Dolapo Ogunleye, a panel member wrote a blog for International Clinical Trials Day that openness is vital to the future of clinical trials.
She wrote; ''I got interested in clinical trials because, as a Black woman who has had cancer, I was used to not seeing myself in the story. Some people in my community do not even believe we can get cancer. And the truth is that some communities have little or no trust to draw on in this area'
Dolapo summarises why genuine co-production should be at the forefront of service design.

PS3A-04

Moving from collaboration to co-production: exploring public and patient involvement in a methodology priority setting partnership

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Introduction

Patient and public involvement aims to improve research quality, relevance, and appropriateness. There is an increasing evidence base of the influence of public involvement on health research, but the role of public involvement in methodology research is less examined. Using a qualitative case study, we explored public and patient involvement in a research priority-setting partnership in rapid review methodology (Priority III - see www.evidencesynthesisireland.ie/priority-iii/).

Methods/Approach

We aimed to identify the experiences and perspectives of the Priority III Steering Group to support public involvement in future methodology research. We used a single intrinsic case study research design. The tools of participant observation, documentary analysis, interviews and focus groups allowed us to explore the context and processes of Priority III and identify the views and experiences of the participants of a steering group regarding public involvement in the Priority III priority-setting partnership.

Results

The findings of this study present three main themes (and six subthemes):

(1) We all bring unique qualities to the table

- Coming from different perspectives towards shared-decision making;
- Public partners bring pragmatism and grounding in reality.

(2) We need purposeful supports and space at the table

- Developing purposeful supports contributed to meaningful involvement;
- Creating safe space to listen, challenge and learn.

(3) We all benefit from working together

- Reciprocity in mutual learning and capacity building;
- Relationships as partners in research, with a feeling of togetherness and trust.

We also found valuing public partners, resourcing, communication and transparency were key to shaping the work together. Despite initial uncertainty and feelings of working outside of comfort zones, public partners contributed meaningfully to a methodology priority-setting partnership when enabled and supported to address the challenges around an abstract topic to which all brought different perspectives.

Conclusion

It is conceptually more challenging, yet possible, to involve people in the more abstract aspects of methodology research such as evidence synthesis or trials methodology, compared with, for example, patients sharing their lived experiences for a medical- or health-focused research study. This perceived barrier may hamper involvement and reduce the relevance of research. Our findings provide an insight into factors that facilitated or hindered public engagement in this research context, and provide examples of practical actions and considerations for future research and research teams.

PS3A-05

How to start a conversation with public partners about estimands: a practical tool

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Introduction

Clinical trials aim to draw conclusions about the effects of treatments, but different trials can address quite different questions. For example, does the treatment work when it is received as prescribed?, or does the treatment work even if not all treatment is received (e.g. not all doses of drug received)? Since different questions can lead to very different conclusions on treatment benefit, when planning a trial it is important to have a clear understanding of precisely what treatment effect it aims to investigate – this is what we call the 'estimand'. Using estimands helps to ensure trials are designed and analysed to answer the questions of interest to different stakeholders, including patients. However, there is uncertainty about whether patients would like to be involved in defining estimands and how. Public partners are patients or members of the public part of the research team. We aimed to (i) explore public partner's perspectives on the importance of discussing estimands when designing a trial and (ii) develop a practical tool with public partners that helps explain what an estimand is and what impact it may have in trial results.

Methods

An online consultation meeting with 5 public partners aged between 20 and 70 years of mixed ethnicities and sex. Public partner opinions were collected using polls and open-ended questions. A practical tool describing estimands, drafted prior to the meeting by the research team, was reviewed. After the meeting the tool was refined, and further feedback sought via email in two rounds of refinement. Discussion notes were summarised and circulated to the group.

Results

Four key areas related to public partner's involvement in defining estimands were identified. These were, (i) the importance of conducting trials that address what matters to patients, (ii) involving patients early on, (iii) a need for education and communication for all stakeholders and (iv) patients and researchers working together and changing the research culture. Public partners found the tool useful to start a discussion about estimands in a trial design context. They recommended the use of storytelling, analogies and visual aids.

Discussion

There was support for public partners to be involved in establishing estimands. The revised tool is available for researchers to use as a first step in facilitating involvement of public partners in estimand discussion. The tool needs to be assessed in different contexts, and we are interested in collecting feedback on using the tool in practice.

PS3B-01

What is the purpose of clinical trial monitoring?

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Introduction

Clinical trial monitoring is an important aspect of clinical trial conduct. The sources of information on clinical trial monitoring are not written in accessible language and do not give guidance on its application. To enable communication and facilitate the creation of clinical trial monitoring tools based on consistent and easy to interpret definitions, we identified the need to define the purpose of monitoring in accessible language.

Methods

We chose the sources to be the clinical trial monitoring guidance provided by organisations that any one of the Trials Methodology Research Partnership Data Quality and Monitoring Group referred to when deciding how to run trials. These included the European Medicines Agency (EMA), US Food and Drug Administration (FDA), Health Research Authority (HRA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Medicines and Healthcare products Regulatory Agency (MHRA) and National Institute for Health Research (NIHR). In a three-step process, the clinical trial monitoring data was collected, rationalised, and then compared between the sources in a consensus meeting, to give the aims of monitoring. The applicability and relevance of each aim was polled at a UK national academic clinical trials monitoring meeting.

Results

The process derived 5 key aims of monitoring

- keeping participants safe and respecting their rights
- having data we can trust
- making sure the trial is being run as it was meant to be
- improving the way the trial is run
- preventing problems before they happen

Discussion

The purpose of monitoring can be summarised simply as 5 aims. These aims, given in accessible language, should form an established foundation for discussion of monitoring of clinical trials and the development of a trial monitoring plan.

PS3B-02

Artificial Intelligence in Trial Monitoring: Using Machine Learning to identify poor performance sites in clinical trials

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Introduction
Site monitoring is a key feature in ensuring safe and robust operation of large-scale clinical trials, with monitoring teams visiting sites to investigate if they suspect poor performance. With finite time resources and with multiple sites to oversee, prioritising sites for inspection can be a complex decision process. Risk-based monitoring via performance indicators is becoming a popular method of aiding this process (Beever and Swaby, 2019; Tantsyura et al., 2015; Macefield et al., 2013). Such approaches have, however, shown limited value with little systematic evidence that the indicators are effective (Stenning et al, 2018). Here we propose a new approach investigating whether machine learning can improve automated monitoring techniques, to more accurately identify sites that should be prioritised for a monitoring visit.

Methods/Approach
A suite of common machine learning models were trained using pre-visit performance indicator data from a large-scale, long-running clinical trial being conducted in the UK. Performance indicators included measures such as the number of incomplete consent forms. Site performance classifications were derived using data from previous site visits and used as the ground truth from which the models could be trained. Each site was classified into one of three categories: no visit required, not usually visited or visit recommended, by summing the number of different issues found at previous monitoring visits and weighting according to issue severity level (critical, major or other).

Results
From the suite of different machine learning model techniques employed, random forest and extreme gradient boost models offered best accuracy (79% and 69% respectively), when determining whether a site required a visit or not. As the number of sites with monitoring visit data was small (n=10 for each class), to exploit the discriminative power of each model, the best performing models were ensembled together to form a ‘Superlearner’ model, enabling a combined higher overall performance to be achieved. The combined ‘Superlearner’ approach offered improved accuracy of 83%.

Discussion
Machine learning has shown promise for aiding monitoring teams to make informed decisions about site monitoring visits. Future work will extend the models to include more information about clinical trial sites. By combining the wealth of raw clinical trial data that performance indicators are derived from, with the findings from previously conducted monitoring visits, models can be developed to predict the types of issues that would be found at a site if it were visited.

PS3B-03

THE COMPLIANCE PLOT: A novel bespoke approach to monitor and examine protocol-adherence in clinical trials

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Introduction
Suboptimal compliance with the protocol is a very common problem in Randomised Clinical Trials (RCTs) that can distort the generalisability and validity of the results. Monitoring compliance is crucial within the conduct of RCTs to tackle arising issues, data quality problems, and recruitment and retention figures. Nevertheless, sole reliance on CONSORT diagram and summary figures might not be adequate to uncover masked patterns in noncompliance. We developed a comprehensive visualisation method that can aid trialists to monitor adherence and identify unanticipated issues.

Methods
The scheme was developed and critically appraised within the STAR clinical trial to assess the impact of COVID-19 pandemic on the trial. STAR recruited patients with age-related macular degeneration to investigate the effect of baseline treatment with stereotactic radiotherapy (SRT) on the number of as needed intravitreal ranibizumab injections during the subsequent two years (evaluated on monthly basis). The following steps are used to construct the plot: (1) define compliance rules (for STAR trial we used a priori set window to categorise visits), (2) assign a colour-coded label for each rule, and (3) the colour-coded visit timelines for all participants are stacked above each other from the first to last recruited patient. We labelled visits as: red (to indicate unattendance), amber (attended but out of the planned window), green (completed per protocol), back (death), and white (withdrawal).

Results
The plot allowed graphical comparison of the overall compliance, death rate, and withdrawals in the trial. Moreover, the impact of COVID-19 pandemic could be viewed and compared before and after the lockdown. The plot showed higher rates of noncompliance during the first few months of the pandemic, however, the preceding pattern was re-established afterwards. The plot informed an ad-hoc sensitivity analysis proposed by the trial management group to weigh the possible impact of the pandemic on the trial results.

Discussion
Future studies can adopt this compliance plot to examine protocol adherence and participant retention within the conduct of clinical trials. Furthermore, the plot provides a simple and more transparent method to report compliance issues in clinical trials.

PS3B-04

The power of visualising harm in randomised controlled trials

Dr Victoria Cornelius[1], Dr Leila Janani1[1], Dr Suzie Cro[1], Dr Xinxue Liu[2], Dr Shuo Feng[2], Dr Alasdair Munro[3,4], Professor Saul Faust[3,4], Dr Rachel Philips[1,5]

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Background

Randomised controlled trials are most frequently designed to determine the benefit of an intervention but an important objective is to monitor the safety and emerging risk-benefit profile. Typically, publications present a table of harm, but visualisations offer an alternative powerful tool for inference and communication. We demonstrate the power of three visualisations using two COVID-19 case studies.

Methods

In the first case study we examined two plots identified from a previous methodological review (Volcano and Dot plot). Both plots are suitable emerging and pre-specified events collected during the clinical trial and can display binary, count and time-to-event data. We reanalyze data reported in a published multi-center, placebo-controlled trial of remdesivir in adults admitted to hospital with severe COVID-19 infections in Wuhan, China. In our second case study of a COVD-19 vaccine trial we developed a new visualization method (Fingerprint plot) suitable for multi-arm (10 vaccination arms, 3 control arms) binary data to summarize the totality of harm from a number of pre-specified 'reactogenicity' events of interest.

Results

Compared to the standard frequency table, the Volcano plot provides a way to immediately identify and communicate signals of harm events to the reader. However, it does not permit a more detailed review. The Dot plot requires more assimilation but incorporates all the information usually presented in a typical adverse event table but has the benefits for a graphical approach. While the Dot and Volcano plot are helpful to examine between arm imbalances of individual events, they lack a summary measure for the 'totality of burden' across events and are hard to extend beyond two arms. We developed a Fingerprint plot based on a Radial graph, that enabled us to examine and identify the most reactogenic vaccines in a multi-arm COVID-19 trial. This graphic provided policy makers and UK regulators a more comprehendible view of harm to examine alongside immunogenicity outcomes. The plot is particularly suitable when there are a number of pre-specified and solicited harm events, enabling an immediate identification of any arm that has a higher burden across all events.

Conclusions

Visualisations are under used in final reports and trial publications. Poor presentation of harm data can obscure an informative assessment of the true harm profile. Graphical approaches offer a powerful way to summarize large amounts of emerging and pre-specified harm data in RCTs facilitating a review of the risk alongside any benefit.

PS3B-05

Recommendations for visualising harms in randomised controlled trial publications: a consensus

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Introduction
Well-designed graphics are a powerful way to communicate information to an array of different audiences. In randomised controlled trials (RCT) where there is an abundance of complex data on harm they can be a highly effective means to summarise harm profiles and identify potential adverse reactions. Trial reporting guidelines such as the CONSORT extension to harm, encourage the use of visualisations for exploring harm outcomes but research has demonstrated that their uptake in journal articles is extremely low. In order to improve communication of harm in journal articles we identified researchers' recommendations for visualising harm outcomes with an aim to improve current practice.

Methods
Three consensus meetings were held comprising of 20 statisticians from 15 UKCRC registered clinical trials units, an academic health economist, an industry statistician, and a data graphics designer from the BMJ. Visualisations were identified via a methodological review of statistical methods developed specifically to analyse harm outcomes plus any put forward by consensus members for consideration. Participants reviewed and critically appraised candidate visualisations against an agreed framework. Appraisals were summarised and presented back to participants to inform discussions. After discussions participants voted on whether to endorse each visualisation. A threshold of 60% was used to indicate endorsement. Scores marginally below this threshold (50-60%) were revisited until a consensus could be reached. Clinician feedback was incorporated into the explanatory information provided in the recommendations to aid understanding and interpretation.

Results
Ten of the twenty-eight visualisations considered are recommended to trialists to consider in publications of main research findings. The choice of visualisations to present depends on outcome type e.g., binary, count, time-to-event or continuous and the scenario e.g., summarising multiple emerging events or one event of interest. We present a decision tree to aid trialists in their choice of visualisations alongside each of the endorsed visualisations, with example interpretation, potential limitations and signposting to code for implementation across a range of standard statistical software (e.g., Stata, R and SAS).

Discussion
Trialists have previously called for guidance on appropriate methods for the analysis of harm outcomes and case studies detailing examples of use. We take one step toward addressing this need by providing

recommendations to support trialists decide which visualisations to use to present harm. Increasing the use of visualisations of harm outcomes in clinical trial manuscripts will enable more informative interpretation, which is especially valuable for assessing the profile of harm alongside any evidence of benefit.

PS3C-01

An enrichment trial design using joint modelling of longitudinal and time-to-event data

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Introduction
Consider a Phase 3 group sequential trial where the primary endpoint is overall survival. Suppose that longitudinal data are observed on a biomarker which is assumed to be predictive of survival, and we believe that there could be a large benefit from using this biomarker information to inform early stopping decisions. For example, we consider a trial for the treatment of metastatic breast cancer where repeated ctDNA measurements are available.

Methods
We present a joint model for survival and longitudinal data and a method which establishes the distribution of successive estimates of parameters in the joint model across interim analyses. Then, we are equipped to use the estimates to define both efficacy and futility stopping rules. Extending upon this idea, we create an adaptive design which incorporates subgroup selection based on this joint model.

Results
With the methodology in place, by simulation we can assess the potential benefits of including biomarker information, how this affects interim decisions and ultimately alters the trial. We demonstrate that by including the longitudinal data in the analysis, the required sample size is dramatically reduced.

Discussion
Further, we consider whether it is necessary to include a mediating effect of treatment acting through the longitudinal data and alternative modelling techniques for this case.

PS3C-02

Combining factorial and MAMS platform designs to evaluate multiple interventions efficiently

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Introduction
Factorial designs and multi-arm multi-stage (MAMS) platform designs each have many advantages, but the practical advantages and disadvantages of combining the two designs have not been explored.

Methods
We propose practical methods for a combined factorial-MAMS design within the platform trial paradigm where some interventions are not expected to interact clinically and could be given together.

Results
We describe the combined design and suggest diagrams that can be used to represent it. Many properties of the combined design are shared with standard factorial designs, including the need to consider interactions between interventions and the impact of intervention efficacy on power of other comparisons, or with standard MAMS designs, including the need to prespecify procedures for starting and stopping intervention comparisons. We also identify some specific features of the factorial-MAMS design: timing of interim and final analyses should be determined by calendar time or total observed events; some non-factorial modifications may be useful; eligibility criteria should be broad enough to include any patient eligible for any part of the randomisation; stratified randomisation may conveniently be performed sequentially; and analysis requires special care to use only concurrent controls.

Discussion
A combined factorial-MAMS design can combine the efficiencies of factorial trials and MAMS platform trials. This will allow the trials community further opportunities to address multiple research questions under one protocol and to test multiple new treatment options, which is particularly important when facing a new emergent infection such as COVID 19.

PS3C-03

Implementing the Bayesian Optimal Phase 2 design (BOP2) in a potentially practice-changing umbrella-basket platform trial for rare cancers: the DETERMINE trial

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DETERMINE (Determining Extended Therapeutic indications for Existing drugs in Rare Molecularly-defined Indications using a National Evaluation) is an umbrella-basket platform trial that aims to evaluate the efficacy of licensed targeted therapies in unlicensed indications in rare adult, paediatric and teenage/young adult (TYA) cancers with actionable genomic alterations, including common cancers with rare actionable alterations. The ultimate objective is to transition positive findings to the NHS Cancer Drugs Fund to provide new treatment options for patients with rare malignancies.

Multiple non-randomised treatment arms, each evaluating a licensed targeted anti-cancer drug or drug combination in a specific molecularly-defined cohort of patients, form the umbrella part of the design. Each molecularly-defined trial cohort allocated to a treatment arm consists of a basket of different cancer types, age groups and molecular subtypes.

The aim of statistical analysis is to determine, for any treatment arm, if there is sufficient signal of clinically-relevant anti-cancer activity to warrant further consideration. Co-primary outcome measures are the occurrence of an objective response (OR) and/or durable clinical benefit (DCB). In this rare disease setting, the trial design needs to be adaptive so that activity can be reviewed as data accumulate. For each treatment arm, OR and DCB rates will be monitored using the Bayesian Optimal Phase 2 (BOP2) design (Zhou et al., Statistics in Medicine 2017). In each case, true rates of >30% and <10% represent clinically-relevant activity or not, respectively. Target recruitment into each treatment arm is 30 evaluable patients with interim analysis at 10, 15, 20 and 25. Assuming a minimally-informative Beta(0.1,0.9) prior, this design yields statistical power of 0.89 for each outcome while controlling the type I error rate at 0.10. Accounting for co-primaries changes the overall type I error rate to 0.13 and statistical power to >0.90.

The evaluation will initially focus on the main trial cohort recruited to the treatment arm. Sub-cohorts defined by cancer type, age group or molecular subtypes will emerge as the trial cohort populations are enrolled. Sub-cohorts will be investigated for differential efficacy at regular interim and final analyses and where promising activity is identified, further expansion of recruitment for those sub-cohorts may be considered. Equally a main trial cohort or sub-cohort could be dropped if the minimum statistical requirement for patients benefiting from the treatment is not reached.

PS3C-04

An evaluation of the impact of outcome delay on multi stage trials

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Background
Adaptive designs are a broad class of designs that allow modifications to be made to trial designs as patient data is accrued. In spite of their flexibility, a delay in observing the primary outcome variable can potentially harm the efficiency of adaptive designs. Principally, in the presence of such delay, we may have to make a choice as to whether to (a) pause recruitment until requisite data is accrued for the interim analysis, leading to a longer trial completion period; or (b) continue to recruit patients, which may result in a large number of participants who do not effectively benefit from the interim analysis. Assuming the latter option is selected, little work has been conducted to ascertain the size of outcome delay that results in the realised efficiency gains of adaptive designs being negligible compared to classical fixed-sample alternatives.

Methods
We measure the impact of outcome delay by developing formulae for the number of overruns in multi-stage group-sequential trials, assuming different recruitment models. We consider both single-arm designs for Bernoulli data and two-arm designs for Normal data. Our formulae enable us to measure the efficiency gains from the multi-stage designs that are lost in the presence of delay. By determining 'delay-optimal' designs, we assess whether careful choice of design can help recover the advantages of sequential designs under outcome delay. A selection of recently conducted phase II oncology trials are also used to assess the impact of delay in practice.

Results
On comparing the expected efficiency gains, with and without consideration of the impact of delay, in real oncology trials that used Simon's two-stage design, we observed that on average 15-30% efficiency is lost due to outcome delay. For two-arm group sequential designs, even small delay can have a significant impact on the trial's efficiency in terms of an increased expected sample size. As delay increases, designs with fewer stages tend to suffer smaller efficiency losses. For small amounts of delay, delay-optimal designs can help recover efficiency losses seen in conventional approaches.

Conclusions
To obtain maximum efficiency gain from introducing an interim analysis in a simple design like Simon's two-stage design, the primary outcome observation length should not be more than 10% of the total recruitment length. If it is greater than 50% of the total recruitment length, the design typically loses all its efficiency advantages compared to a single-stage approach.

PS3C-05

A Practical Adaptive Designs Toolkit: Making adaptive designs more accessible

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Introduction

Adaptive designs (ADs) can help improve the way we conduct clinical trials. However, the lack of practical knowledge in ADs among diverse clinical trial stakeholders hinders their routine use, although it is steadily improving. To help address this, we developed an online, open-access, comprehensive, flexible, and practical educational toolkit on ADs for clinical trial stakeholders including non-statisticians.

Methods

We iteratively developed practical educational material covering several different topics relating to ADs. This was informed by prior work and diverse practical knowledge and experience of the project team in ADs and non-adaptive trial designs. The Practical Adaptive and Novel Designs & Analysis (PANDA) toolkit was developed using "Ruby on Rails" with a React frontend and is hosted on the University of Sheffield servers. We sought feedback from users on the toolkit design, webpage content, and structure throughout the project. Further feedback is continuously collected from users via email (panda.sheffield.ac.uk) to improve the toolkit.

Results

The PANDA toolkit is available at https://panda.shef.ac.uk. PANDA allows self-paced practical learning that is easily accessible to anyone involved in clinical trials research. PANDA users can learn remotely about ADs at a time that suits them, and easily find content relevant to them focused on different stages of a trial with the aid of the search function. Topics covered include:

- lay description of an AD, the goals of different types of ADs, and research questions they can help address;
- potential benefits and limitations of different types of ADs;
- advice on communicating ADs to key stakeholders;
- how to cost an adaptive trial in a grant application;
- statistical methods underpinning different ADs, focusing on the design, monitoring, and analysis;
- case studies illustrating the design (with Stata and R code), communication, monitoring and analysis;
- reporting guidance;
- considerations for health economics evaluations in adaptive trials;
- measures to minimise operational and statistical biases when running an adaptive trial.

Discussion

The PANDA toolkit is a globally accessible resource that will evolve in response to research needs and feedback from users. We hope it will be a vital educational resource to increase practical knowledge and appropriate uptake of adaptive trials for years to come, improving clinical trial efficiency.

Funding received from the NIHR Clinical Trials Unit (CTU) Support Funding (NIHR129761) to support efficient/innovative delivery of NIHR research focusing on “developing skills for trials staff”.

PS3D - Spotlight Session: Update and Future Directions in Surgical Trials Methodology

Royal College of Surgeons of England Surgical Trials Centre (STC) Spotlight Symposium

Prof Peter Hutchinson[1], Prof Jane Blazeby[2], Prof David Beard[3], Prof Marion Campbell[4], Prof Joy Adamson[5], Prof Deborah Stocken[1]

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Most people will benefit from surgery at some point in their lifetime and rely on robust, effective, evaluated treatments. The Royal College of Surgeons of England (RCSEng), partnered with NIHR and charities, initiated a UK wide surgical trials programme partnering surgical speciality leads with Surgical Trials Centres (STC).

This RCSEng sponsored symposium shares the achievements and the future of surgical trials methodology from STC experts, in a “world of surgery which is embarking on a time of innovation and change that promises to bring huge benefits to patients” (RCSEng).

PS4A-01

Using social media as recruitment tool in a dermatology clinical trial

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Introduction

Social media advertising has been identified as a potentially successful recruitment tool in different health areas, however, evidence of benefit in dermatology trials remains limited. This Southampton CTU study aims to compare the success of two recruitment strategies used in the NIHR SAFA trial (Spironolactone for Adult Female Acne; ISRCTN12892056): social media advertising and GP postal mail-out.

Methods

410 participants (female, ≥18 years, with persistent facial acne) were randomised to take placebo/spironolactone over 24 weeks with primary outcome at week-12 using Acne-specific QoL. Patients were invited through social media advertising, GP postal mail-out (search of patients lists for relevant acne diagnosis/prescription), through referral letter screening in secondary care. Recruitment strategies were compared based on (i) ability to reach patients, (ii) eligibility of screened patients, (ii) baseline characteristics of enrolled participants and (iii) costs/enrolled participant.

Results

5.3% (108/2,058) of patients invited through GP postal mail-out were screened, 60.2% (65/108) enrolled, contributing 15.9% (65/410) to recruitment. 1.0% (540/51,981) of people who visited the study website following social media advertising were screened, 40.9% (221/540) enrolled, contributing 53.9% (221/410) to recruitment.

Enrolled participants were of similar age: primary care 29.0 years (mean±s.d.7.8), social media advertising 28.7 years (mean±s.d.6.6). Enrolled participants identified through social media advertising had more severe acne (IGA≥3 56.8% (109/192)) and a larger proportion had acne for ≥5 years (59.4% (114/192) compared to enrolled participants identified through primary care postal mail-out (IGA≥3 45.3% (29/64); acne ≥5 years 50.0% (32/64)). A larger number of participants recruited through social media advertising came from an ethnic minority background (10.1% (17/168)) compared to participants recruited through primary care (3.5% (2/58)).

Social media advertising cost £145.73/enrolled participant (221 participants) whereas GP postal mail-outs were £131.94/enrolled participant (65 participants) (costs exclude staff time). However, social media advertising was led by a digital marketing company prior to Covid-19 for 3 months requiring £109.20/enrolled participant (12 participants). After the restart in June 2020, social media advertising was run in-house for 13 months until the end of recruitment, requiring £36.53/enrolled participant (209 participants).

Discussion

Social media advertising has the potential to enhance recruitment (e.g. shortening time required to reach the recruitment target, increasing recruitment rate) or improving the diversity of the patient population. If run in house by coordinating centre (like a UKCRC CTU), some staff time is required to triage patients who expressed interest to respective trial sites, maintaining social media pages and answering patient queries.

PS4A-02

Training trial Recruiters: An educational INtervention (TRAIN) for recruiters to neonatal trials

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Introduction
Training trial recruiters may help improve recruitment to randomised trials, yet the effectiveness of education and training on recruitment rates remains largely unknown. The TRAIN project was established to develop an educational and training program for recruiters to neonatal trials and assess its acceptability.

Aim
To describe the development and acceptability of TRAIN

Methods
A multi-method study completed in three phases. Phase 1 involved evidence synthesis activities to inform phase 2 (i.e., systematic review, content analysis and concept analysis). Phase 2 involved a cross-sectional survey (UK and Ireland) of neonatal trial recruiters' opinions of education and training requirements, succeeded by a partnership intervention development process (co-design/co-production workshops) to develop and refine the program. In phase 3 (acceptability testing), the TRAIN education and training program was delivered online to neonatal trial recruiters on two occasions and feedback sought. Ethical approval for the study was granted by the Research Ethics Committee of the lead researcher's Institution.

Results
Ninety-six recruiters responded to the phase 2 survey. The most popular training method was face-to-face presentation or lecture format, followed by webinars. The top three topics that recruiters wanted more training on were background information on the study, informed consent, and participant eligibility. Additional topics included communication skills (building rapport and empathy, approaching distressed parents), public and patient involvement in trial design, and trial monitoring. Eleven partners, representing trial researchers, neonatal clinicians and parents of neonates who previously took part in a neonatal trial, used these findings to co-design/co-produce the program. The TRAIN program consisted of three Units designed for online or face-to-face delivery over two hours. A mix of PowerPoint content, parent video vignettes, interactive exercises, and practical resources support the Units. Eleven recruiters from three countries (Italy, Ireland, US) registered to attend an online training session and four attended. Of the 11 who registered, seven did not attend or sent apologies closer to the training date. Of those who attended, TRAIN was deemed acceptable and valuable for enhancing recruitment, with some resources highlighted as particularly valuable (e.g., the recruiter lanyard and the parent video vignettes). Suggestions for further program refinement and consideration were made (e.g., breaking the two-hour session into two shorter sessions).

Conclusion

Although deemed acceptable, minor refinements are required to the TRAIN program before evaluation in an effectiveness trial.

PS4A-03

Effectiveness of a simple recruitment animation for increasing rates of recruitment and retention of ethnic minority participants in a large multicentre stroke trial: A SWAT

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Objective
To determine whether the use of an animated video available in five languages (Urdu, Punjabi, Bengali, Polish and English), alongside standard participant information sheets (PIS) available only in English, improves the provision of deferred consent and retention into the TICH-3 trial, and whether this is specifically improved in individuals from ethnic minority communities.

Background
Members of ethnic minority communities in the UK are under-represented in research in general and specifically in stroke research. In trials in emergency settings, this is often seen in differential deferred consent and retention rates. Recruitment and retention strategies that consider the needs of a diverse population of potential participants could help improve research efficiency and minimise the risk of bias resulting from incomplete trial data. This SWAT aims to establish whether the addition of an animated video translated into four commonly spoken languages, improves deferred consent and retention into a large stroke trial (TICH-3), and further, whether it specifically improves this in participants from ethnic minority communities. It will have a cluster-randomised design (stratifying for the size of site and ethnicity mix) thus minimising the risk of delivery error and contamination between groups.

Population
Individuals being hospitalised for an intracerebral haemorrhage (haemorrhagic stroke) who are invited to join or remain in the TICH-3 trial.

Intervention
Animated video available in five languages (Urdu, Punjabi, Bengali, Polish and English) co-developed, refined and piloted with a group of patient representatives and clinicians, together with standard English language PIS.

Comparator
Standard English language PIS without the animated video.

Outcomes
Primary - Follow up trial completion rates. Secondary - Proportion of participants providing consent for follow up for the 1) UK study population as a whole and 2) by ethnic minority versus non-ethnic minority subgroups

Progress to date

The animated video, together with the accompanying text has been created, translated into four commonly used languages and ethically approved. It was co-created with focus groups from the University of Leicester's Centre for Ethnic Health Research PPI community, who reviewed the content for clarity and suitability, for both primary and non-primary English speakers. They further provided insight into improving the generalisability and acceptability to the public including people from ethnic minority communities.

Approximately 80 sites across the UK will be randomised to either provide access to the animated video alongside the standard patient information, or to solely provide the standard patient information. The sites are expected to recruit over 4000 participants.

PS4A-04

Questioning approaches to consent in time critical obstetric trials: insight from a mixed methods study within a trial

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Introduction
Royal College guidance recommends that consent methods in obstetric trials should vary according to individual underlying risk of complication, but there is no evidence to support this strategy, quoted levels of risk, or design of consent processes. If a mother lacks capacity, proxy consent from a relative or doctor may be sought. More commonly, as women are conscious during birth, verbal consent is sought prior to enrolment. However, there is no legal basis for verbal consent, which may cause burden. Seeking consent could also delay potentially lifesaving treatments. Trials legislation enables research to be conducted without prior consent (RWPC) in emergency situations, yet some clinicians have legal and ethical concerns about the use of RWPC in this setting.

Methods
COPE is a double-blind, randomised controlled trial comparing the effectiveness of Carboprost vs Oxytocin as the first line treatment of Postpartum Haemorrhage after child birth. A study within a trial involving questionnaires, recorded recruitment discussions, interviews and focus groups took place in the first year of recruitment. We explored mother, birth partner and staff views and experiences of recruitment and consent processes, including antenatal recruitment and RWPC.

Results
286 participants, including 190 women and 96 birth partners took part, linked to 198/ 391 (51%) COPE RCT participants at 9/11 (82%) sites. Of these 271 completed a questionnaire, 22 took part in an interview and 12 matched consent discussions were recorded. Twenty-seven staff took part in three focus groups and nine took part in an interview.
The majority (61%) of consent discussions were RWPC, although 42 (16%) women recalled that COPE was discussed when they were haemorrhaging. There was strong support for the use of RWPC as COPE interventions were used in clinical practice and viewed as low risk. It was recommended that information about the study should be more visible for those women who wanted some prior knowledge of the trial before they were approached. Women involved in verbal consent discussions whilst having a haemorrhage also supported RWPC due to poor recall about the trial. The antenatal consent pathway was rarely used. Most women did not think it would be appropriate to discuss the trial during pregnancy, or early labour, as it may cause 'unnecessary panic'.

Discussion
Findings support the use of RWPC in COPE and questions the appropriateness of commonly used consent pathways in obstetric trials for time critical interventions, including antenatal and verbal consent.

PS4A-05

‘A whole greater than the sum of its parts’: synergies and outputs of a trials’ conduct working group focused on Complex and Alternate Consent pathways.

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Introduction

The UK Trials Methodology Research Partnership Trials (TMRP) Conduct Working Group is an umbrella encompassing cross-institutional subgroups, including one focused on Complex and Alternate Consent pathways within trials research. Established April 2021, this interdisciplinary group currently has 12 members across eight UK institutions. Its remit includes addressing research inequity by developing recruitment practices in the context of complex/alternate consent pathways, to enhance diversity and inclusion in trials. Identified interests include alternative decision-makers (family member or professional), research without prior consent in pediatric and adult emergency situations, fluctuating capacity to consent, loss of/gaining capacity to consent, and supporting consent where cognitive, speech, language or sensory impairment adds challenges for communication or understanding of information. A main aim of the group is to promote interdisciplinary and cross-institutional collaboration to address ethically and methodologically challenging areas of trials, and increase inclusivity of historically under-served groups.

Approach

The group’s work has involved drawing on subject expertise to pool knowledge on existing resources to support best practice in trials that face these challenges for consent. The aim was to map existing tools, publications and content experts, making these readily available to the trials research community and identifying topics for publications, future PhD research and funding bids. Group members were encouraged to invite colleagues with relevant expertise to join, where gaps in group expertise were identified.

Results

The collaborative mapping activity resulted in 3 outputs. (1) A spreadsheet was created and populated by members of the group, listing the population, setting, challenges, available resources, publications, links to other relevant TMRP projects and potential gaps to target in future research relevant for alternate/complex consent pathways in trials. (2) Resources identified on this spreadsheet were used to ascertain gaps/updates required to the existing MRC/NIHR Clinical Trials Toolkit section on informed consent and provide updates for the Toolkit website. (3) A paper (for submission to Trials) summarizing methodological and ethical challenges, current evidence, resources, and opportunities for future research has captured the current evidence base.

Discussion

Despite being a small group, we have achieved concrete outputs useful to the trials community over an initial 18-month period and are planning further work to address gaps and opportunities identified. Collaborative working has allowed individuals working in different disciplines and at varying career stages to create a community of practice with others and has produced outputs useful across recruitment contexts to promote the inclusion of multiple populations in clinical trials.

PS4B-01

A good use of time? Providing evidence for how effort is invested in primary and secondary outcome data collection in trials

Dr Heidi Gardner[1], Dr Adel El Feky[1,3], Mr David Pickles[4], Mrs Annabel Dawson[2], Dr Katie Gillies[1], Prof Shaun Treweek[1]

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Introduction

Data collection is a substantial part of the work involved in a trial for participants and staff alike. How these hours of work are spent is important because stakeholders are, by definition, more interested in some outcomes than others. The ORINOCO study compared the time spent collecting primary outcome data to the time spent collecting secondary outcome data in a cohort of trials.

Methods

We searched PubMed for Phase III pragmatic effectiveness trials indexed between 2015 and 2019. From these, we randomly selected 120 trials evaluating a therapeutic intervention plus an additional random selection of 20 trials evaluating a public health intervention. We also added eligible trials from a cohort of 189 trials in rheumatology that had used an established core outcome set (COS).

We then obtained the time taken to collect primary and secondary outcomes in each trial. We used a hierarchy of methods that included (by order): data in trial reports, contacting the trial team, and approaching individuals with experience of using the identified outcome measures. We calculated the primary:secondary data collection time ratio and notional data collection cost (in GBP) for each included trial.

Results

We included 161 trials (120 Phase III; 21 COS rheumatology; 20 public health), which together collected 230 primary and 688 secondary outcomes. Complete primary and secondary timing data were obtained for 130 trials. The median time spent on collecting primary outcomes was 57 hours (range 0.7 – 10,747) and the median time spent collecting secondary outcomes was 191 hours (range 1.5 – 14,322). The median primary:secondary data collection time ratio, across the 161 trials, was 1:3.1 (i.e for every minute spent on primary outcomes, 3.1 were spent on secondaries). The ratio varied by trial type: Phase III trials were 1: 3.2, core outcome set 1:3.4 and public health trials 1:2.2. The median notional overall data collection cost was £7,635 (range £53 – £337,541).

Discussion

Depending on trial type, between two and three times as much time is spent collecting secondary outcome data than collecting primary outcome data. Trial teams should explicitly consider how long it will take to collect the data for an outcome and decide whether that time, and cost, is worth it given importance of the outcome to the trial.

PS4B-02

Blinding Of Trial Statisticians: Developing guidance for a risk-proportionate approach to blinding statisticians within clinical trials

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Introduction
There has been limited empirical evidence to guide the practice of blinding statisticians in clinical trials. As there is substantial variation in practice between Clinical Trial Units (CTUs) when it comes to blinding statisticians, this suggests a need to devise evidence-based guidance on when and how to blind statisticians. The aim of the Blinding of Trial Statisticians (BOTS) study was to develop guidance to advise CTUs on a risk-proportionate approach to blinding statisticians within clinical trials.

Methods
The BOTS study employed a mixed-methods approach involving three stages: (I) a quantitative study to assess the impact of blinding on the proportion of trials reporting a statistically significant finding for the primary outcome(s); (II) a qualitative study to determine the perspectives of key stakeholders on the practice of blinding trial statisticians; and (III) Combining the results of stages I and II to develop a first draft of provisional guidance statements. Before finalising the guidance, a virtual stakeholder meeting was conducted to discuss the provisional statements. Stakeholders represented included statisticians, methodologists, trial management and data management professionals, CTU directors, as well as members of independent trial oversight committees and representatives from the NIHR and the MHRA.

Results
The triangulation between stages I and II resulted in development of provisional guidance with 40 statements rated independently via survey by the participants of the stakeholder meeting. Ten statements reached agreement with no agreement on 30 statements. At the meeting, statements that did not reach agreement were discussed and adapted appropriately. Various factors were identified that could influence the decision of whether to blind the statistician, including timing, study design, types of intervention, and practicalities. Guidance including 21 statements was developed alongside a BOTS Risk Assessment Tool (BRAT) to provide CTUs with a framework for assessing the risks associated with blinding/not blinding statisticians and for developing appropriate mitigation strategies.

Discussion
This is the first study to develop a guidance document to enhance the understanding of CTUs of how and when to blind statisticians and to provide a framework for the decision-making process. The guidance and risk assessment tool should prove useful in expanding the understanding of how and when to blind trial statisticians and help in the decision-making process. We believe this will lay the groundwork for clinical trialists to apply evidence-based decision-making regarding blinding of statisticians.

PS4B-03

Potential for bias due to unblinded outcome assessment in multi-arm multi-stage (MAMS) clinical trials

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Introduction

Blinding has been recommended in multi-arm multi-stage trials (MAMS), in part because it can reduce bias in the assessment of outcomes. However, some MAMS trials are open label and others are partially blinded, where there is blinding of active versus control but the comparator arm is known. We aimed to explore the potential for bias in MAMS trials without full blinding. Our motivating example is a two-stage three-arm trial assessing treatments for progressive multiple sclerosis. We considered bias in assessment of the stage 2 outcome, disability progression.

Methods

We consider a trial with unconditional 90% power to detect a benefit at the stage 2 analysis for each pairwise comparison of active to control at 2.5% one-sided significance level. There is a binding stopping rule for lack of benefit at stage 1, designed with 95% power at 35% one-sided significance level. We consider three scenarios: 1) blinded, 2) unblinded, 3) partial blinding. The blinded scenario has no bias with event rate under the alternative hypothesis of 38% in the active arms and 47% in control. In the other scenarios we introduced 2% bias in the event rate. In the unblinded scenario the bias favoured the active arms over control and in the partially blinded scenario it favoured the first comparator. We used numerical calculations to determine the expectation of the test statistics for the stage 1 and 2 analysis under the null and alternative hypotheses, and therefore the power and type 1 error rate for each pairwise comparison. We assumed correlation of 0.5 between the test statistics at stage 1 and stage 2.

Results

In the fully blinded scenario, power for each pairwise comparison was 87% with type 1 error rate 2%, below the 2.5% nominal level. In the unblinded scenario, power was 95% but type 1 error rate was inflated to 17%. In the partially blinded scenario, the power for the first comparison was 92% but was 82% for the other two comparisons. The type 1 error rate for the first comparison was inflated to 5% but for the other two comparisons it was 1%.

Discussion

Bias in assessing an outcome can inflate the type 1 error rate in both unblinded and partially blinded designs. With partial blinding, bias towards more favourable ratings in patients who may receive one comparator can reduce the power for other comparisons.

PS4B-04

TOTAL OR CONTROL EVENTS: CHOOSING APPROACH FOR TIMING OF TRIAL ANALYSES

Dr Babak Choodari-Oskooei[1], Dr Sharon Love[1], Professor Matt Sydes[1], Professor Ian White[1], Professor Max Parmar[1]
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Introduction
In randomised controlled trials with time-to-event outcomes, the timing of interim or final analyses may be defined in terms of the required control arm events or total events across all arms at the time of the analysis. We explore each of these monitoring schemes in terms of the expected timing of analysis and their impact on the operating characteristics of the design. We will outline the pros and cons of each approach and make practical recommendations to trial statisticians, regulators and sponsors of RCTs in the phase III setting.

Methods/Approach
We use real trials in renal cancer and analytical derivations to show the impact of the control or pooled event monitoring on the trial timelines and expected power of trials with time-to-event outcomes. We also investigate the impact of a different underlying treatment effect to that of the targeted effect size on both trial timelines and power of the design when the control or total events are monitored.

Results
Our analytical derivations indicate that if the underlying treatment effect between control and research arms is larger than expected, using control arm events gives an earlier analysis time. This has also been confirmed in the reanalysis of two past trials in renal cancer. Considering the statistical power, this is always achieved whether control or total events are used. However, the type 1 error rate can be inflated when a large treatment effect is targeted (e.g. HR≤0.5), and control events are used to decide the timing of the analysis.

Discussion
In randomised controlled trials with time-to-event outcomes, monitoring the control or pooled events has little impact on the timing of the analysis in two-arm designs. Power is also preserved under both monitoring schemes. However, in superiority designs with an unfavourable outcome and small number of events, say with a total event of < 100, the type I error rate can be marginally inflated. Therefore, regulators may want to ask trialists to carry out simulations to ensure that the type I error rate is controlled at the desired level, particularly in designs where a large effect is being targeted. Finally, it is imperative that researchers choose the most suitable approach for their design in advance and adhere to it throughout the course of the trial.

PS4B-05

Loss of equipoise: tackling the challenge in the Perfused Liver Utilisation Study

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Introduction
Less than 2/3 of deceased organ donors in the UK result in a liver transplant, because the livers from many donors are less suitable, due to older age, medical conditions or circumstances of death, and are much more likely to cause complications. To use these higher-risk livers safely, we need to find better ways to preserve, repair and test livers so that organs can be transplanted without compromising the survival rate. Normothermic machine perfusion (NMP) is a novel method of organ preservation which replaces the conventional icebox, using a machine which restores the flow of blood at body temperature allowing the liver to function during storage.

Methods
The Perfused Liver Utilisation Study (PLUS) was originally designed as a two-arm parallel group trial of NMP vs static cold storage (SCS). However, rapidly evolving research in this area and wider use of machine perfusion resulted in a loss of equipoise such that most centres would not consider randomising certain high-risk livers to SCS. The PLUS team therefore needed to re-design the study to tackle this challenge, while still delivering high quality evidence regarding the clinical and cost-effectiveness of NMP.

Results
The comprehensive national UK Transplant Registry enabled the study to be re-designed using a "threshold-crossing" design as described by Eichler et al. Clinical Pharmacology and Therapeutics 2016. In this design a real-world historic control cohort was identified, and an efficacy threshold specified a priori to minimise risk of bias. The efficacy threshold requires a higher standard of evidence to conclude clinical benefit, to mitigate against the risks of using a non-randomised design. The registry enabled all consecutive livers meeting entry criteria in a pre-COVID era without NMP to be identified and the event rate in this group calculated. The event rate and threshold were specified in the protocol prior to opening recruitment of a single-arm prospective cohort where NMP is available in April 2022. Livers are enrolled centrally to avoid any selection bias in the single-arm group.

Discussion
Randomised controlled trials are the gold standard for assessing interventions but are not always possible where there is a lack of equipoise. PLUS is a national study that has capitalised on a comprehensive central registry and organ offering process to enable the design and delivery of an alternative study design. This uses a historic control cohort, a prospective single-arm recruitment and requires a prespecified efficacy threshold to be achieved to conclude benefit.

PS4C-01

Trial designs with co-primary superiority and non-inferiority endpoints: methodological discussion points and practical guidance

Dr Philip Pallmann[1], Dr Simon Schoenbuchner[1], Dr Abin Thomas[1], Dr David Gillespie[1]
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Introduction
In clinical trials where the experimental intervention involves withholding the current standard of care in whole or in part, conclusively demonstrating that no additional harm is caused is crucial for successful adoption into clinical practice. A common example of this are antimicrobial stewardship interventions which stipulate delaying, reducing, stopping, or entirely withholding antibiotics under certain conditions, for example after a negative biomarker test for bacterial infection. To conclude that such an intervention is worth implementing, it is not sufficient to show that it has the intended effect in terms of reducing exposure to antibiotics (thereby reducing the risk of generating antibiotic resistance). Additionally, evidence is required that it does not have unintended consequences for patient safety, such as increased rates of complications due to inadequately treated bacterial infections.

Methods/Approach
Trial designs which assess both these aspects as part of their primary objective are attractive as they provide the rigour of a prespecified non-inferiority margin, strict type I error rate control, and power to demonstrate both objectives conclusively. One such design which has gained popularity in recent years uses co-primary endpoints: an effectiveness endpoint which is assessed for superiority, and a safety endpoint which is assessed for non-inferiority. The intervention is only considered successful if both superior effectiveness and non-inferior safety are demonstrated. Motivated by ongoing trials such as BATCH and PRONTO, we discuss methodological and practical challenges commonly arising in co-primary superiority and non-inferiority designs. Whilst some of these are unique to this specific type of design, others are also commonly seen in more conventional co-primary outcome trials or non-inferiority trials.

Results
The challenges we describe and propose solutions for include: 1) choosing appropriate outcome measures; 2) calculating a sample size taking into account the correlation between the outcomes; 3) selecting the most appropriate primary analysis population (which could be intention-to-treat for one and per-protocol for the other outcome); 4) dealing with differential (and partially or largely non-overlapping) missingness for the two outcomes; 5) analysis techniques including the possibility of fitting a joint model for both outcomes; 6) defining estimands. Further complexities arise when the design features interim analyses allowing early stopping for efficacy, futility, or both using group-sequential boundaries.

Discussion
Trial designs with co-primary superiority and non-inferiority endpoints allow for a comprehensive and rigorous assessment of benefits and harms. A thorough understanding of their methodological complexities will help facilitate their wider use in antimicrobial stewardship research and beyond.

PS4C-02

Definitions, limitations, acceptability, guidance in use and reporting of surrogate endpoints in randomised controlled trials: A scoping review to support development of SPIRIT/CONSORT-SURROGATE

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Introduction

Surrogate endpoints (substitutes and predictors of patient-relevant outcomes) are often used to improve efficiency of randomised controlled trials (RCTs). Nevertheless, their use is controversial. Meta-analysis of RCTs have found that use of surrogate endpoints overestimates health benefits compared to patient relevant outcomes. Additionally, some trials have demonstrated that surrogate endpoints resulted in approval of interventions that had no health benefit or were harmful. Despite these limitations, trials that use surrogate endpoints rarely report the uncertainty and risks associated with their use. As part of the MRC funded project aimed to develop SPIRIT and CONSORT extensions for RCTs with a primary surrogate endpoint, we conducted a scoping review on the current understanding, advice, and guidance on using and reporting surrogate endpoints in RCTs. Specifically, we explored how surrogate endpoints were defined; limitations of using surrogate endpoints in RCTs; acceptability of surrogate endpoints; and guidance/advice in designing and reporting RCTs using surrogate endpoints.

Methods

We searched records using electronic bibliographic databases (EMBASE, MEDLINE, Cochrane Methodology Register); grey literature (Google and relevant website search); handsearching of reference lists; and solicitation for additional literature from colleagues. Title, abstract, and full-text screening for relevant records was done by two reviewers. Data from included records has been extracted and is being thematically analysed in Microsoft Excel.

Timing of potential results

We have included 86 records whose data we are currently synthesising. Definitions were covered in 74% of records (64/86), limitations in 71% (n=61), acceptability of surrogate endpoints in 78% (n=67) and guidance and advice in designing and reporting of surrogate endpoints in 57% (n=49) of the records. We target to complete synthesis and generate items on the design and reporting of RCTs using surrogate endpoints by the end of June 2022.

Potential relevance and impact

The items generated in this review will be rated by an international multidisciplinary group of stakeholders via an e-Delphi survey (tentatively from September 2022). Rated items will then be discussed in a consensus meeting after which SPIRIT and CONSORT extensions for the reporting of surrogate endpoints will be finalised: SPIRIT-SURROGATE and CONSORT-SURROGATE. The review findings will summarise how surrogate endpoints are defined, their limitations, when/what form they are acceptable, and current guidance and advice in design and reporting of trials using surrogate endpoints.

PS4C-03

Surrogate endpoints in regulatory use: how many are actually statistically valid?

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Introduction
Surrogate endpoints replace clinical endpoints, and are thus expected to predict the clinical benefit or risk of an intervention. Biomarkers or earlier clinical outcome measures are often used as surrogates. With their increasing adoption linked to accelerated regulatory pathways, it is vital that surrogate endpoints have been statistically and clinically validated. Validation involves showing that the treatment effect on a surrogate endpoint has a sufficient and reliable association with that on the clinical endpoint.
The majority of recent literature findings share one key result: most surrogate endpoints approved by regulators are statistically inadequate when assessed under existing validation frameworks. However, most of these findings have either been limited to single therapeutic areas such as oncology, or to endpoints approved by one regulatory agency.

Methods/Approach
A systematic review is being undertaken to identify i) validated surrogate endpoints across all therapeutic areas, and ii) the methods used for validation. Five electronic databases were used to search for surrogate validation studies, yielding 18,904 hits. In terms of regulators, the websites of United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) were searched for instances of surrogate endpoints supporting drug approvals.
Literature screening in the title/abstract and full-text stages will be completed by one reviewer, with a second independent reviewer performing a 10% partial screening to confirm reliability. Items to be extracted include names of surrogate and primary endpoints, statistical measures of surrogacy evaluation, whether the surrogate was valid and whether FDA/EMA has approved the surrogate endpoint of interest; consequently, non-validated surrogate endpoints in regulatory use will also be identified.
The status of validated surrogate endpoints will be summarised through a tabular list by scores described in three surrogate validation frameworks (IQWiG, BSES3 and a three-level hierarchy) which will be compared to the surrogate lists in FDA and EMA. Data will be grouped by framework score, therapeutic area and statistical method of evaluation to identify any patterns in the validation status.

Timing of Potential Results
Full-text screening with data extraction, and analysis of results expected to be completed by July and September 2022 respectively.

Potential Relevance and Impact
This systematic review will be the first to present the status of validated surrogate outcomes across all therapeutic areas. The review will act as a comprehensive list to inform regulators, and will guide them and statisticians on the range of thresholds of statistical metrics observed and the surrogate evaluation methods used.

PS4C-04

The Win Ratio: A developing approach for analysing composite outcome measures in randomised controlled trials

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Introduction
Clinical trials commonly use composite endpoints in order to evaluate interventions with analyses focussing on time to the first occurrence of an event. This approach has limitations. For example, the individual endpoints which make up the composite usually have different clinical importance. Further it is the earlier, often less severe, outcomes which contribute to any time-to-first event analysis with subsequent, often more serious, events excluded.

Methods
A method to deal with many of the problems which arise with composite endpoints is the Win Ratio first proposed in 2012 with further practical guidance based on experience published in 2020. Over this time the Win Ratio is an increasingly recognised approach in the analysis of major cardiovascular trials but is rarely used in other areas. The Win Ratio allows a hierarchy of the events with the most serious outcome taking priority over less severe outcomes. The approach compares each individual in the intervention arm with each patient in the control arm according to the hierarchy with each comparison resulting in a “winner”, a “loser” or a “tie”. The Win Ratio is the number of winners divided by the number of losers with methods available to estimate a confidence interval along with a p-value.

Results
This approach is designed to optimise the impact of individual components of a composite endpoint, by allocating greater weight to more important events, increasing the range of outcomes considered, including continuous measures, and allowing capture of recurrent events. In this presentation the Win Ratio will be introduced using examples of its use in cardiovascular trials. This will include the EMPULSE trial in patients with acute heart failure which used the Win Ratio on a hierarchical composite outcome of all-cause death, number of heart failure events, time to first heart failure event and a ≥5 point difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score after 90 days of treatment (Win Ratio 1.36, 95% confidence interval 1.09-1.68, p=0.0054). The practicalities of using the Win Ratio will be considered in undertaking such an analysis.

Discussion
The pros and cons of the Win Ratio will be discussed as well as consideration of the situations in which the use of this approach is appropriate. With such explanations of the practicalities and use of the Win Ratio it is hoped it will be more widely used in the analysis of clinical trials outside of the cardiovascular field.

PS4C-05

Comparison of win ratio, win odds and win difference for dealing with composite outcomes

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Introduction
Many clinical trials include a composite outcome as a primary endpoint. Conventional analysis of a composite outcome uses the time to the occurrence of first event, ignoring the clinical importance of each component event. To address this limitation, win statistics (win ratio, win odds and win difference) have been proposed and applied. However, a systematic comparison of their statistical properties is unavailable.

Methods
We examine the statistical properties of these three win statistics for the analysis of composite outcomes. First, we describe the point estimates and variances, and the relationships among the three win statistics, and the relationship between the win difference and the Mann-Whitney U statistic. Then, we explain that the three win statistics, which are based on the same win proportions, test the same null hypothesis of equal win probabilities between two groups. We also apply the IPCW (inverse-probability-of-censoring weighting) adjustment to correct censoring bias (i.e., IPCW-adjusted win statistics). We perform the statistical computing using the R package, WINS, available on the Comprehensive R Archive Network.

Results
We show that the Z-values of the statistical tests for the win statistics are approximately equal, therefore, the three win statistics provide very similar p-values and statistical powers. Using simulation studies and data from a clinical trial, we demonstrate that the three win statistics complement one another to show the magnitude and strength of the treatment effect.

Discussion
Win ratio, win odds and win difference together can provide alternative measurements of treatment effect for a composite outcome. In addition, the IPCW-adjusted win statistics are effective at correcting bias from censoring.

Reference
Dong G, Huang B, Verbeeck J, Cui Y, Song J, Gamalo-Siebers M, Wang D, Hoaglin DC, Seifu Y, Mütze T and Kolassa J. Win statistics (win ratio, win odds and net benefit) can complement one another to show the strength of the treatment effect on time-to-event outcomes. Pharmaceutical Statistics. 2022 (in press)

PS4D-01

RACER-Knee and RACER-Hip: challenges of conducting randomised controlled trials of novel robotic interventions in the orthopaedic setting.

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Introduction
Robotic-assisted joint replacement systems are being introduced in clinical practice in an effort to improve outcomes for patients; with limited high-quality evidence that are clinically effective. Knee and hip replacement surgery is increasingly common, with an estimated 160,000 procedures a year undertaken in the UK alone. Robotic-arm systems may improve surgical accuracy and contribute to reduced pain and improved function but conventional instruments may be just as effective. There is an essential need for a robust evaluation of this technology to assess whether it should be used widely. However, delivering high quality evidence from a complex clinical trial in the current climate of orthopaedic research is a major challenge.

Methods
The Robotic Arthroplasty Clinical and cost Effectiveness RCT for knees (RACER-Knee) and Robotic Arthroplasty Clinical and cost Effectiveness RCT for hips (RACER-Hip) studies are multi-centre, participant-assessor blinded, randomised controlled trials to evaluate the clinical and cost-effectiveness of robotic-assisted joint replacement compared to joint replacement using conventional instruments. The primary outcome measure for both studies will be the Forgotten Joint Score at 12 months post-randomisation.
We will introduce a series of methodological challenges which have arisen in the study design and conduct; followed by detailed explanation of how the study team are planning to reduce the impact of each of the known challenges. Challenges common to both studies will be presented and the innovative solutions to the problems will be discussed. An inexhaustive list of issues include: the development of a study-specific blinded operation note, the use of sham incisions in the control group, controlling potential learning effects in the study, equipoise of surgeons and the impact of COVID-19 on elective surgery waiting lists.

Results
The presentation will not include any formal statistical results as both studies are currently in recruitment phase. Results of both studies should be available in 2024.

Conclusion
There is a real need for high quality evidence to assess whether the widespread use of robotic-assisted joint replacement is appropriate and effective. The RACER studies will provide the best evidence to date. The methodological challenges in the study design have been considered in depth and best practice for future studies in the orthopaedic setting will be shared.

PS4D-02

New frontiers in surgical site infection (SSI) assessment: developing reliable, valid and efficient electronic patient-reported methods for remote and blinded trial outcome assessment and follow-up

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Introduction

Surgical site infections (SSI) are infections that occur in the part of the body where surgery took place. It is the most common complication after surgery with rates as high as 25% for some procedures. Accurate SSI assessment is essential for evaluating interventions to address this debilitating and expensive problem. Reviews highlight the difficulties encountered with measuring this endpoint in trials. Measurement is additionally challenged as most SSI present after hospital discharge which is increasingly occurring earlier. In-person wound review or telephone follow-up by a healthcare professional is resource intensive and costly and impedes blinded outcome assessment. The Bluebelle Wound Healing Questionnaire (WHQ) has been developed and validated to overcome these issues but its widespread automatic electronic use has not been examined. This study will examine i) feasibility of collecting automated, electronic patient-reported SSI outcome data and ii) validation of WHQ scores for discriminating SSI/no SSI against a reference SSI assessment.

Methods/Approach

A prospective study at a large acute NHS trust, commencing in August 2021. Adult patients undergoing surgery from 9 specialties are included. The 18-item WHQ is administered via electronic survey (text/email) to patients 30 days after surgery. Clinical and sociodemographic variables are extracted from electronic patient records. Routinely collected SSI diagnosis (using established SSI diagnostic criteria obtained via postal questionnaire and follow-up phone call) for a subset of patients will be used to validate WHQ scores for discriminating SSI/no SSI (sensitivity and specificity values). True and false positive (TP and FP) rates for different thresholds of WHQ score will be calculated to determine an optimum WHQ SSI 'cut-off' score.

Results Structure and Timelines

Some 2207 surveys have been administered over 6 months (August 2021-January 2022). Data collection is ongoing. Overall response rates were 1111/2207 (50.3%) with higher response for patients aged 60-79 and lower for those undergoing gynaecological surgery. Up-to-date results, including characteristics of non-responders and missing data patterns will be presented. Sensitivity and specificity values, and TP and FP rates, will be presented compared with the reference SSI diagnosis to examine validity of e-PROM data against current diagnostic methods.

Potential Relevance and Impact

Findings will demonstrate whether remote e-PROM SSI outcome data is feasible, reliable and acceptable in providing accurate SSI outcome data in trials evaluating interventions to minimise SSI. This will have significant methodology advantages particularly for trials with large sample sizes, reducing costs and staff and patient burden.

PS4D-03

Understanding quality assurance and protocol adherence in surgical trials: the power of digital imaging

Dr Natalie Blencowe[1], Ms Anni Skilton[1], Dr Beverly Shirkey[1], Dr Eleanor Gidman[1], Dr Graziella Mazza[1], Mrs Rachel Brierley[1], Professor Chris Metcalfe[1], Professor Chris Rogers[1], Professor Jane Blazeby[1]
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Introduction
Methods for monitoring standards of surgery and protocol adherence (i.e. quality assurance, QA) in surgical randomised controlled trials (RCTs) are limited. A systematic review of 80 RCTs found that less than a third attempted to standardize procedures or monitor intervention adherence. Advanced peri-operative digital imaging is becoming more available, especially for minimally invasive surgical procedures, and is emerging as a potential method to enhance QA processes. We developed and incorporated QA measures for the surgical interventions under evaluation in two NIHR multi-centre surgical RCTs: ROMIO (open vs laparoscopic oesophagectomy) and By-Band-Sleeve (bypass, banding or sleeve gastrectomy for severe and complex obesity).

Methods
Three QA methods were developed in the pilot phase and incorporated into the main study (NB digital imaging data were only collected within ROMIO): i) entry criteria for centres (case load) and surgeon expertise (analysis of submitted videos), ii) establishing 'key' intervention components and boundaries of delivery (i.e. development of intervention protocols), incorporating mandatory, optional and prohibited elements, and iii) methods for monitoring protocol adherence using case report forms (CRFs) and intra-operative digital photos.

Results
The two RCTs, ROMIO and By-Band-Sleeve, included 8 and 12 centres, 328 and 1351 participants, and 40 and 50 surgeons, respectively. All centres met the entry criteria and 32 of 40 ROMIO surgeons submitted videos before participation, of which 91% achieved scores expected for trial participation. Standardised intervention protocols were developed for all five procedures. In ROMIO, 34 patients did not receive their randomized procedural allocation and of the 1178 who have had surgery in By-Band-Sleeve, 111 (9.4%) did not receive their allocated surgery, instead receiving one of the other study procedures. In By-Band-Sleeve, deviations to the intervention protocol were rarely documented in CRFs: intervention components/steps were delivered as planned in ≥95% of cases. In ROMIO, adherence to agreed protocols assessed using photographs was consistently lower than the CRFs. For example, left gastric artery lymphadenectomies were reported as complete in >98% CRFs and 48% in intra-operative photographs.

Conclusions
It is possible to monitor standards of surgery and delivery of key intervention components in surgical RCTs. Collection of high quality intra-operative digital imaging adds value to data from CRFs alone, uncovering differences between what surgeons say they do and what actually happens. Providing an a priori specification of intervention adherence may facilitate the appropriate standardization and monitoring of surgical interventions within pragmatic RCTs, as well as informing reproducibility and interpretation of findings.

PS4D-04

Interpreting chaos: a priori account of expected variation in treatment compliance and fidelity

Professor David Beard[1], Dr Loretta Davies[1], Mr Jamie Stokes[1], Mrs Heidi Fletcher[1], Miss Katie Chegwin[1], Mrs Akiko Greshon[1], Dr Arsenio Paez[1], Prof. Andrew Price[1], Prof. Jonathan Cook[1]
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Introduction
Randomised controlled trials (RCTs) evaluating complex interventions such as surgery or rehabilitation can involve convoluted clinical pathways. As a result, the compliance and fidelity to the intended intervention can be troublesome for interpretation. Whilst intention to treat analyses (ITT) provide a valid way to address this and will signal any sufficiently large effect, any differences dependent on compliance may be potentially masked. Early consideration of compliance and fidelity issues in the Statistical Analysis Plan are vital to avoid misinterpretation whilst maintaining robustness of findings.

Method/Approach
We present a case study of a recently successfully completed NIHR HTA funded trial, ACL SNNAP (ISRCTN 10110685), to demonstrate the problem and exemplify the a priori considerations needed to account for compliance variation in the Statistical Analysis Plan. ACL SNNAP is a two group "management" trial comparing surgical and non-surgical pathways with expected compliance and fidelity issues.
All possible potential pathway profiles were considered during the trial design and in the data collection phase. A structured and layered categorisation of groups, according to compliance and fidelity, was required. Outside the intention to treat profiles (top level, two groups), complete pathway profiles were first established (three categories) to account for the expected change from non-surgical to surgical treatment. A third layer of pathway profiles (seven categories) was considered and constructed to account for incomplete treatment in either group. For example, those allocated surgery that never underwent surgery, or patients who started rehabilitation but had insufficient treatment to satisfy fidelity rules. Two per protocol analyses were then planned based on the compliance groups; a conservative analysis excluding all patients who did not fulfil minimum requirements, and a "pragmatic" per protocol analysis which included patients who may have fallen short in compliance, but represented real life care in the NHS. A complier average causal effect (CACE) analysis was also carried out.

Results
For SNNAP the ITT analysis found a treatment effect. However, the pathway dependent per protocol analyses did provide useful reassurance about the robustness of the main finding. The CACE analysis, suggested a much large treatment effect but likely overestimated the true efficacy.

Discussion
Consideration of likely compliance issues in complex intervention trials for the Statistical Analysis Plan is critical for correct interpretation. Constructing a priori compliance "categories" and including them in different compliance secondary analyses may be required to provide a full picture regarding the treatment effect.

PS4D-05

Measuring effectiveness in randomized controlled trials of complex interventions: examples from de-implementation research

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Introduction

Complex and multifactorial pathways of behavioural change highlight the need for high quality randomised controlled trials (RCTs) to measure the effectiveness of interventions. We aimed to identify and synthesise randomised controlled trials (RCTs) on de-implementation interventions, and to provide guidance to improve future research.

Methods

In this systematic scoping review, we searched MEDLINE and SCOPUS up to May 24, 2021, for individual and cluster RCTs comparing de-implementation interventions to usual care, another intervention, or placebo. We applied independent duplicate assessment of eligibility, study characteristics, outcomes, intervention categories, implementation theories, and risk of bias. Finally, we created recommendations for future de-implementation research through discussion and consensus-building.

Results

Of the 229 eligible trials, 146 (64%) were cluster trials (median 24 clusters; median follow-up time 306 days), and 83 (36%) were individual trials (median follow-up time 274 days). Of the trials, 119 (52%) were published after 2010; 151 (66%) were conducted in a primary care setting; 165 (72%) aimed to reduce the use of drug treatment; 199 (87%) measured the total volume of care; and 64 (28%) the use of low-value care as outcomes. Of the trials, 49 (21%) described a theoretical basis for the intervention, and 41 (18%) had the study tailored by context-specific factors. Of the de-implementation interventions, 195 (85%) were targeted at physicians, 117 (51%) tested educational sessions, and 153 (67%) multicomponent interventions. Missing data led to high risk of bias in 137 (60%) trials, followed by baseline imbalances in 100 (44%), and deficiencies in allocation concealment in 57 (25%).

Discussion

Most outcomes used in de-implementation research are indirect, and as such, leave uncertainty on how well they represent the primary aim of de-implementation, which is improvement in health care quality and patient health. Value of RCTs on complex interventions is limited when complexity leads to non-replicability. Therefore, conducting RCTs with simpler and more replicable interventions is preferable. De-implementation RCTs could further be improved by having theoretical basis for the intervention, tailoring the intervention to study context, including larger number of clusters in cluster trials, having higher number of intervention deliverers and randomising at the same level of intervention participants as measuring the intervention effect. Addressing these issues would increase the trustworthiness results and replicability of the interventions, leading to identification of helpful de-implementation interventions and, ultimately, to decrease in the use of low-value practices.

PS5A-01

What influences participant satisfaction with how trial results are shared with them? Patient and site staff views from the Show RESPECT study

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Introduction
Sharing trial results with participants is an ethical imperative but often does not happen, and there is insufficient guidance. Show RESPECT tested ways of sharing results with participants in an ovarian cancer trial: an Enhanced Webpage versus a Basic Webpage, Posted Printed Summary versus No Posted Printed Summary, and Email List Invitation versus No invitation. We report study participants' and site staff views on what influences participant satisfaction with how trial results are shared with them.

Methods
Within Show RESPECT (ISRCTN96189403), 43 hospitals were allocated to share results with trial participants through one of 8 intervention combinations. Semi-structured interviews were carried out with participants and site staff to explore their views and experiences around communication of results to trial participants. Interview transcripts were coded, analysed thematically and triangulated using a 'following the thread' approach.

Results
13 trial participants with ovarian cancer and 11 site staff (research nurses, trial coordinators and clinicians) were interviewed.
PARTICIPANT CHARACTERISTICS INFLUENCE APPROPRIATENESS OF COMMUNICATION APPROACHES
Printed summaries were viewed as being easy to access for all participants (including older participants and those who are not confident computer users), facilitated sharing results with others, and being kept for future reference. The links to further information and support and the opportunity to send in questions to the enhanced webpage were seen as being potentially useful to patients with less access to support with processing the results. Interviewees thought the video on the enhanced webpage would be useful for those who are not comfortable reading.
THE NATURE OF THE TRIAL (RESULTS) AFFECTS HOW RESULTS SHOULD BE SHARED
Interviewees felt that had the trial results been different, it may have required different communication approaches, with more personal approaches possibly required if the results were complex or perceived as bad news. This may be less important for trials in less serious conditions.
For some, communication of trial results occurred within the context of relationships between site staff and participants developed over years, so some level of personalisation (e.g. via a covering letter or phone call) was important to those site staff and participants.

Discussion
We must share results with trial participants but there is no one-size-fits-all approach. When deciding the communication mode, trial teams need to consider participant characteristics, how the results may affect

them emotionally, what participants may want to do with the results, and the context of relationships developed with site staff during the trial.

PS5A-02

Integrated Participant Digital Storytelling (IPDS): an innovative method for disseminating complex participant stories

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Background
To help ensure trial findings have a meaningful impact, it is essential that study results and conclusions are effectively shared in an engaging and accessible way. Using innovative methods not only captures the thoughts, experiences, and needs of study participants but also illustrates the nuances and complexity of their journeys in a meaningful and diverse way. We have developed Integrated Participant Digital Storytelling (IPDS), a method which explores and conveys the journeys of multiple participants in an integrated and streamlined manner.

Methods
IPDS is a method of applying oral storytelling techniques to data gathered using qualitative approaches. Many people's stories are integrated into one participant's journey; an output based on a constructed person telling their story using multimedia tools such as graphics, audio recordings, or video.
This is achieved through 5 stages; stage 1, understanding the story, involves collecting, analysing, and interpreting qualitative data and determining key experiences (themes). Stage 2, creating the storyteller, involves drawing on study participant characteristics. Stage 3, shaping the narrative draws on key points/events in the data. Stage 4, produce the story through storyboarding and scriptwriting using anonymised participant quotations and, stage 5, review the story by sharing, revising, and finalising the product of stage 4 with team members.

Findings
We used IPDS to produce digital stories for two case studies.
Case 1: Within the Research on Surgeons and Engagement with Trials (ReSurgEnT) study, data from 32 semi-structured interviews and a stakeholder workshop with 13 methodologists, surgical trainees, consultants, and research nurses, was used to develop five key strategies for enhancing trainee engagement with trials. Using IPDS we produced a 6-minute animated story, using 'storytellers' to represent study participants and their experiences. The digital story was shared internationally via YouTube and Twitter and trainee research collaborative websites.
Case 2: Developing an online Massive Open Online Course (MOOC) for the use of digital tools for recruitment and retention to trials. Using the five themes developed from 16 qualitative interviews with five stakeholder groups we developed four digital stories (2-3 minutes each). These videos were shared via YouTube and formed part of the MOOC.

Discussion
Using IPDS allowed us to share complex participant stories in an accessible and engaging manner that preserved the participants' narratives in their own words. Those conducting qualitative research in trials should consider using IPDS to help draw the attention of stakeholders and enhance visibility and comprehension of study findings.

PS5A-03

Use of the h-index and Scientific Quality Index to measure the quality of the output of health services researchers

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Introduction
Academic performance is often measured using bibliographic metrics such as the number of peer-reviewed papers published, the number of citations, and the h-index. The h-index in particular is increasingly used to rank, appoint and promote research staff. However, despite its increasing use and popularity there are numerous criticisms of the h-index, for example, one being that it cannot decrease and therefore favours older, more established, researchers compared with younger academics. A recent attempt to devise an alternative, or complementary, method to the h-index is the 'Scientific Quality Index' (SQI). The aim of this paper was to assess the use of the h-index and SQI to measure the quality of the output of health services researchers.

Methods
Data were extracted from the Google Scholar profiles of staff members based in health services departments of UK institutions that were part of the 2014 Research Excellence Framework (REF). Metrics extracted from Google Scholar included: h-index; number of publications; number of citations; and number of publications with ≥10 citations (i10-index). The SQI was also calculated.

Results
Data were retrieved for 5997 individuals from 36 institutions. Health services researchers from a range of roles (research assistant through to professorial staff) were included. The median h-index was 20, with 90th and 95th quantiles of 64 and 84, respectively. While the median SQI was 63.4, with 90th and 95th quantiles of 127.5 and 160.5, respectively. The h-index correlated strongly with the number of publications, number of citations, and i10-index (r=0.9, 0.94, 0.99, respectively), but less so with the SQI (r=0.61). The SQI correlated less strongly with the other metrics (number of publications, r=0.31; number of citations, r=0.68; i10-index, r=0.58). Of the bibliometric measures, the h-index appeared to be the best discriminator of seniority based on the standardised mean difference between professorial and non-professorial staff.

Discussion
As far as we are aware this is the largest sample of bibliographic metrics so far published, which can be used as an indicator of average and above average performance of health services researchers in a wide range of metrics. The SQI, a relatively new metric, did not appear to be a better discriminator of seniority compared with other metrics.

PS5A-04

Reminding peer reviewers of the most important reporting guideline items to improve completeness in published articles: Primary results of two randomized controlled trials

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Introduction

Reporting guidelines have been available since 1994. Numerous studies have shown that adherence to reporting guidelines is suboptimal, raising the question of whether a specific targeted intervention for peer reviewers might improve reporting. We aimed to evaluate whether asking peer reviewers to check if specific reporting guideline items were adequately reported in manuscript submissions they were reviewing, would improve adherence to reporting guidelines in published articles.

Methods

Two parallel-group, superiority RCTs (RCT-1 and RCT-2) using 'submitted manuscripts' as the unit of randomisation. Manuscripts in both RCTs were randomised (1:1) to intervention or control; the control group received usual journal practice only. In RCT-1 we included manuscripts (June 2020-May 2021) containing RCT protocols submitted to BMJ Open and sent out for peer review. In RCT-2 we included manuscripts (July 2019-July 2021) describing RCT primary results, submitted to one of seven journals (5 BMJ Publishing Group; 2 Public Library of Science [PLOS]). In the intervention group (both trials), peer reviewers received an email reminding them to check if items were adequately reported in the manuscript. In RCT-1 this was the 10 most important and poorly reported SPIRIT-items (Standard Protocol Items: Recommendations for Interventional Trials) and for RCT-2, the 10 most important and poorly reported CONSORT-items (CONsolidated Standards of Reporting Trials). In both RCTs, peer reviewers and authors were not informed about the purpose of the study and outcome assessors were blinded. The primary

outcome was the difference in mean proportion of adequately reported items of the 10 SPIRIT/CONSORT items between intervention and control in the final published article.

Results (preliminary)
In RCT-1 we randomised 245 protocols. Of those, 178 were published (90 intervention; 88 control). A mean proportion of 46.1% (95% confidence interval [CI] 41.8-50.4%) of the 10 SPIRIT-items were adequately reported in the intervention group and 45.6% (95% CI 41.7%-49.4%) in the control group (mean difference: 0.5% 95% CI -5.2-6.3%). In RCT-2 of the 511 randomised manuscripts, 243 were published (121 intervention; 122 control). 67.4% (95% CI 63.8-71.1%) of the 10 CONSORT-items were adequately reported in the intervention group and 65.9% (95% CI 61.9%-69.9%) in the control group (mean difference: 1.5% 95% CI -3.8-6.9%).

Discussion
Asking peer reviewers to check if the most important and poorly reported items are adequately reported in a manuscript did not improve the reporting completeness of the final published protocol article.

Funding
Swiss National Science Foundation

Registration
Open Science Framework (https://osf.io/c4hn8 and https://osf.io/z2hm9).

PS5A-05

Publication bias - a cross-sectional study of randomised trials in Sub-saharan Africa: ongoing challenges of research waste

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Trial investigators have a responsibility to disseminate their findings. This is traditionally done by publishing in peer-reviewed journals. Whether the tested intervention is shown to have no effect, benefits or harms, and whether or not the findings are significant, the results should be made available. However, this does not always happen.
When results of trials are unavailable to other researchers, regulatory authorities, practitioners or the public, it weakens the evidence available in the health literature, impedes evidence-based care and slows scientific projects. This is particularly of concern where resources are limited, such as in sub-Saharan Africa, where evidence about what works or not can have major implications for cost-effective care.

Aim
To provide an overview of the extent of publication bias in randomised trials in Sub-saharan Africa.
Objectives
To map randomised trials in Sub-saharan Africa that began randomisation after 1 January 2010 and evaluate the publication rate for completed trials.
Settings
Sub-saharan Africa.

Methods
We searched the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) for randomised trials conducted in Sub-saharan Africa from 2010. We conducted a descriptive analysis of the trials. As a next step, we plan to identify linked trial publications in PubMed, Cochrane Library, and Scopus in order to perform a survival analysis to assess whether completed trials published their results and the time to publish.

Results
The WHO ICTRP listed 8292 trials conducted in at least one country in sub-Saharan Africa. The registries with the largest proportion of these trials were Clinicaltrials.gov (53.51%, n = 4437), Pan African Clinical Trials Registry (17.72%, n = 1469), and EU Clinical Trials Register (12.78%, n = 1060). More than two-thirds of trials were flagged as having been retrospectively registered (79%, n=6560). Approximately one in seven trials had posted results in the register (13.42%, n=1113). Our next step is to search the bibliographic databases for published reports of completed trials and conduct a survival analysis to show the distribution of their publication times.

Relevance and Impact
Sub-Saharan Africa is a poorly-resourced region, with poor health systems and a substantial burden of disease. Additionally, the region receives relatively less funding and support to conduct and publish randomised trials. The extent of publication bias of randomised trials in Sub-saharan Africa is unknown. This study will contribute to filling this knowledge gap as part of a larger project to develop an intervention to reduce publication bias.

PS5B-01

Exploring Treatment Effect Heterogeneity and novel methods to obtain data driven subgroups: application to critical care randomised controlled trials

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Introduction
Traditionally, subgroup analysis in randomised controlled trials involves testing for an interaction between treatment and a patient characteristic. However, discovery of a treatment-covariate interaction may not always lead to clinically actionable subgroups, particularly for continuous covariates. Non-parametric causal machine learning approaches are flexible alternatives for estimating heterogeneous treatment effects.

Methods
We present a secondary analysis of the VANISH trial, which compared early use of vasopressin with norepinephrine on renal-failure-free survival for patients with septic shock over 28 days. We compare a traditional regression approach to subgroup analysis as well as a data-adaptive, and a non-parametric causal machine learning method for 28-day mortality. In the traditional approach, separate logistic regressions are carried out for each subgroup covariate and its interaction with the treatment on the outcome of interest is identified. The data-adaptive method applied hierarchical lasso penalisation to a fully specified model with first order covariate-treatment interactions. The hierarchy ensured interaction terms were included in the model only if the main covariate was included. Finally, we used causal forests to estimate the Conditional Average Treatment Effect (CATE) across patient characteristics to assess where treatment effects differ. Causal forests comprise of honest causal trees. Honest causal trees create splits along variables which maximise the difference in CATEs of the resulting leaves.

Results
The traditional logistic regression approach showed a strong interaction between serum potassium and treatment for mortality (RD -0.175, 95% CI [-0.173, -0.177], p<0.0001). The lasso method kept the interaction between treatment and serum potassium, as well as sodium level, minimum temperature, platelet count and presence of ischemic heart disease. The causal forest approach identified treatment effect heterogeneity for mortality, differential forest prediction 1.17 (p = 0.06). When extracting roots splits, the most popular split was on serum potassium (mean applied threshold of 4.6 mmol/L). When dividing the patient population into subgroups based on the mean threshold, average treatment effects were risk differences of 0.074 (95%CI [-0.030, 0.18]), -0.27 (95%CI [-0.39, -0.15]) for patients with serum potassium ≤4.6 and >4.6 respectively.

Discussion
The causal forest agreed with the data adaptive method and traditional method of subgroup analysis in identifying treatment effect heterogeneity with potassium variation. Whilst traditional and data adaptive methods may identify sources of treatment effect heterogeneity, they cannot suggest subgroups splits which are clinically actionable. The extraction of roots splits in causal forests is a novel approach to obtaining data-derived subgroups which can be further investigated.

PS5B-02

Estimating marginal treatment effects in multi-centre trials: design and analysis considerations.

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Introduction
Many trials recruit participants from multiple centres to increase generalisability and ensure timely recruitment. Randomisation is often stratified by centre, for both practicality and because centre is associated with outcomes. Stratification variables are required to be adjusted for in the primary analysis model as fixed effects to ensure unbiased effect estimates. Another approach is to include a random intercept to allow for clustering due to lack of independence from participants at the same centre. This deals with the centre variation as a nuisance parameter, and allows for marginal and centre-specific effect estimates. Treatment effect heterogeneity due to centre can be modelled by including centre-randomisation interactions. The impact of ignoring this heterogeneity on the estimates of the marginal treatment effect (MTE) are not generally considered.

Methods
We compare statistical analysis approaches to allow for between-centre heterogeneity when considering the MTE. This includes fitting a centre-randomisation interaction as a fixed effect. We compare with models excluding the interaction, assuming no between-centre heterogeneity, and with mixed models with random intercept for centre. We perform a Monte Carlo simulation study to compare these approaches with respect to bias, efficiency and Mean squared error under data generating models with a null and a moderate treatment effect. We vary the number of centres, and the number of participants per centre to replicate real trial scenarios. We compare the methods on a randomised trial in people with psychosis (SoCRATES, N=309) which recruited from three centres and previously showed between-centre variation in effects.

Results
The simulations show that ignoring between-centre heterogeneity can lead to bias in the MTE even when accounting for centre as a fixed effect. Including the interaction term in the model can remove this bias, but different results are obtained when estimating the marginal effect depending on whether the centres are assumed to be equally sized or proportionally weighted by their number of participants. Efficiency is gained by having equally sized centres, and in the unlikely scenario that all have the same number of participants then ignoring the interaction does not lead to bias. The SoCRATES analysis shows variation in the effect estimates depending on analysis method.

Discussion
Multi-centre trials should optimally aim to recruit an approximately equal number per centre. The analysis models should consider including an interaction term, at least as a sensitivity analysis to the assumption of no between-centre heterogeneity.

PS5B-03

Subgroup analyses for continuous variables: A review of methods in randomised controlled trials

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Introduction
Stratified medicine aims to identify patient subgroups that are most likely to benefit from an intervention, and those that will likely receive no benefit (or may be harmed). This is typically achieved by performing a subgroup analysis, which investigates the effect of intervention(s) versus control in different subgroups to detect differential treatment effects. In this work, we investigate how subgroup analyses of published Randomised Controlled Trials (RCTs) are performed when subgroups are formed from continuous variables.

Methods
We searched PubMed for RCTs that included subgroup analyses during 2016–2021. The papers were reviewed and relevant information was extracted, including whether any of the subgroups were based on continuous variables and, if so, how they were analysed.

Results
Out of 428 reviewed papers, 258 (60.4%) reported RCTs with a subgroup analysis. Of these, 178/258 (69%) had at least one subgroup formed from a continuous variable and 14/258 (5.4%) were unclear. The vast majority (169/178, 94.9%) categorised the continuous variable and treated the subgroup as categorical. The most common way of categorising was to use a pre-specified cutpoint (129/169, 76.3%), followed by a data-driven cutpoint (26/169, 15.4%) such as the median.

Discussion
It is common for subgroup analyses in RCTs to use continuous variables to define subgroups. Most analyses categorise the continuous variables and, consequently, substantial amounts of statistical information may be lost (equivalent to reducing the sample size by at least a third). Alternative methods that directly use the continuous information or optimally choose cutpoints can improve efficiency yet are rarely used in current practice.

PS5B-04

Performance of interim analyses in a two-by-two factorial design with a time-to-event outcome: a simulation study of the VAPOR-C trial

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Accumulating data during a randomised controlled trial may be monitored for the purpose of stopping the trial for early superiority or futility. In general, these repeated looks at the data prior to the planned completion of the trial are guided by statistical stopping rules that maintain the overall Type I and Type II error. This topic has been well documented for parallel group randomised controlled trials but there is limited guidance in the literature for factorial randomised trial designs. The Volatile Anaesthesia and Perioperative Outcomes Related to Cancer (VAPOR-C) trial is a two-by-two factorial randomised trial with a time-to-event outcome, which will conduct an interim analysis at 50% of the accumulated data using pre-defined stopping rules for early superiority. To examine the performance of conventional stopping rules (e.g. Haybittle-Peto, O'Brien Fleming), in a two-by-two factorial design with a survival outcome and a single interim analysis at 50% of the planned number of events, we conducted a simulation study, under the scenarios of no, synergistic, or antagonistic interaction. If we observe a statistically significant interaction at interim, data will be analysed as multi-arm (i.e., test each active arm vs the control). If any of the treatment effects are statistically significant, the active arm will be dropped, followed by a final analysis as multi-arm, otherwise all three active arms will proceed at interim and an interaction test will be performed at final analysis. If we do not observe a statistically significant interaction at interim, data will be analysed as factorial (i.e., test factorial group A vs no A and B vs no B). We drop A or B based on the statistical significance of the marginal treatment effects, followed by a final two-arm analysis, otherwise all three active arms will proceed at interim and an interaction test will be performed at final analysis. In this study, we investigate the probability of a statistically significant interaction when testing for interaction between the main treatment effects at interim and final analyses. Following the interaction test, we investigate the probability that the trial is analysed as factorial only, multi-arm only, or a combination of factorial and multi-arm across the interim and final analyses, and the Type I error rates and Powers when testing for treatment effects using the stopping rules at interim and final analyses.

PS5B-05

Health economic analyses following an adaptive design: a simulation study in the group sequential design setting

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Introduction
Adaptive designs use data collected as a study progresses to inform modifications to the trial based on pre-specified rules. It is not appropriate to use the same analysis methods as for a non-adaptive trial. Currently, health economic analyses that use data from adaptive designs do not adjust for the adaptive nature of the trial, potentially introducing bias into cost-effectiveness analyses and healthcare decision making. This could penalise patients who cannot receive the treatment they need as something that is not cost-effective is being funded instead.

Methods
We describe how existing methods for the adjustment of analyses following a group sequential design could be operationalised into a health economic analysis. Using simulations based on a hypothetical case study, we assess the impact that the: trial design; number of interim analyses and correlation between primary and health economic outcomes has on the analyses. We compare point estimates and confidence intervals that do, and do not, adjust for the adaptive nature of the trial. We report the standardised bias, coverage and relative difference for the within trial and model-based incremental net benefit (INB) for five design options including the fixed-sample size design and group sequential designs using either the Pocock or O'Brien-Fleming stopping rule with two or five analyses.

Results
High levels of correlation between primary and health economic outcomes introduce bias into point estimates and confidence intervals of health economic outcomes. For the designs considered, the risk of bias is greatest when a Pocock stopping rule is used with up to five analyses. For this design, the unadjusted and adjusted estimates of within trial INB were -£96 and -£121 respectively for a correlation of 0.2 and £4 and -£99 respectively for a correlation of 0.8. For the model-based INB the unadjusted and adjusted estimates were £10,476 and £10,203 respectively for a correlation of 0.4.

Discussion
A health economic analysis is shown to be sensitive to the: choice of stopping rule; number of interim analyses and correlation between primary and health economic outcomes following a group sequential design. Failing to adjust for the design could lead researchers to draw incorrect conclusions on the cost-effectiveness of an intervention. We recommend that both adjusted and unadjusted analyses are presented when conducting a health economic analysis that uses data from a clinical trial with an adaptive design.

PS5C-01

Characteristics, progression, and output of randomized platform trials – a systematic survey

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Introduction

Randomized controlled trials (RCTs) are considered the "gold standard" of evidence-based clinical research. However, RCTs are often inflexible, inefficient, and costly. Platform trials promise to solve some of the difficulties associated with RCTs.

Aim

In this study, we aim to record all platform trials since their inception and to determine their characteristics, progression, and output over time.

Methods/Approach

We conducted a systematic search of Medline, Embase, Scopus, and several trial registries for all planned, completed, ongoing and terminated randomized platform trials in January 2021. For each platform trial, we determined the availability of publications and protocols as well as the status of individual interventions/arms. We recorded baseline characteristics, number of arms which were added or dropped (inclusion criteria), as well as further information on specific platform trial components such as use of a common control arm, non-concurrent control data, additional adaptive designs, recruitment, registration, and statistical framework. We are currently updating our search (June 1, 2022).

Results

Our search resulted in 94 randomized platform trials. The first platform trial started in 2005. Over the last years, the number of platform trials increased, reaching a peak in 2020 with 34 initiated platform trials. Preliminary data showed that the majority (70.2%) of randomized platform trials were still ongoing, 17.1% were completed, 6.4% were discontinued/terminated and 3% were in planning. All trials were registered and master protocols were available for 80.9%. Most commonly, platform trials were conducted in the field of oncology (49.5%) or dedicated to COVID-19 research (34.4%). A common control arm was used in most trials (81.7%). Response adaptive randomization (20.2%) followed by seamless design (19.1%), sample size readjustment (17.0%), and adaptive enrichment (6.4%) were additional adaptive features integrated into platform trials. A Bayesian (36.6%), frequentists (32.3%) or both statistical frameworks (4.3%) were used. However, for 26.9% of trials this information was not available. One or more arms were added in 50.0% and dropped in 52.1% of all platform trials, respectively. No arms were added or dropped in 26.6% of all trials. Any results were available for 53.2% of all platform trials. For the conference, we will include the new trials identified in our updated search.

Discussion

Preliminary results show that platform trials are becoming more common in clinical research, especially during the COVID-19 pandemic. Half of platform trials added new arms. It remains to be seen if they can hold their promise to solve known challenges associated with RCTs.

PS5C-02

Deciding whether a multi-arm trial should adjust for multiple comparisons

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Introduction
Since 2020, several articles in the literature have suggested that multi-arm trials do not need to adjust for multiple comparisons if treatments are distinct. In this presentation, we clarify the meaning of "distinct treatments" and present a basic conceptual framework to help guide researchers in making multiplicity decisions in multi-arm trials. Our motivation for this paper stems from an article by Molloy et al. who query the meaning of "distinct treatments" and ask for clearer guidance in this area.

Methods/Approach
This is a philosophical presentation. We first show how almost any multi-arm trial can be described in some way as having distinct treatment arms. We then critique the use of rigid decision tools for making multiple testing adjustment decisions based on the study design, before suggesting a simple approach to aid decision making when considering multiplicity adjustment in practice. The method will be applied to real trial examples in the literature.

Results
We introduce the concept of "risk of generalised interpretation" to help guide multiplicity decisions in multi-arm trials, and show how this basic conceptual framework can be applied to the design of multi-arm trials in practice. "Generalised interpretation" involves making a general non-specific interpretation of the results from a multi-arm trial such that we lose the distinction between the individual treatment comparisons. For example, in a multiple dose finding trial, instead of concluding that "a specific dose of the study drug is effective" we can easily reduce our conclusion to be that the "study drug is effective" without reference to the specific dosage. Similarly, in a multi-arm trial where the treatments have different modes of administration but are otherwise identical, a "generalised interpretation" would involve a failure to recognise and refer to the different modes of administration in our understanding of the results.

Discussion
We argue that attention should be directed primarily to the way that the results of a multi-arm trial are expected to be actioned on and interpreted. Studies with a moderate or high risk of generalized interpretation must adjust for multiple comparisons to control the overall familywise-error rate or false discovery rate. In contrast, studies with little or no risk of generalised interpretation should have confidence in taking a non-adjustment approach. Whichever approach is used, this must be pre-specified, and the justification should be based on this generalised interpretation risk.

PS5C-03

Implementation of a novel dose allocation system for early phase platform trials with non-comparative arms

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Introduction
One feature of early phase platform designs is the opening and closing of arms at different times. With dose finding objectives incorporated into a platform, simple approaches of randomisation to allocate patients to arms do not fully account for some of the additional complexities. Here we introduce the competing aims and objectives of allocation in this setting with an application of a method developed in ProMMise - a phase I platform trial with dose finding and dose expansion phases to evaluate the safety and initial efficacy of novel treatment combinations for patients with relapsed/refractory multiple myeloma.

Methods
Aims of allocation in early phase platform trials with multiple non-comparative arms include: maintaining recruitment momentum by accounting for the dose finding design of accrual in cohorts; ensuring participants ineligible for some arms can still be treated within the trial; allowing new arms to open to recruitment at different times; ensuring equipoise in the trial by ensuring recruiting clinicians are unable to ascertain which treatment a patient will receive; and ensuring there are no large imbalances over time between recruitment to open arms.

Results
The dose allocation system developed in our trial prioritises allocation to open dose finding cohorts to ensure rapid evaluation of doses. However in ProMMise, if a cohort is full then a participant could enter an arm in dose expansion, allowing continuous recruitment. If there are multiple arms open in expansion, we want to randomise to ensure equipoise. Big stick is a method of randomisation that allocates with equal probability unless a large imbalance between arms arises, then prioritising allocation to arms with fewer participants. We adopt it here to ensure that large imbalances do not arise between arms. Therefore, if the participant is eligible for at least one expansion arm the system will select an arm with equal probability unless a large enough imbalance arises, then allocation is heavily skewed in favour of the arms with fewer participants. When a new arm opens in the expansion phase, the imbalances between arms are re-evaluated. The algorithm adapts in the moment to allow a participant to be randomly allocated even if ineligible for some arms, unlike block randomisation for example.

Discussion
ProMMise generated some non-unique challenges for setting up a dose allocation system when we have multiple non-comparative arms. The method applied in ProMMise can easily be adopted to other trials with similar objectives.

PS5C-04

Shifting the balance: optimising the design and delivery of trials with diverse comparisons

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Introduction
Randomised controlled trials (RCTs) evaluating surgical interventions can be difficult to design and conduct, especially when including a non-surgical comparison. Several methodological challenges have been identified in these types of trials where the intervention comparisons are so diverse. Strong patient and clinician treatment preferences can lead to recruitment difficulties, potential for non-compliance with treatment allocation, and differential loss to follow-up. In addition, there are often differences between interventions in the complexity of intervention content and delivery and potential for imbalance in timing of follow-up. If not adequately addressed, these issues may introduce significant bias and threaten the viability of the trial, and also the validity of the results.

Method/Approach
We will present a case study of a recently successfully completed NIHR HTA funded trial, ACL SNNAP (ISRCTN 10110685), which exemplifies a surgical and non-surgical comparison. Specific issues considered and addressed during the design phase and challenges experienced during the conduct of the trial will be discussed to provide insight into the implications and potential solutions for future trials.

Results
Issues addressed during the design and conduct of the study included; (a) trial format and design to account for potential analytic and interpretation challenges, (b) balancing strong treatment preferences (and equipoise), particularly towards surgery, of patients and clinicians to facilitate/optimise recruitment, (c) standardisation and subsequent monitoring of the diverse interventions which were delivered by different specialities, (d) data collection to capture individual patient treatment pathway to explore the impact of treatment delivery and compliance, (e) exploring retention challenges to maximise follow-up, (f) appropriate analyses to explore the impact of treatment delivery and allocation compliance on trial results.

Discussion
Designing and conducting trials with such diverse comparative interventions (such as ACL SNNAP) provide unique challenges. Understanding and addressing the potential methodological challenges of such comparisons, at both design and conduct stages, can be hugely beneficial. Incorporation of this understanding enables trial teams to make more considered choices and improve efficiency and delivery of such complex intervention trials.

PS5C-05

Implementation of an Australian-wide master cancer protocol - an operational analysis of the Molecular Screening and Therapeutics program

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Introduction

Innovative trial methodologies are increasingly used to advance biomarker-dependent drug development in oncology. The Molecular Screening and Therapeutics (MoST) program efficiently assesses the activity of novel drug treatments matched to targetable genomic findings through large panel sequencing, governed by a master protocol. A novel operational process was essential to accommodate the significant expansion of this program from a pilot platform study in 3 centres, to a national program across more than 20 centres with 4 molecular screening subprograms. Here we discuss learnings from implementing this approach in the Australian investigator-initiated study setting.

Methods

To understand the perspective from academic trialists, the University of Sydney undertook a qualitative review of the MoST program through interviews, working groups and self-evaluation of how standard trial processes were used to deliver the program. Major themes were discussed and summarised.

Results

The MoST program provided over 5000 patients with molecular screening and treated over 480 patients through 19 signal-seeking trials in rare and advanced cancer. Useful platform efficiencies included iterative protocol amendments through streamlined ethics review, site staff familiarity with the design and accelerated development of trial databases through reusable components and evaluating multiple treatments in parallel.

We encountered challenges. Access to investigational products for developing investigator-initiated studies was constrained by external factors, including industry engagement and drug importation logistics, exacerbated by the COVID-19 pandemic. Changes in ethics management systems, staff turnover at sites meant higher than anticipated resources for training and oversight, and less actualisation of the potential efficiencies of a master protocol. Additional resourcing is required to adapt systems typically hardwired to prioritise statistical rigour over pragmatism.

Important factors that significantly contributed to the success of this nation-wide program included the identification of key clinical and operational leadership to resolve unanticipated issues in study management, addressing financial and personnel resource constraints at project/central and site co-ordination levels and distribution of local site workload, regular briefings and sharing strategies across partner organisations, and setting realistic milestones for individual trials and developing strategies to mitigate risks.

Discussion

Practical challenges are often discovered when implementing innovative trial frameworks within the established trial ecosystem. Our experiences in this nation-wide program have identified appropriate support, resourcing, and leadership as important considerations to the successful delivery of trials at scale. Developing a broad network of committed pharmaceutical partners, flexible and responsive trials processes, and co-ordination of appropriately resourced and trained sites are intrinsic for platform studies.

PS5D-01

Back to the Future: using past recruitment data to predict future performance: retrospective analysis of a 10-year CTU portfolio

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Introduction
Recruitment of participants into clinical trials is a fundamental process, yet it can be extremely challenging to predict. At the design stage, once the target sample size has been calculated, recruitment projections and the requisite number of sites are estimated. Trialists often make assumptions about the performance of recruiting sites, typically based on an average monthly rate. It is rare to formally review recruitment data, overall and at site level, from previous trials when planning new trials. Using site recruitment data from the Nottingham Clinical Trials Unit (NCTU) portfolio, we aim to explore site recruitment performance, in order to inform site selection and future recruitment projections.

Methods
Retrospective analysis of site recruitment data from all NCTU-managed trials between January 2010 and December 2019 (pre-pandemic). To be eligible for inclusion, trials must be UK multi-centre with individual participant randomisation via a NCTU randomisation system. Recruitment data per site will be collated alongside data (e.g. site opening/closing date and key trial information) from trial master files and trial management tracking systems.

Potential results
NCTU manages a broad portfolio of clinical trials - characteristics of each trial will be summarised descriptively. Mean (SD)/median (IQR, min-max) monthly recruitment rates per site (and overall) will be displayed graphically. The proportion that each site contributes to the overall recruitment total achieved will also be reported by trial, and patterns described across trials. Informal classification, using proportions, of trial sites into poor/adequate/good/outstanding categories may be possible. Results will be available for presenting at the conference.

Potential relevance and impact
Estimating recruitment projections is challenging, even for very experienced teams. Assumptions are often made about how sites may perform. The results from this retrospective analysis will help inform future recruitment projections by providing evidence-based assumptions, rather than anecdotal. Whilst recruitment varies greatly depending upon the trial, the NCTU trial portfolio is broad in clinical area and type of trial (e.g. CTIMPs, device trials, complex interventions) and these results are therefore of relevance to all trials.

PS5D-02

Predicting participation in clinical trials to inform design choices

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Introduction
Less than 50% of clinical trials meet their recruitment targets. Moreover, most trials tend to not include diverse individuals. We use an example of a treatment for people with scleroderma to explore how using techniques to elicit patient-preferences can help predict participation rates. We show how the results can help designers of clinical trials understand how changing some of the modifiable aspects of treatments or trial design could have on participation rates and promote inclusion of individuals from diverse populations.

Methods
In this patient-oriented project, we used focus groups and a discrete choice experiment (DCE) survey to elicit preferences of people with scleroderma for a novel treatment for this condition, autologous hematopoietic stem cell transplant (AHSCT) treatment. We used an existing trial of AHSCT treatment, which had failed to recruit the required sample size as a case-study. In the DCE, participants made a series of choices between hypothetical AHSCT treatments (which had varying levels of effectiveness, immediate and long-term risk, care team composition and experience, cost, travel distance), or no treatment. Preferences were estimated using a mixed and latent class logit models and used to predict participation for different clinical trial designs in diverse populations.

Results
In total, two hundred seventy-eight people with scleroderma completed our survey. All seven of the AHSCT treatment attributes were found to significantly influence preferences. The potential effectiveness of treatment and the risk of late complications were found to contribute most to patient preferences and the choices they made, however there were important modifiable factors that affected preferences; such as travel distance and out-of-pocket costs. Our prediction of participation rates (33%) aligned with the reported participation rates of the previous trial (34%), suggesting the validity of predictions. The models enabled us to predict participation could have been as high as 51% if a treatment could be offered closer to a patient's home, at lower out-of-pocket cost, and supported with holistic, multidisciplinary care. These predictions varied across some population demographics.

Discussion
We used a patient engaged approach to predict participation in a clinical trial of AHSCT treatment. Our results can guide future trials of AHSCT treatments about what designs will likely enrol the most and more diverse patients. We believe a structured approach to understand the trade-offs people are willing to make can be used routinely to inform clinical study design, which both improve participation rates, and participation of diverse, representative populations.

PS5D-03

Recruitment patterns and prediction in randomized clinical trials – a meta-research study

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Introduction
The main reason for premature discontinuation of randomized clinical trials (RCTs) is slow recruitment of participants. Evidence-based guidance and tools are needed to better predict and monitor participant recruitment in RCTs. Haidich and Ioannidis suggested in 2001 that participant enrolment during the first two months would be highly predictive for further recruitment in a clinical trial. However, their empirical sample of individual participant recruitment data was limited to 77 RCTs conducted by the AIDS Clinical Trials Group (ACTG) between 1986 and 1996.
We aim to investigate recruitment patterns of RCTs in a broader, larger, and more current sample to assess the predictiveness of the first few months and to empirically evaluate the performance of different recruitment prediction models.

Methods
Overall, we plan to gather individual participant recruitment data from a convenience sample of 300 RCTs through personal contacts. Eligible RCTs have parallel groups with individually randomized participants, are completed or terminated, and investigate a health care intervention. So far, we have collected the characteristics from 189 RCTs on three different levels: patient-level information, site-level information and trial-level information.

Results
Up to present, we have included individual recruitment data of 102‘777 participants from 189 RCTs, conducted between 1986-2021. Seventy-six RCTs were provided by the ACTG, 44 by a pharmaceutical company, 30 by individual investigators, 24 by the Swiss Group for Clinical Cancer Research, and 15 by the Study Center of the German Society of Surgery. RCTs were mostly investigator-initiated (75%; 142/189), 43% (82/189) were multi-national, and the median planned sample size was 266 participants (interquartile range [IQR], 104-504). The median duration of recruitment was 20 months (IQR, 11-34). Most common medical fields were infectious diseases (43%, 83/189) and oncology (12%, 24/189). Overall, 77% (147/189) of RCTs achieved to recruit more than 80% of the planned sample size. At the time of the conference, we will be able to present the distribution of identified recruitment patterns (e.g. linear, exponential, sigmoid) on a trial and site level, results about the predictiveness of early recruitment data, and preliminary results on prediction model evaluation. Moreover, we will have integrated recruitment data of another 80 RCTs.

Potential Relevance and Impact
This research will lead to a better understanding of trial recruitment patterns and more precise predictions of recruitment duration. Based on the results, we will be able to provide hands-on guidance and user-friendly tools to support participant recruitment in RCTs.

PS5D-04

Predicting the impact of study design on participation rates: StudyGage - a simulation tool using patient choice data.

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Introduction
Engaging patients in the design of clinical studies has been demonstrated to improve enrolment, but study timeframes often limit engagement to small, non-representative samples of patients, using qualitative methods undertaken later in the design process. Consequently, it is currently not possible to reliably quantify how changing the design of a study will influence the likelihood that patients will participate. We will report on a study that aims to address this limitation by using choice-based methods to develop a model that simulates changes in participation with study design.

Methods
A discrete choice experiment (DCE) is being undertaken to quantify how willingness to participate varies with elements of study design – including but not limited to, study location and duration, the amount of time required of patients (both at home and away from home), the types of procedures involved, and the support provided to patients. To understand diversity, the DCE will be conducted with at least 3,350 people from 8 countries, 8 disease groups and includes a general population sample for vaccine trial design. A wide range of sociodemographic and clinical characteristics are being collected to explore whether these are predictive of differences in participation decisions. The resulting dataset will provide a unique insight into how patients make study participation decisions. Applying cutting edge choice modelling techniques to this data, algorithms will be constructed that describe how participation rates vary with study and patient characteristics.

Results Structure and Timelines
We will report the design features that influence participation decisions and how this varies between subgroups of patients. We will also report on the predictive validity of the simulated participation rates. Finally, we will demonstrate how the simulations can be used to support study design.

Potential Relevance and Impact
Understanding and quantifying patients' preferences for trial designs can aid sponsors in enhancing study design and improving enrolment rates. Choice methods are an important addition to the menu of approaches sponsors can use to ensure studies are patient centric.

PS5D-05

A practical approach to addressing barriers to trial participation for LGBTQIA+ people: progress of initiative by the NHMRC Clinical Trials Centre, The University of Sydney

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Introduction
Lesbian, gay, bisexual, transgender, queer, intersex and/or asexual (LGBTQIA+) people experience substantial health inequalities compared to heterosexual and cis gender people. An important step to addressing this inequality is the inclusion of LGBTQIA+ people in clinical trial research. The NHMRC Clinical Trials Centre (CTC) is a large academic coordinating centre based at the University of Sydney, Australia. This project aims to identify and address organisational barriers to participation in CTC-run trials for LGBTQIA+ people.

Methods/Approach
A working party was formed to promote diversity, equity, and inclusion in trials conducted at the CTC with a sub-group focusing on inclusion of LGBTQIA+ people. The group conducted a scoping exercise to identify useful resources to guide identification of, and opportunities to address, organisational barriers. Next, a review of internal Standard Operating Procedures (SOPs), templates, documents, and systems, was conducted to identify potential barriers for LGBTQIA+ people, and to determine how these could be addressed.

Results
An initial review of SOPs, templates, documents and systems was completed in 2021. Issues identified included: unnecessary use of gendered terminology (e.g. “men with prostate cancer”, “women with ovarian cancer”); use of non-inclusive pronouns; non-inclusive language and requirements relating to contraception, pregnancy and childbearing; imprecise and non-inclusive collection of data on sex/gender.
To address these barriers a three step-approach is being implemented. Firstly, SOPs, templates and guidance documents are being updated to remove non-inclusive and incorrect wording, and to provide guidance on inclusivity. Guidance will be developed in collaboration with LGBTQIA+ community and patient groups, and alongside similar initiatives in other research organisations and networks. Secondly, CTC professional and academic staff will receive training (commencing July 2022) to improve awareness and knowledge around LGBTQIA+ people and the potential barriers to their participation in trials. Thirdly, trials teams will be encouraged to undertake reviews of existing trial materials and processes to identify and to address barriers using the guidance provided. Each step will be evaluated to enable future reporting.

Discussion
Existing trial processes, systems, procedures, and documents may be inadvertently excluding LGBTQIA+ people from trial participation. Our initiative seeks to implement and evaluate steps to address these barriers to improve inclusivity in trials conducted at the CTC, and to contribute to international efforts to improve diversity and inclusion in trials more broadly.

PS6A-01

Sensitivity of results to missing data for clinical trials with discrete, longitudinal outcome measurements

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Introduction
Multi-state models (MSM) represent transitions of patients through different disease categories (states). Analysis of discrete, interval censored longitudinal data using MSM is established and can lead to increased power for clinical trials, compared to analysis of aggregated data using binary or time to event methods. However, longitudinal data often suffer from intermittent missing measurements, which may depend on the true disease state. If the state definition is derived from composite data, consideration of the quantity and reason for missing components, and the potential association with the latent (missing) state is required. The aim of this work was to investigate methods for handling non-ignorable missing data in a MSM framework using a pressure ulcer prevention trial as a case study.

Methods
Joint (selection) models can be used for the multi-state process and the probability of missing data. We show that such selection models are equivalent to hidden Markov models, where an additional 'state' is used to represent a misclassification of the underlying latent state, whilst the observed data are assumed to be accurate. For interval-censored data, misclassification probabilities and transition intensities for the MSM may be estimated simultaneously using the 'msm' program in r-CRAN library.
The model was applied to a dataset from a pressure ulcer prevention trial, where different assumptions for the missing state were considered.

Results
Exploration of the motivating trial dataset identified 'key' components in the definition of the disease that would be associated with the true disease state and would be informative if missing. Based on these key components, three candidate definitions for disease state in the presence of missing data were considered for our motivating example.
In our case study, the treatment effects for each transition, estimated from applying hidden Markov models, were not sensitive to different state definitions in the presence of missing data. As expected, the probability of missing state was estimated to be higher for non-healthy true (latent) states compared to the healthy state for all definitions.

Discussion
Sensitivity to non-ignorable missing data can be accommodated in MSM using hidden Markov models and can be implemented using readily available software. Further work is required to explore the impact of missing data on the power and sample size requirements of trials designed using MSM. The definition of missing data for an endpoint derived from composite data needs careful consideration.

PS6A-02

Targeting the right population in trials with outcomes missing-at-random given covariates

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Background
Missing outcome data are ubiquitious in randomised clinical trials. When data are missing-at-random, the received wisdom is that complete-case analysis is unbiased and efficient, while multiple imputation may be slightly less efficient. This true in some cases, for example when missingness depends only on randomised arm, or when there is no effect modification by covariates. When missingness in an outcome depends on covariates, complete-case analysis may subtly change the population targeted by the trial. The estimated treatment effect is relevant to individuals with observed outcome data rather than to all randomised individuals, whether or not the analysis adjusts for covariates.

Methods
Numerical examples without random variation are used to highlight when and how the received wisdom can go wrong, and to outline some solutions. We apply the solutions to an existing trial with a more complex structure that the numerical examples.

Results
When there is non-zero effect modification by a covariate on the scale of the estimand's summary measure, the average treatment effect estimated using the complete cases is an average of stratum-specific effects, weighted by the distribution of the effect-modifying covariate among the complete cases. When data are missing-at-random given the covariate, this differs from the weighted average among all randomised individuals. If all covariates are measured that (i) modify the treatment effect and (ii) predict missingness in outcomes, three approaches to estimation can be used to target the all-randomised population. One uses weighting, one multiple imputation, and one standardisation. These methods rely on an assumption of no unmeasured effect-modifying covariates. Further, there can be estimation issues when applying these approaches to more complex, realistic examples.

Conclusions
Simple complete-case analysis and simple multiple imputation approaches estimate an effect that, we argue, targets the wrong population. By default, the estimand should target all individuals randomised rather than only individuals who provide outcome data. The analysis solutions we describe resolve bias only if all effect modifiers are measured and accounted-for. The only truly 'safe' solution is to prevent – or at least minimise – missing data.

PS6A-03

How much is that data in the window? A comparison of strategies for analysing data recorded outside pre-specified visit windows in randomised controlled trials

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Background
Follow-up data in RCTs is often recorded at two pre-specified time-points with associated visit windows. When visit windows are missed, data is either delayed or missing. Implications of missing data have been well explored, however that of delayed data less so. We introduce a new taxonomy for mechanisms of delayed data, and compare four analysis strategies to better understand the implications of delayed data on RCTs.

Methods
We define three delay mechanisms: (i) independent delays [IDs], with delays independent of participant characteristics; (ii) allocation-dependent delays [ADDs], with delays dependent on treatment-arm allocation; (iii) outcome-dependent delays [ODDs], with delays dependent on outcome values.
We simulated continuous data for baseline and a trajectory of 50 follow-up time-points assuming an AR(1) covariance structure. We sampled observed measurements based on delays around two pre-specified time-points.
Four strategies using baseline-adjusted linear mixed models with predictors time (categorical/linear), treatment, and time-treatment interaction were examined: (a) 'strict', which only included values recorded inside visit-windows; (b) 'lenient', which included all values; (c) 'time-dependent', which included all values in a linear-time analysis; (d) 'time-covariant', which included all values in an AR(1)-covariance-structure linear-time analysis. Strategy performance was assessed on statistical properties of effect estimates at pre-specified time-points. Outcome values at 12 and 24 weeks from the SlowMo trial were also re-analysed.

Results
With independent delays and no interactions, all strategies were found to be unbiased. 'Lenient' was most powerful at the early time-point, and linear-time models most powerful at the later time-point. Allocation-dependent delays and/or interactions led to 'lenient' giving biased estimates, and linear-time models the most powerful of the strategies giving unbiased estimates. However, linear-time models gave biased estimates when nonlinear interactions were present. Outcome-dependent delays led to all strategies giving biased estimates. Accounting for the AR(1) structure gave little performance improvement. Consistent precision gains on 12 and 24 week effect estimates from the SlowMo data were also observed.

Discussion
Modelling time continuously is a powerful strategy, allowing data recorded outside visit windows to be incorporated under an untestable assumption of no outcome-dependent delays. If a linear interaction cannot be assumed, strict enforcement of visit windows in a categorical-time analysis is most likely to give

unbiased estimates. Trial analysts must consider the appropriate use of time, and how best to use available trial data.

PS6A-04

An extended ‘tipping point’ approach for missing data in binary outcomes when estimating relative risk in clinical trials

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Introduction
In randomised controlled trials (RCT), missing outcome data is a common issue and can affect the interpretation of trial results. Sensitivity analyses are recommended and routinely performed to assess the impact of missing data. Methods incorporating multiple imputation (MI) are commonly used, however in instances where only the outcome variable has missing values and no additional auxiliary variables are identified, MI has been shown to not provide any added value over a complete case analysis. Furthermore, for binary outcomes where we are estimating a relative risk from e.g. a log-binomial or Poisson regression model, or we have additional model complexities such as random effects, we can run into compatibility issues between our analytical model and MI model. As a result, alternative missing data methods are sometimes utilised for binary outcomes such as best-worst and worst-best case scenarios. Whilst these methods allow us to evaluate the robustness of our findings under two extreme missing data assumptions, these scenarios may not be plausible or informative.

Methods
We have considered an alternative method for the assessment of the impact of missing data in binary outcomes using an extended ‘tipping point’ approach. This approach builds on best-worst and worst-best case scenarios, but allows us to consider a range of assumptions around the event rate in our missing data in each treatment group. We are able to identity (should one exist) the ‘tipping point’ at which our sensitivity analysis result differs from that of our primary finding. This allows us to judge the plausibility of our assumptions regarding the event rate in our missing data. Using this method, we apply the same statistical methods as used in our primary analytical model, overcoming some of the issues that can be faced with MI for binary outcomes. This method naturally extends to more complex analytical models (e.g. models which include random effects or interaction terms). In addition, this method allows us to demonstrate graphically the potential impact of missing data to aid interpretation and understanding for clinical colleagues.

Results Structure and Timelines
We will present our ‘tipping point’ analyses using data from recently published RCTs. Results will be available by July 2022.

Potential Relevance and Impact
This method can offer an alternative approach to assessing the impact of handling missing data in binary outcomes that is readily accessible and interpretable.

PS6A-05

Treatment group outcome variance difference after dropout as an indicator of missing-not-at-random bias in randomized controlled trials

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Introduction
Randomized controlled trials (RCTs) are the gold standard for assessing the causal effect of an exposure on an outcome, but remain vulnerable to bias from missing data. When outcomes are missing not at random (MNAR), for example when dropout depends on the unobserved outcome value itself, estimates from complete case analysis and multiple imputation will be biased. There is no statistical test for distinguishing between outcomes missing at random (MAR) and MNAR, and current strategies rely on comparing dropout proportions and baseline covariate distributions. We propose using the observed variance difference across treatment groups as a tool for assessing risk of MNAR bias.

Approach
In an RCT, at randomization, the distributions of all covariates should be equal in the populations randomized to the intervention and control arms. Under the assumption of homogeneous treatment effects, the variance of the outcome will also be equal in the two populations over the course of follow-up. We show that under MAR dropout, the observed outcome variances at follow-up, conditional on the variables included in the model, are equal in both groups, while MNAR dropout may result in unequal outcome variances. Consequently, unequal observed conditional group variances are an indicator of MNAR dropout and possible bias of the estimated treatment effect. We estimate the variance difference using the studentized Breusch-Pagan test.

Results
We illustrate our method in simulation and in application using data from an RCT investigating acupuncture treatment for patients with chronic headaches (ISRCTN96537534). We show that a variance difference at follow-up is an indicator of MNAR bias, and how violation of the assumption of homogeneous treatment effects impacts inference. Heterogeneous treatment effects affect the intervention group variance and are another potential cause of observing different outcome variances. We show that, for longitudinal data, we can isolate the effect of MNAR outcome-dependent dropout by considering the variance difference at baseline in the same set of patients that are observed at final follow-up, and, in doing so, assess if the average treatment effect is likely to be biased.

Discussion
We propose employing the (conditional) variance difference as a MNAR bias assessment tool, which is easily implemented using standard available software, and has a straightforward interpretation. This method can be applied to individual-level data, as shown in our application, and to summary-level data, using published group variance statistics.

PS6B-01

Quantifying the carbon footprint of current clinical trials: Development and prototype testing of a method to inform future lower carbon clinical trial design

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Introduction

Well before the acceptance that the climate crisis poses a real and present threat, the conclusion had been made that clinical trials contribute substantially to greenhouse gas emissions. Yet, there is currently no bespoke, published method for calculating the carbon footprint of a clinical trial. We now propose a method of conducting such assessments.

The NIHR-funded "Enabling lower carbon clinical trials" project works with UKCRC registered CTUs and Environmental Resources Management (ERM) to develop a prospective, reproducible method for quantifying the carbon impact of a trial.

Approach

A process map is under development to capture relevant activities in the clinical trial lifecycle. The scope of the activities included in the map will be informed by materiality and screening assessments. Discovery meetings have been held to engage with 6 participating CTUs to gain insight into their trials portfolio, ensuring a wide range of academic CTIMP and non-CTIMP trials are represented.

Qualitative sampling will be performed to select 10-15 trials from the 6 participating CTUs. Activity data from selected trials will be captured in a questionnaire. Following data collection and cleaning, a carbon footprint emission factor will be attributed to each of the identified activities in the process map. Feedback will be collected from CTUs on data that was unavailable or challenging to provide.

Patients' attitudes to actions taken to minimise environmental impact when considering participation in clinical research are crucial to the interpretation of findings. Therefore, patient views will be incorporated via PPIE focus groups and discussion of results.

Results Structure and Timelines

Data collection will be conducted over Summer 2022. Descriptive statistics will summarise the carbon footprint data for the selected trials and identify hotspots where stakeholder interventions could lower the environmental impact of trials.

Potential Relevance and Impact

The results will inform future research in this area and engage the UK clinical trials community in considering climate change when designing trials.

It also provides the foundation for a planned second phase of work, to develop an open-access, online carbon calculator to assist the design and conduct of clinical trials with a lower carbon footprint. Ultimately, an approach to quantifying the carbon footprint of a trial will support organisations like the NHS and NIHR to meet their carbon reduction commitments and allow stakeholders to incentivise a reduction of the carbon footprint of trials in their portfolios.

PS6B-02

Moving towards sustainable clinical research

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Introduction
Health research is the cornerstone to delivering high-quality, safe and effective healthcare, but clinical trials and health research are responsible for a considerable carbon footprint (due to substantial patient travel, resources for patients, shipments of medications and site resources among others). There is a need to make clinical research more sustainable. Innovative technology is rapidly enabling decentralised trial models, with patients being assessed more at home. The time is therefore ideal to evaluate the environmental impact alongside these methods. The first step is to quantify the carbon associated with methodological decisions in the conduct of clinical trials.

Methods
This project will conduct a retrospective audit of trials conducted at the Clinical Research Centre. Data sources will be based on data held at the CRC, the trial protocol, the trial master file and the final report. Data collected will be used to estimate CO2 equivalents for trial activities using standard conversion factors. This carbon audit will include trial activities such transport (including national and international for (1) individual patients based on number of study visits and distance from the study centre, (2) visits for oversight and monitoring, and (3) steering group travel), shipment of deliveries (including investigation medicinal products and technology related to the trial), and the carbon cost of trial related materials.

Results Structure and Timelines
The results of this study will include estimates of CO2 emissions for trial related activities.
Full results are anticipated August 2022 and will be available for presentation at the conference. Based on this, a list of actionable guidelines to promote sustainability in clinical research will be developed. In additional, this will provide the first step toward development of a carbon estimator for clinical trials.

Potential Relevance and Impact
This study will allow identification of trial related activities with the highest contribution to CO2 emissions. The data from this will form the basis of guideline development for methodological considerations in clinical research study design and conduct to minimise greenhouse gas emissions. Our goal is to develop a carbon calculator, to ultimately reduce CO2 emissions in clinical research.

PS6B-03

Reducing the carbon footprint of the NightLife study

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Introduction
As the leading funder of NHS health research, the NIHR strives to meet the targets set by the Climate Change Act (2008), namely an 80% reduction in carbon emissions by 2050. The COVID-19 pandemic presented opportunities to better align research management/practice with global climate change commitments. Here, we report the efforts to reduce the carbon impact in the first 18 months of the NightLife study.

Methods
Randomised Controlled Trial (Workstream 1)
Site initiation visits (SIVs), and trial management group, oversight committee and patient and public involvement (PPI) meetings were reconfigured and held online. In line with UK Government guidance, staff worked from home wherever possible.

Process Evaluation (Workstream 2)
A protocol amendment was submitted to add remote elements: electronic consent, virtual interviews and 'photovoice.' A study smartphone and iPads were used to support this.

QuinteT Recruitment Intervention (Workstream 3)
Meetings and provision of feedback at recruiting units were done remotely. Virtual interviews were favoured over face-to-face interactions.

Results
Adaptive working resulted in a net carbon emission reduction of 136 tonnes. All changes were made within the original study budget. Here, we report results for each workstream.

Workstream 1
The net saving was 12 tonnes (emissions reduced 12 tonnes; emissions used 0). Individual contributions to net savings included virtual SIVs, meetings and PPI activities.

Workstream 2
The net saving was 20 tonnes (total emissions reduced 20.74 tonnes; emissions used 0.74 tonnes). 50% of participants opted for virtual interviews/'photovoice' rather than face-to-face interviews. Travel to base hospitals and satellite haemodialysis units was reduced by 50%. The purchase of a smartphone and two iPads incurred a carbon increase.

Workstream 3
The net saving was 0.32 tonnes (total emissions saved 0.32; emissions used 0). Travel was reduced by 100% due to remote meetings, interviews and provision of feedback to recruiting units.

Other
Additional savings were incurred through virtual attendance at national and international conferences, saving 71 tonnes. Reduced travel due to homeworking resulted in an estimated reduction of 66 tonnes.

Conclusion
To date, innovative changes to trial management resulted in a net reduction of 136 tonnes, equal to 586 return flights from London to Rome, or the yearly heating consumption of 50 UK households. Other benefits included the use of technologies to assist remote working and interviews and geographical diversity of the PPI group. Extrapolating these data forward, we would estimate an even bigger saving over the five year study period.

PS6B-04

Late-phase academic-led trials for potential regulatory use: Lessons and recommendations from one trials unit's experience

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Setting
Clinical trials, particularly CTIMPs and ATIMPs, are run within complex regulatory frameworks. Industry trials are commonly designed for Marketing Authorisation, but Industry cannot and will not run all the trials needed by the healthcare community. The intended role of an Academic-led trial in a regulatory package may change over time. Therefore, it is important that any Academic-led trial that *may* be used in a submission is designed, conducted and analysed in way that facilitates regulatory review. Yet Academic-led trials may cost 1 to 2 orders of magnitude less than an Industry trial. MRC Clinical Trials Unit at UCL has >30 years experience of running clinical trials, nationally and internationally, across many disease areas, often working with Industry, and many of the unit's trials have been used in regulatory submissions. By reviewing the experiences from trial teams that have engaged with industry, we extracted a series of recommendations.

Method
We used a structured internal workshop and structured interviews with selected researchers to develop an initial list of recommendations for those Academic-led clinical trials which, in collaboration with an Industry partner, "will" definitely be used in a regulatory submission, or "may" be used (where there remains uncertainty over whether they might be used, at, and beyond, the time the trial is developed).

Results
Key recommendations from across the trial cycle included: (1) Adding regulatory elements retrospectively is difficult, so prospective planning is required; (2) Discussions with Competent Authorities to be held jointly with clear academic contribution to applications; (3) Clarity over sponsorship is important, and conditions under which Sponsorship might transfer from academia to industry should be established; (4) Co-primary outcome measures can be acceptable to allow emphasis on what is needed; (5) Delegation of responsibilities and oversight must be clear, especially if involving a CRO, with adequate resourcing from the planning stage; (6) Sampling can be used to provide the greater intensity of e.g. biomarker substudies, patient assessment or monitoring, typical in an industry trial without needing implementation at all sites; (7) Site payments should be higher in trials that "may", and higher still in those which "will", be used in regulatory submissions. Further recommendations will be presented.

Discussion
Academic-led trials often have an under-appreciated role in the regulatory process. We have highlighted areas for joint consideration in trials which may contribute to regulatory submission. We welcome discussion on these recommendations.

PS6B-05

Tolerating bad trials: the continuing scandal

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Introduction
At the 2015 REWARD/EQUATOR conference on research waste, the late Doug Altman revealed that his only regret about his 1994 BMJ paper 'The scandal of poor medical research' was that he used the word 'poor' rather than 'bad'. More than 20 years later, how much research is still bad? And what would improve things?

Methods
We focused on randomised trials and considered quality, size and cost. We randomly selected up to two quantitative intervention reviews published by each clinical Cochrane Review Group between May 2020 and April 2021. Data including risk of bias, number of participants, intervention type and country were extracted for all trials included in selected reviews. High risk of bias trials were classed as bad, low risk of bias trials were classed as good, and uncertain risk of bias trials were classed as just that, uncertain. A range for the cost of high risk of bias trials was estimated using three published estimates of trial cost per participant.

Results
We identified 96 eligible reviews authored by 546 reviewers from 49 of the 53 clinical Cochrane Review Groups. These reviews included 1,659 trials done in 84 countries. Of the 1,640 trials for which risk of bias information was available in the review, 1,013 (62%) were high risk of bias (bad), 494 (30%) were unclear (uncertain) and 133 (8%) were low risk of bias (good). Bad trials were spread across all clinical areas. Well over 220,000 participants (or 56% of all participants in the 1,640 trials) were in bad trials. The low estimate of the cost of bad trials was £726 million; our high estimate was over £8 billion.

Discussion
Most randomised trials are bad and most trial participants will be in a bad trial. We make five recommendations: trials should be neither funded (1) or given ethical approval (2) unless they have a statistician and methodologist on the team; trialists should use a risk of bias tool at design (3); more statisticians and methodologists should be trained and supported (4); and more funding should be put into applied methodology research and infrastructure (5).

The research community has tolerated bad trials for decades. This has to stop: we need to put rigour and methodology where it belongs– at the centre of our science.

PS6C-01

How should I justify the sample size for my pilot trial? A methodological systematic review of sample size guidance for external randomised controlled pilot trials

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Introduction
Before embarking on a resource intensive randomised controlled trial (RCT), health researchers often conduct randomised pilot studies, also called pilot trials, to clarify uncertainties, such as the design, conduct and analysis. Pilot trials address questions of feasibility, not efficacy or effectiveness, therefore conventional methods for justifying the sample size of RCTs, such as power calculations, are not appropriate. Health researchers are faced with a quandary; the pilot sample size must be large enough that lessons can be learned about the design and conduct of the pilot trial, yet not too big to waste clinician and patient resources. There is confusion amongst health researchers, despite several approaches published within the literature, as to the appropriate methods to justify the sample size of pilot trials. We aimed to review and describe the published sample size justifications available to health researchers.

Methods
Four sources of data were used: Embase, MEDLINE, the PAFS collaboration website (https://pilotandfeasibilitystudies.qmul.ac.uk/), and two methodological systematic reviews of empirical pilot trials conducted by the authors. After screening and extraction, 25% of records will be independently validated. Eligible sample size justifications will be within human health research in any setting, location or medical speciality, and originate from empirical pilot trials, or methodological publications describing the method. The protocol for this review can be found at https://osf.io/937hx .

Results Structure and Timelines
Overall, 1,174 records were identified. In total, 354 duplicates were removed, leaving 820 publications to be screened. The review is ongoing and we anticipate identifying publications that provide pragmatic or practical guidelines, statistically based methods involving simulations or methods based upon statistical theories, and justifications used within empirical pilot trials. We anticipate screening, data extraction and analysis to be completed by the end of June 2022.

Potential Relevance and Impact
This methodological systematic review will be the first to provide health researchers with a comprehensive summary of the sample size justifications available for pilot trials. This review will inform the first questionnaire of a modified Delphi study. The modified Delphi study aims to achieve consensus among a multidisciplinary panel of experienced health researchers about which pilot trial sample size justifications are appropriate. This methodological systematic review and modified Delphi study will inform pilot trial sample size guidance. We aim to produce accessible sample size guidance suitable for health researchers, through usability testing with health researchers, who will also suggest organisations to distribute the guidance.

PS6C-02

Recommendations for using progression criteria in external randomised pilot trials to determine feasibility

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Introduction
External randomised pilot trials aim to assess whether a future definitive Randomised Controlled Trial (RCT) is feasible. Pre-specified progression criteria help guide the interpretation of pilot trial findings to decide whether, and how, a definitive RCT should be conducted. There is no evidence-based guidance for how progression criteria should be used to determine external randomised pilot trial feasibility. This lack of guidance can negatively impact transparency, rigour and usability of pilot trial findings and lead to inadequate feasibility assessment with pilot trials progressing to future definitive RCTs inappropriately.

Methods/Approach
Four distinct but complementary research studies were conducted to investigate current use of progression criteria in external randomised pilot trials: A methodological review of pilot trial publications, a cross-sectional study of research funding applications, a qualitative research interview study with members of pilot trial research teams, and an international web-based survey of corresponding authors of pilot trial publications. The findings of these studies were triangulated to inform the development of draft recommendations for how to determine feasibility of external randomised pilot trials using progression criteria. Initial recommendations will be presented to stakeholders in two engagement workshops in July 2022 and will be refined following discussion.

Results
The research conducted examined the inclusion of progression criteria in pilot trial funding applications, researchers experiences of designing and assessing progression criteria, and progression criteria reporting in pilot trial publications. Key concerns and areas for improvement were identified, including: Who should decide on progression criteria? Should specific targets be used and what should they be based on? How should progression criteria interact with other feasibility considerations e.g. findings of qualitative research or unanticipated challenges faced? How should progression criteria be reported in external pilot trial protocol and result publications? Draft recommendations have been produced to support researchers who are designing, analysing and reporting progression criteria for external randomised pilot trials. These recommendations will be finalised following stakeholder engagement workshops and final recommendations will be presented at the conference.

Discussion
This research has provided a comprehensive understanding of how progression criteria inform feasibility assessment of external randomised pilot trials, and some of the associated challenges. Initial recommendations to support researchers using progression criteria for external randomised pilot trials have been drafted. It is hoped that these recommendations will provide a useful tool for researchers and inform future development, or update, of guidelines for the design, conduct, analysis and reporting of external randomised pilot trials.

PS6C-03

Completion of PROMS – Electronic versus paper versus a Pandemic

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Introduction
Patient Reported Outcome Measures (PROMs) are a widely used method of collecting outcome data in research. In the TOPSY trial (including women with prolapse) participants were given the option of completing their follow-up PROMS via paper or online. During ICTMC 2019, we reported some preliminary findings on the relationship between different demographic data and participants' choice of mode of PROM completion and some preliminary PROM return rate results (n=143). We recruited 340 women to the trial and had a 95% return rate of PROM data at 18 months. We now have a rich data set to investigate further, to enhance our knowledge about mode of collection and its impact on retention with additional process changes due to a pandemic.

Methods
Recruitment to TOPSY was completed prior to the pandemic (Feb 2020). All women were contacted in April 2020 and those who completed their PROMS via the paper method were given the option to change this to online if they desired. Our retention protocol included a phone call (3rd reminder after 2 postal or online reminders). The trial team felt that there was an increased number of participants needing a 3rd reminder call (compared with work load prior to the pandemic), thus a shorter version of the PROM with a subset of the questions could be completed if the participant wished.
From analysis of the TOPSY dataset we will report on the following:
1. What associations exist between demographic factors and mode of completion choice, using complete TOPSY dataset (previously reported on 42% of the cohort).
2. What is the proportion and profile of participants who changed their mode of data collection due to the pandemic (including change of paper to online method; completion of short form instead of full questionnaire?
3. What associations exist between mode of completion choice and the following factors:
a. Number of reminders sent
b. Trial retention
c. Questionnaire completion
4. Did any of these change since the start of the pandemic?

Timing of potential Results
The findings presented will provide important evidence on retention rates when participants are given a choice of how they complete their PROMS and any effects that the pandemic had on these choices.

Potential relevance and Impact
The results will further aid the development of a methodology project/collaboration looking at IMPACT of mode of participant PROM completion on trial retention.

PS6C-04

"Have you tried turning it off, and back on again?": Running trials involving digital home monitoring technologies - lessons from the I-TRAC feasibility Study.

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Introduction
Digital technology use in health care is increasing exponentially, heightening the need for high quality evidence to support their use in practice. Patients with glaucoma, a progressive eye condition, may be suitable for home monitoring due to the necessity for regular visual tests, currently undertaken in clinics. Doing these tests at home could reduce both patient and clinic burden. The In-home Tracking of glaucoma: Reliability, Acceptability, and Cost (I-TRAC) study explored the feasibility of home monitoring technologies for patients with glaucoma. In addition to the study specific challenges identified, significant challenges in designing and delivering trials involving digital technologies were also highlighted. We present recommendations for researchers involved in the design and delivery of digital technology for home monitoring trials.

Methods
The I-TRAC study involved recruiting patient participants to home monitor their glaucoma weekly for 12 weeks using a tonometer and tablet-based App. We collected quantitative and qualitative data by survey, interviews and focus groups from key stakeholders to determine acceptability and feasibility of a future large scale evaluation of digital technology for home monitoring of glaucoma. We kept detailed records of issues with, or changes to, planned design and conduct, with reasons as to why these occurred, the impact of these issues and suggestions to mitigate these in the future. Where applicable, these were mapped to the ADePT (A process for Decision-making after Pilot and feasibility Trials) framework.

Timing of potential results
August 2022

Potential Relevance and Impact
Our findings identify important considerations for both a future I-TRAC trial and digital technology trials for home monitoring generally. Findings suggest significant under estimation of human resource requirements to support these studies, additional technology costs in relation to requiring spare and replacement devices, accessories (e.g. chargers, software licencing, batteries), transport logistics (e.g. regulations preventing some items from being shipped by air), regulation (e.g. the new CE/CA marking system, MHRA medical device rules), site differences in medical device approval processes, managing commercial relationships, little institutional or within team technology expertise, the complexity of the technologies themselves, meeting patients' needs and making devices accessible to all. Linking these issues to ADePT, we will present a set of recommendations which we believe should be considered in the design and delivery of future trials of digital technology home monitoring interventions.

PS6C-05

A process evaluation and data triangulation of the Awareness and Beliefs About Cancer 3 trial

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Introduction
Process evaluations are commonly conducted in trials of complex interventions to assess underlying mechanisms that may have impacted on effectiveness. The Awareness and Beliefs About Cancer (ABACus3) trial tested the effectiveness of a targeted and facilitated health check to increase cancer awareness (cancer symptoms, screening and risk factors) among UK adults living in socioeconomically deprived areas (Moriarty et al 2021). As part of this trial, we undertook an embedded process evaluation following the MRC framework for evaluating complex interventions (Moore et al. 2015). This included triangulation of three data sources (participant interviews, lay advisor interviews, session observations/audio recordings) following the Tonkin-Crine et al. (2016) method to assess levels of agreement between sources. Although triangulation of data is commonly reported, it is not clear exactly how this is done and what the outcome of triangulation means in relation to the process evaluation or wider trial results. In this paper we present a practical application of this method using the ABACus process evaluation as a case study and present recommendations for future triangulation methods.

Methods/Approach
Each data source was independently analysed using thematic analysis and detailed results were written up in a report where key findings were independently identified by two researchers and listed in a table. Results per data source were coded to one of six process evaluation domains (reach, fidelity, dose, mechanism of impact, context, contamination). A convergence coding matrix was used to display key findings across data sources. Key findings were compared to be either in agreement (convergence), partial agreement (complimentary), dissonant (contradictory), or silent (where only one data set contained the finding).

Timing of potential results
Following publication of trial results in late 2021, process evaluation analysis will be completed in July with results available in August 2022.

Potential relevance & impact
Preliminary triangulation results indicate that while key process evaluation findings, such as the importance of building rapport and personalising the results, received agreement across data sources, other findings such as the requirement for lay advisors to often diluted the symptom awareness message (primary outcome) in order to tailor to participants' interests were silent. Future triangulation methods need to

consider the purpose of triangulating and the importance and meaning placed against reaching agreement as potential key results which could help explain main trial results could become lost. Coding against process evaluation domains could be more helpful in identifying overarching findings to help explain trial results.

PS6D - Spotlight Session: Better Trials Together, UKCRC CTU Network

UKCRC Registered Clinical Trials Unit Network, "Better Trials Together"

Professor Kerry Hood[1],
[1]*Centre for Trials Research*

This panel session presented by UKCRC CTU Network Director Julia Brown and chaired by Nick Lemoine CRN Medical Director. This session look's at:

i) Lessons from the PANORAMIC trial, PANORAMIC is a platform trial of novel anti-viral drugs for COVID in the community for people at increased risk of adverse outcomes. It has required rapid set-up, innovation in approaches to trial design and delivery, at a scale previously unseen in community-based trials of medications. It has been led by the Primary Care CTU in Oxford in partnership with the Oxford Respiratory CTU and the Centre for Trials Research in Cardiff. This talk will discuss the model of collaboration across CTUs and how that contributed to the ability to deliver this ambitious trial.

ii) Low carbon research building on adaptations driven by the pandemic. Clinical trials sector contributes to greenhouse gas emissions, notably through energy use in premises, drug supply, and air travel. Governments, companies, and many organisations, including NHS England, have committed to reaching net-zero carbon before the middle of the century, and so too should clinical trials units (CTUs). The NIHR Annual Efficient Studies funding call for CTU projects in 2021 funded, "Development and prototype testing of a method to quantify the carbon footprint of current clinical trials to inform future lower carbon clinical trials design," which was inspired by the environmentally friendly adaptations made during the COVID-19 pandemic, many CTUs' desire to decarbonise clinical trials, and collaboration with Environmental Resources Management (ERM). The NIHR has developed Carbon Reduction Guidelines, but little has been done to reduce the emissions of clinical trials. We will present progress with developing this tool, which ultimately will enable CTUs and other stakeholders to measure and reduce carbon consumption in clinical trials.

iii) Clinical trials challenges and future perspective: recent turbulence for clinical research, and for clinical trials units, highlight the importance of having a strong network of CTUs in the UK. In this talk I will give a personal view on how the challenges facing CTUs, and the support gained from being a member of a network, have changed over the years and been accelerated by the pandemic. Looking to the future, I will discuss how we might address some key issues to ensure UK CTUs continue to drive the excellence in trial design and conduct required to underpin world-leading clinical trials research.

PS7A-01

Using estimands to inform trial choices: upending conventional wisdoms

Dr Brennan Kahan[1], Prof James Carpenter[1]
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Introduction
Conventional wisdom dictates that intention-to-treat (ITT) analyses be the default choice in randomised trials, due to its protection against bias from post-randomisation exclusions, and because ITT is often seen to estimate a more "pragmatic" treatment effect (e.g. the effect of treatment if introduced into usual care). However, with the increasing focus on estimands, there is recognition that we should first define the precise study question (i.e. the treatment effect to be estimated from the trial), and then tailor the design and analysis of the trial around the chosen estimand.

Methods
Using the estimands framework, we evaluated the treatment effect provided by an ITT analysis under certain common intercurrent events, and compared this to the "pragmatic" treatment effect of an intervention being introduced into usual care.

Results
We find that in many trials (i) exclusion of participants experiencing certain types of intercurrent events (such as failure to start treatment), while in contradiction to the ITT principle, can still provide valid (unbiased) results, if done correctly; (ii) exclusion of such participants can sometimes provide more generalisable and clinically relevant treatment effect estimates than strict ITT; and (iii) for certain intercurrent events, ITT does not estimate a pragmatic treatment effect, and alternatives such as the treatment effect under hypothetical compliance or the principal stratum effect are more generalisable to everyday clinical practice. We illustrate these concepts using a series of case studies from published or ongoing clinical trials.

Discussion
While ITT remains an invaluable tool for analysing clinical trials, the conventional wisdom that it is necessary to estimate "pragmatic" treatment effects is not always right. Use of the estimands framework can help ensure that analytical methods are aligned to the desired treatment effect.

PS7A-02

Accounting for use of rescue medication in mental health trials: application of the estimand framework for intercurrent events

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Introduction
An intercurrent event is one that occurs after treatment initiation and either precludes the outcome, or affects its interpretation. For example, participants in some RCTs may start additional non-randomised rescue medication because of a worsening of symptoms or insufficient therapeutic effect or a participant's prognosis. Typically, the use of rescue medication reduces the observed treatment effect in intention-to-treat analysis, since this estimand ignores post-randomisation information, and is most challenging when rescue medication is differentially associated with randomisation groups and is associated with outcome. The use of rescue medication is routinely collected in RCTs as part of the concomitant medication but rarely incorporated into research hypotheses.

Methods
We discuss methods of analysis which take account of rescue medication, to achieve a more meaningful comparison of the randomised treatments and unbiased treatment effect estimates. Focusing on trials within mental health, we consider alternative research questions such as:
"What is the effect of the treatment if no trial participants had received rescue medication?" and
"What is the effect of the treatment in different subgroups of participants, such as the population of patients who would not need rescue medication?"

Results
Ignoring all data after rescue is likely to be biased because rescued patients are a highly selected group. Instead, we propose how rescue medication can be incorporated into the analyses and formulated in the context of the estimand framework. For example, the hypothetical strategy censors participants at the use of rescue medication, or the principal stratification strategy defines the effect of the treatment in people who would have taken rescue medication regardless of randomised group. We compare the assumptions and implementation of causal inference approaches to estimate these estimands including causal mediation analysis, inverse probability weighting and discrete latent class models.
We illustrate these methods in the SlowMo trial which randomised 362 people with psychosis to a brief blended digital therapy targeting reasoning compared to usual-care with the primary outcome of paranoia at 24 weeks. The trial recorded use of Clozapine, an effective antipsychotic, during the intervention period leading to the question "What is the effect of SlowMo accounting for differential use of Clozapine?" We define and estimate the estimands to answer this question.

Discussion
An estimand is a way to explicitly state how intercurrent events will be dealt with and ensure analyses are consistent with this approach. We illustrate their application to a common challenge in mental health trials.

PS7A-03

Choosing estimands in hospice/palliative care clinical trials

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Introduction
In hospice/palliative care clinical trials, participants have a limited life-expectancy and experience worsening functioning. This results in missing data due to post-randomisation events including death, adverse events, off trial or rescue treatment or trial discontinuation due to deteriorating health, and inability to participate in all planned assessments due to their illness. In many cases these post-randomisation events are unrelated to the intervention itself. A systematic review of 108 trials in palliative care reported at least 20% missing data in the primary endpoint in over 50% of the included trials. This missing data pose a significant challenge in the analysis of these trials. Heterogeneity in analytic approaches adds further difficulties when interpreting data across trials. Using the estimand framework (ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials), we describe commonly encountered post-randomisation events leading to missing data and propose estimands for efficacy and safety in hospice/palliative care.

Methods/Approach
We use the five elements of an estimand (treatment, population, variable, summary measure and intercurrent event handling) and outline different strategies for handling post-randomisation events in end-of-life trials. Using these five elements, we construct efficacy and safety estimands.

Results
We describe common intercurrent events in palliative care trials and discuss and justify what analytic strategies could be followed with each. The most appropriate strategy for the handling of the intercurrent events depends on the context and is informed by the reason for the intercurrent event and the estimand of interest.

Discussion
When planning a palliative care trial, stating the estimand explicitly, including how intercurrent events will be handled in the analysis, is of great value to link trial objectives, design, and analysis. Informed by the scientific objectives of the trial, this framework will support the interpretation of the results.

PS7A-04

Accounting for differential uptake of treatment-as-usual in open-label RCTs: a comparison of methods and illustration in mental health trials

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In randomised trials of complex interventions the comparator is often usual care, and the new treatment is tested in addition to treatment-as-usual for both ethical and scientific reasons. It is unethical to deny trial participants the usual care available to non-trial participants and showing that the new treatment is more effective than current usual care is an important question when deciding whether to implement it.

Randomisation cannot be assumed to equally distribute the uptake of components of usual care that occur post-randomisation between treatment and the control arms. Knowledge that a participant is receiving the new intervention may mean less uptake of components of usual care, or knowledge that a participant is not receiving the new intervention may increase their uptake of usual care. These decisions could also relate to a participant's prognosis.

For example, in mental health trials, psychological therapies are compared to medication and show differential use of medication between the arms during the post-randomisation intervention window, often lower medication use in the intervention arm. This differential uptake of components of usual care creates challenges for the interpretation of study results based on an intention-to-treat analysis, since this estimand ignores post-randomisation information, and as the components of usual care are part of the trial protocol, these are not considered as intercurrent events.

We describe methods to answer alternative research questions including: How do we take account of differential uptake of usual care components? What is the effect of the new treatment if every trial participant had received a specific component of usual care? Or what is the effect of the new treatment if no trial participants received this component? We illustrate this in the SlowMo trial which recruited 362 people with psychosis and compared a novel blended therapy plus usual care to usual care alone (antipsychotic medication and psychological therapy).

We define and estimate the estimands to answer these alternate research questions using the treatment policy estimand (effect estimate: -5.47, 95% CI: -11.10, 0.16), mediation estimands comparing the effect of the intervention if everyone received additional therapy (7.85, 95% CI: -11.63, 26.10) and if no one received additional therapy (-8.41, 95% CI: -14.36, -2.61), and the balanced estimand (-0.21, 95% CI: -2.42, 1.53).

This scenario is common in many open-label RCTs, and we summarise how trialists can approach this analysis challenge, and suggest which estimands might be most appropriate.

PS7B-01

A survey of knowledge, perceptions and use of core outcome sets among clinical trialists

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Background

Core outcome sets (COS) are standardised sets of outcomes, which represent the minimum outcomes that should be measured and reported in clinical trials. COS can enhance comparability across health trials by reducing heterogeneity of outcome measurement and reporting and potentially minimising selective outcome reporting. Examining what researchers involved in trials know and think about COS is essential to increase awareness and promote COS uptake. The aim of this study is therefore to examine clinical trialists' knowledge, perceptions and experiences of COS.

Methods

An online survey design was used. Participants were clinical trialists, operationalised for the current study as researchers named as the contact person on a trial registered on the International Standard Randomised Controlled Trial Number (ISRCTN) Trial repository between 1 January 2019 and 21 July 2020. Survey items assessed clinical trialists' familiarity with and understanding of COS, along with experiences of COS use and development.

Results

Of 1913 clinical trialists contacted to participate, 62 (3%) completed the survey. Forty (65%) participants were familiar with COS and, of those familiar with COS, 21 (55%) had been involved in a trial that used a COS. Of clinical trialists who used COS in a trial(s), less than half (n = 9, 41%) reported that all COS outcomes were used. The main barriers to using COS are poor knowledge about COS (n = 43, 69%) and difficulties identifying relevant COS (n = 42, 68%). Clinical trialists also reported perceptions of COS as restrictive and often containing too many outcomes. The main enablers to using COS are clear understanding (n = 51, 82%) and perceived importance of COS (n = 44, 71%).

Conclusions

Enhancing clinical trialists' use of all COS outcomes is needed to reduce outcome heterogeneity and enhance comparability across trial findings. Enhancing awareness of COS importance among researchers and funders is needed to ensure that COS are developed and used by clinical trialists. Education and training may further promote awareness and understanding of COS.

PS7B-02

Improving uptake of core outcome sets in clinical trials and systematic reviews

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Introduction
It is increasingly recognised that insufficient attention has been given to the choice of outcomes that are measured in clinical research, often neglecting those of greatest importance to decision-makers, including patients and the public. We review what is known about the uptake of core outcome sets (COS) in research, where a COS is defined as an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in a specific area of health or health care. We review similarities between COS and outcomes recommended by relevant stakeholders in the evidence ecosystem, and describe actions taken by those stakeholders to facilitate COS uptake.

Methods/Approach
The COMET database, https://www.comet-initiative.org/, was searched in May 2022 for publications classified as 'COS methods research', 'COS uptake study' and 'systematic review of COS uptake studies'. The database is populated from annually updated systematic reviews of COS development studies, with other papers related to COS also being included and classified in the database. Eligible studies were those describing assessments of COS uptake or factors affecting uptake. We also added articles related to endorsement of COS and other references that were known to the authors. Evidence was classified according to the relevant stakeholder group as well as COS developers.

Results
COS uptake is low in most research areas. Common facilitators relate to increased trialist awareness and understanding of COS. Common barriers were not including in the development process all specialties who might use the COS, and the lack of recommendations for how to measure the outcomes. Increasingly, COS developers are considering strategies for promoting uptake earlier in the process, with some including actions beyond traditional dissemination approaches. The overlap in outcomes between COS and those in regulatory documents and health technology assessments is good. An increasing number and variety of organisations are recommending COS be considered.

Discussion
Greater emphasis on encouraging and facilitating COS uptake is essential to minimise research waste. Where possible, COS developers should collaborate with key organisations from the outset to identify uptake strategies for their health area, and provide consensus recommendations on how to measure the core outcomes. Stakeholders from many organisations and communities should do more to promote the uptake of COS, and research to identify and develop evidence-based strategies for increasing uptake amongst trialists is needed. This may include initiatives and interventions that can push and pull trialists towards considering COS for their studies.

PS7B-03

Multi-Round vs Real-Time Delphi for achieving consensus in core outcome set development: a randomised trial

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Background

A core outcome set (COS) is an agreed, standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care. COS development often includes consensus techniques such as Delphi surveys and consensus meeting(s). The Delphi surveys frequently include two or three rounds where participants receive feedback between rounds and can amend their score based on knowledge of other groups' responses. In the Real-Time Delphi (RTD) approach, participants see group responses in real-time and can amend their score in the same sitting of the survey based on group responses. This trial compares a three-round, Multi-Round Delphi (MRD) with a RTD in developing a COS to treat neonatal encephalopathy.

Methods

We recruited 269 participants (parents/ caregivers, healthcare providers, and researchers/ academics), of which 111 were randomised to the MRD and 111 to the RTD groups. We investigated the outcomes prioritised in each survey and other outcomes including feedback and iteration effects to identify if there were differences between the survey types.

Results

The RTD was live for 14 weeks and the MRD was live for 20 weeks. 92 participants completed the RTD fully. For the MRD, 94 (85%) completed Round 1, 72 (65%) completed Round 2, and 60 (54%) completed Round 3. Of the 91 outcomes, 26 (n=29%) were prioritised differently (i.e. scoring 1-3 (out), 4-6 (undetermined) or 7-9 (in)), between the two surveys. Significantly fewer respondents changed their scores following feedback in the RTD than in the MRD (feedback effect). Most participants in the RTD did not change their scores following group response feedback (iteration effect) and, where they did, ratings were amended

substantially toward greater convergence. In the MRD, variance in scores reduced with consecutive rounds. Overall, greater convergence in scores was seen in the RTD.

Conclusion
Although the feedback effect was significantly different, this may be due to the large sample size rather than a large effect. There did not seem to be much advantage in making it obligatory for participants to re-rate their outcomes (as in the MRD). Overall, convergence in the RTD, where re-visits were allowed but not compulsory, was greater. Advantages of using the RTD method include reduced time to complete overall as participants can amend their scores in the first sitting following knowledge of the group responses and better convergence on outcome ratings.

Trial Registration: NCT04471103. Registered on 14 July 2020.

PS7B-04

Core outcome sets: Bridging the gap between research and routine care

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Introduction
Core outcome sets (COS) represent the minimum set of outcomes to be measured in a given health condition. Whilst predominantly used in research, there is growing interest in using COS in routine care for patient-focused care and in particular value-based health care. Whilst COS for research are regularly mapped, little is known about COS developed for routine care and how they relate to COS for research.

Aim
To systematically map COS developed for use in routine care and compare them to COS for research.

Methods
Medline (OVID), Scopus and WoS core collection will be searched for studies reporting the development of a set of health outcomes for measurement in routine care. COS for routine care are defined as sets of health outcomes not collected solely for clinical research purposes. COS developed for registries will be included given their broad role globally. Data extracted from eligible records will include COS scope, development methods and stakeholder involvement. A purposive sample of COS developed for different settings (research, routine care or both) but matched by health condition will be identified from the review and COMET records. Outcomes within matched COS will be categorised against the outcomes taxonomy to explore the influence of setting on outcome selection.

Results
Searches were run in May 2021 identifying 25,106 records. Following title/abstract screening, 1600+ full texts were reviewed. Data extraction of over 250 eligible records is nearing completion. Unique COS will be grouped according to setting. Summary statistics will be presented for clinical area, stakeholder groups, and consensus methods and compared to the recent COMET review of COS for research. The frequency and extent of patient involvement in COS development will be reported by group and over time.

Relevance
Application of COS in routine care will encourage regular collection of patient important outcomes which can be made available for future trials and real-world evaluations helping bridge the gap between research and routine care. Whilst a significant number of COS have been developed for research it is unknown to what extent these are transferable to routine care. If the outcomes in COS for research/care, matched by condition, are broadly similar, this opens up possibilities of applying existing COS beyond the setting in their original scope. Even if not, mapping the coverage, key stakeholders and drivers of outcome selection will indicate where sets need to be adapted to fill current gaps and how this may be facilitated.

PS7C-01

Optimising First in Human trials via dynamic programming

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Introduction
What is the best design for a First in Human trial? The answer to this question depends on the aims and constraints of an individual trial.
First in Human trials are conducted sequentially, allocating a dose to one cohort at a time. After observing results from one cohort, trial teams must decide which dose to give the next cohort. We have developed a framework to make these decisions optimally. The emphasis is on fully specifying the aims of the trial up front: if you tell us what you want the trial to do, we can find the optimal design for your specific trial.

Methods
We obtain optimal designs via dynamic programming. This requires a set of calculations to be performed for every possible data set at each stage of the trial. Even with a small sample size this state space is large, and prohibitively large when it comes to considering phase I trials with a safety and an efficacy endpoint. We consider reformulating the state space as the space of posterior density functions for the dose-response model parameter and adapting the dynamic programming algorithm to a sample of this space. To produce this approximate dynamic programming algorithm we employ generalised additive models. We evaluate the operating characteristics of designs produced by both the exact and approximate dynamic programming algorithms through simulation. Further, we compare to commonly implemented First in Human trial designs.

Results and Discussion
Our approximate dynamic programming algorithm produces a design that is a good approximation to the optimal rule produced by performing dynamic programming on the space of all possible data sets. This approximation enables us to produce optimal designs for larger First in Human trials, which includes trials that incorporate a binary efficacy endpoint in addition to the binary safety endpoint.
Different sets of aims lead to different optimal rules. This highlights the importance of clearly defining the trial aims up front and choosing a design that meets those aims. This framework enables objective comparison of First in Human trial designs to find the optimal design for a specific trial. The optimal design provides a benchmark to which alternative designs can be objectively compared through the expected loss/utility associated with the design.

PS7C-02

A road map for designing phase I clinical trials of radiotherapy-novel agent combinations

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Introduction
The design of phase I trials of radiotherapy-drug combinations brings challenges not typically encountered in standard phase I trials of drug-drug combinations. Most notably the timeframe for observing toxicities can be significantly longer, requiring specific attention when identifying an appropriate statistical design. There is growing interest in evaluating radiotherapy-novel agent combinations, and a drive to initiate this earlier in clinical development of the novel agent, where scientific rationale and pre-clinical evidence for a radiotherapy combination approach is high. Optimal design, delivery and interpretation of phase I studies is critical to an efficient development strategy, to determine safety and dosing.

Methods
To enhance trial design, optimize safety, and promote efficient trial conduct, we developed a road map to inform phase I radiotherapy-novel agent combination study development, from consideration of the research question and intervention through to identifying an appropriate statistical design. A literature search of phase I trial design methodology was performed. Data were extracted on key design aspects, and designs grouped according to: maximum tolerated dose (MTD) determination, dose limiting toxicity (DLT) categorisation, interventions to be escalated, subgroup inclusion, software availability and performance evaluation.

Results
37 full text articles describing unique phase I designs were identified. Key design characteristics extracted from these papers were used to define a road map and design selection process for phase I radiotherapy-novel agent trials. Design selection is on the basis of: single or dual therapy dose escalation, dose limiting toxicity categorisation, maximum tolerated dose determination, subgroup evaluation, software availability and design performance. Fifteen of 37 designs were identified as being immediately accessible and relevant to radiotherapy-novel agent phase I trials. Applied examples of using the road map to identify novel statistical approaches will be presented.

Discussion
The road map enables researchers to make informed decisions relating to the choice of statistical design for phase I radiotherapy-novel agent combination trials. Developing these studies is intensive, highlighting the need for funding and statistical input early in trial development to ensure appropriate design and implementation from the outset. Specifically designed to be practically implemented, this road map has the potential to enhance design of such trials, optimize potential for trial funding, and promote efficient trial conduct, enabling a more efficient development pathway.

PS7C-03

Working under short timescales to deliver a national trial: a case study of the ComFluCOV trial from a statistician's perspective

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Introduction

In 2021 a vaccination strategy to manage the ongoing need for mass COVID-19 vaccination and predicted higher rates of seasonal influenza was urgently needed. Co-administration of COVID-19 and influenza vaccine could facilitate uptake of both vaccines and reduce the number of healthcare visits but data on safety and immunogenicity were lacking. We responded to a commission from Department of Health and Social Care (DHSC) to provide data on concomitant vaccination to inform autumn 2021 policy.

Methods

We used a novel approach to deliver the data in time for the influenza season;
two study statisticians, supervised by a senior statistician, worked together on statistical tasks including: advising on the study design, randomisation system, dataset and associated database specifications, and statistical analysis plan. Data collection was fully electronic. Automated data reports were prepared for the study team, sites and oversight committees; data were cleaned, interim and final analyses completed; and reports prepared for the DHSC and peer-review publication. Analyses were performed independently in parallel and results compared.

Results

Set-up was achieved in three weeks and 679 participants were recruited over 8 weeks. Automated reports included i) a twice-daily report of recruitment, adherence, and data quality, produced following each clinic session, to allow issues to be dealt with as soon as they arose and ii) a daily report of participant electronic 'symptom' diaries sent to sites to help identify any missed entries; these diaries provided primary outcome and adverse event data.
An interim analysis of validated data took place 7 days after 473 participants had completed the reactogenicity primary outcome to inform DHSC policy. Final datalock took place 6 weeks after the final participant follow-up and the definitive analyses were completed 3 weeks later. A pre-print publication was submitted within 14 days of the results being made available. The results of the trial were published 10 months after first discussions about the trial (Lazarus R et al. Lancet. 2021;398(10318):2277-87).

Discussion

Working in a new clinical area to tight timescales is challenging. Daily contact with the core team (trial managers and IT staff) was critical. Working together allowed reports to be prepared and checked in a timely manner; ensured coding errors were not missed, data were interpreted correctly, and the process was quality assured. Lessons learnt from this experience (e.g. two statisticians deriving and analysing outcomes, real-time quality assurance, monitoring and feedback to the trial teams) are being applied to other studies.

PS7C-04

Achieving consistency of results across statistical software packages for models with a random effect – why are our results not always replicable?

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Introduction
Validation of statistical programming guidelines recommends that results of statistical analyses are reproducible, and this is a common feature of MHRA inspections. Replicating the results of statistical analyses using independent programming by another statistician is a common approach to validation. This replication process is often referred to as double coding. Using the same dataset, and fitting ostensibly identical models, two independent statisticians may obtain different results if they use default settings in different statistical packages. The differences between results can be more pronounced when fitting more complex models that include a random effect. We examine the level of consistency across commonly used statistical software packages for statistical models and propose guidance to improve the consistency of double coding models including random effects.

Methods/Approach
We examine the output obtained from commonly used statistical software packages (SAS (v9.4), Stata (v16 and v17), and R (v4.0.2)) and their associated procedures (e.g. PROC GENMOD, GLM, PROC GLIMMIX, GLLAMM, GLMER, etc.). The range of analysis procedures examined include linear, log-binomial, and Poisson regression and the use of robust standard errors. We apply these analysis procedures to both binary and continuous outcomes from a range of recently published trials. We examine the impact of increasing the model complexity by moving from a simple model where treatment is the only covariate, to a model that includes a random effect, and finally a model that includes a random effect and one binary covariate as a fixed effect. Estimates of treatment effect, and associated standard errors and p-values will be produced and compared for all models. Estimates of the random effect and associated standard error will be produced for the models including random effects. The output obtained using the default model settings of each software package will be compared, and we will present options to improve the consistency of model output across different procedures.

Results Structure and Timelines
Results from these analyses will be available by August 2022.

Potential relevance and Impact
Replication of results via independent analysis is a common approach in statistical analysis Quality Control. Default settings in different statistical packages can lead to inconsistent model output, and therefore the failure to replicate results. We believe this work will raise awareness of inconsistency of output across a variety of statistical software packages and procedures.

PS7D-01

How effective and acceptable is digital, multimedia information when recruiting children and young people to trials?

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Background
The information provided to potential trial participants plays a crucial role in decision-making. Printed trial information sheets (PIS) have received recurrent criticism as too long and technical, unappealing, and hard to navigate. An alternative is to provide information through multimedia (text, animations, video, audio, diagrams and photos). However, there is limited evidence on its effects on recruitment rates, particularly in children and young people.

The study objectives were:
1. To develop template MMIs through participatory design, for use when recruiting CYP to trials.
2. To evaluate the MMIs in a series of SWATs, to test the effects on recruitment and retention rates, and participant decision-making, by comparing MMI provision instead of printed information, and comparing MMI provision in addition to printed information.

Design: Two-phase study in which the MMIs were:
- first developed through a qualitative study; user testing; readability metrics; and enhanced PPI.
- then evaluated in six UK SWATs, recruiting children and young people, and the data combined in prospective meta-analysis.

Interventions: MMIs (comprising text, audio, 'talking heads' video, trial-specific and trial-generic animations); Printed trial information sheets (PIS).

Outcome measures:
- primary: trial recruitment rate comparing MMI-only with PIS-only provision.
- secondary: trial recruitment rate comparing combined MMI & PIS with PIS-only provision; trial retention rate; quality of participant decision-making questionnaires.

Results
We generated two MMI templates: (i) for children aged 6-11; (ii) for children aged 12-18 and parents.
In the Phase 2 SWATs the MMIs improved trial recruitment, compared to PIS-only (OR=1.54; 95%CI 1.05, 2.28; p=0.03; I-squared=0%).
Combined MMI&PIS provision compared to PIS-only provision did not affect trial recruitment (OR=0.89; 95%CI 0.53, 1.50; p=0.67; I-squared=0%).
There were no effects on trial retention or participant decision-making quality.

Limitations
It was only possible to include data from three SWATs in the meta-analysis. Questionnaire return rates were low, reducing the strength of findings.

Conclusions

Use of multimedia information may increase the rate of recruitment to trials involving children and young people, but further evaluation is needed.

PS7D-02

Randomised study within a trial (SWAT) of an enhanced patient information leaflet for recruitment of participants into a clinical trial of breast cancer treatment.

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Introduction
POSNOC is a pragmatic, randomised, multicentre, non-inferiority trial comparing adjuvant therapy alone with adjuvant therapy plus axillary treatment for women with early-stage breast cancer and one or two sentinel node macrometastases (ISRCTN54765244; ClinicalTrials.gov NCT02401685).
The aim of this SWAT was to determine the effect of an enhanced patient information leaflet (PIL) on participant recruitment in the POSNOC trial.

Methods
The SWAT used a two arm, parallel group, cluster randomised design, with UK sites participating in POSNOC as the unit of allocation. Stratifying by recruitment in the previous 12 months (0, 1, 2, >2 participants) sites were randomly allocated to either continue using a standard PIL, or a PIL that additionally included a pictorial flow diagram representation of POSNOC, including randomisation, treatment in each of the two arms, and follow up. All women at a site who were identified as potentially eligible and were approached about the POSNOC trial were provided with the PIL as per SWAT allocation. Patients were also offered a patient information film or had access to one explaining the POSNOC study which contained diagrams and cartoons. The primary outcome was participant recruitment during the remainder of the host trial. We compared groups using analysis of covariance, adjusting for participant recruitment in 12 months prior to the SWAT, and time since site opening.

Results
The SWAT took place from 29 January 2020 until POSNOC recruitment was completed 13 July 2021. Eighty UK sites were included, 40 allocated to each arm, of which 23 (11 (28%) in enhanced PIL arm, 12 (30%) in standard PIL arm) did not recruit any participants. A total of 102 participants were recruited in sites in the enhanced PIL arm (mean=2.5), compared with 122 in the standard PIL arm (mean=3.0). There was no evidence of a between-group difference in recruitment (adjusted difference in mean in enhanced vs standard PIL = -0.58, 95% CI -1.87 to 0.70, p=0.38).

Interpretation
We found no evidence of effect on recruitment of adding a pictorial representation of the host trial to the patient information leaflet. However, the confidence limits do not exclude important potential effects in either direction, particularly for large trials such as POSNOC with many recruiting sites. These data may contribute to future systematic reviews of randomised studies of recruitment interventions.

PS7D-03

A SWAT to determine the impact of data collection frequency on participant retention in a trial with decentralised follow up: The HEAL COVID Trial

Professor Carrol Gamble[1], Dr Efstathia Gkioni[1], Mr Ashley Best[1], Dr Ashley Jones[1], Dr Elin Haf Davies[2], Dr Paul Wicks[3], Dr Mark Toshner[4], Prof Charlotte Summers[4], on behalf of the HEAL-COVID Collaborative HEAL-COVID Collaborative

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Introduction

HEAL-COVID is a randomised controlled trial that aims to identify treatments that may be beneficial for people discharged from hospital after recovering from COVID-19. HEAL-COVID was designed during the pandemic and aimed to reduce site burden by using a decentralised approach to follow up. HEAL-COVID outcomes require routine data and Patient Reported Outcomes (PROs). The primary mechanism for collecting PROs is via an app, with provision for telephone calls from a central team to accommodate participants unable to use this. A SWAT was designed to determine whether the frequency of PRO data collection impacted participant retention in the decentralised trial follow up.

Methods

Participants are randomised to their treatment intervention and then to whether their PROs would be collected weekly to week 4 and then monthly, or weekly to week 12 and then monthly. Duration of participant follow up is 12 months. A statistical analysis plan for the SWAT was developed prior to analysing data collected.

Results Structure and Timelines

Over 1,000 participants have been randomised to the HEAL-COVID SWAT. SWAT results will be presented on engagement and retention at 12 weeks after randomisation for PRO outcomes. Additional results will be presented on participant preference for PRO data collection methods and changes over time. The influence of being randomised to the no treatment arm on PRO collection and retention will also be presented. The impact of the SWAT on consequent changes to ongoing trial delivery will be shared.

Potential Relevance and Impact

The post pandemic environment has placed increased emphasis on conducting decentralised trials to minimise site burden. This means that trials need to be designed to allow evaluation of retention strategies within a decentralised environment. Given the additional emphasis on collecting outcomes via apps and other digital platforms, the development of an evidence base regarding participant engagement and retention is key to ensure the design of future trials can benefit from known advantages and disadvantages. HEAL-COVID provides results on frequency of data collection and participant retention and the acceptability of app collection when telephone calls are offered as an alternative.

PS7D-04

Developing principles for a more comprehensive, modernised approach to managing clinical trial participation changes through the UKCRC Registered CTU Network's PeRSEVERE project

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Introduction

In most clinical trials, some participants will stop or reduce their participation before it was originally due to end. Ethical and regulatory conventions address this possibility mainly through the well-established 'right to withdraw consent'. This typically follows the principle that participants may withdraw their consent at any time, without detriment to ongoing care or any need to provide justification. While essential in research ethics, this basic right does not fully address complexities such as how participation changes may vary in nature and extent, whose decision the changes are, and the limitations on types of changes in a given trial. Variation in understanding and implementing these nuances leads to untoward impacts on trial validity and participants' rights. The PeRSEVERE project (PRincipleS for handling end-of-participation EVEnts in clinical trials REsearch) is a collaborative UKCRC Registered CTU Network initiative, aiming to develop high-level principles to guide how clinical trials are set-up and conducted in light of these complexities.

Methods

We developed the PeRSEVERE principles through discussion and debate within a large, multidisciplinary collaboration, including various research professionals and patient contributors. We built on existing principles of ethical research conduct, our knowledge of existing research regulations and our collective experience of involvement in clinical trials. We took an inclusive approach to principle development, incorporating all new ideas as long as they were within our scope. We agreed the final content through informal consensus. Our draft principles were then scrutinised through a public consultation, focussing on the principles' clarity, feasibility, novelty and acceptability. We used pre-defined rules to guide how the feedback should be used.

Results

Our final, comprehensive set of guiding principles aims to exhaustively address all areas of clinical trial conduct, with overarching principles to support more detailed recommendations. In total, 281 people from 9 countries took part in the consultation exercise. Feedback showed strong support for the principles with nearly 90% of respondents agreeing that all the principles were already clear and acceptable. Comments provided were nonetheless used to enhance the final principles and associated guidance.

Discussion

There remains a need to extend existing regulatory and ethical guidance to address the real-world complexity of clinical trial participation changes. The PeRSEVERE principles, and the process used to develop them, provide a comprehensive and legitimate grounding, pointing the way towards improved, standardised approaches. In the presentation, we will give an overview of the principle set and explore priorities for further work.

PS8A-01

What are the re-identification risk scores of publicly available anonymised clinical trial datasets?

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Introduction
There are increasing incentives for anonymised datasets from clinical trials to be shared across the scientific community. Some anonymised datasets are now publicly available for secondary research. However, we do not know if they pose a privacy risk to the involved patients. We aimed to collect a broad sample of publicly available anonymised clinical trial datasets in order to calculate their re-identification risk scores using El-Emam's[1] three derived risk metrics (equations) under the prosecutor and the journalist scenarios. These equations calculate the re-identification risk scores for an entire anonymised dataset, using information in the anonymised dataset. These equations only generate numbers, and they do not aim to actually re-identify individuals in the datasets

Methods
Step 1.- We have located 16 data repositories and drawn a random sample of up to 5 datasets from each repository.
Step 2.- We have contacted the data repositories and requested access to their anonymised datasets following the data holders' local procedures.
Step 3.- We will identify the number of indirect identifiers present in each of the datasets as described by Hrynaszkiewicz et al. [2].
Step 4.- Re-identification risk scores will be calculated for each dataset.
Step 5.- We will investigate what characteristics of the datasets are associated with increased or decreased risk scores, compare the risk score features, their usability, and discuss our findings.

Results Structure and timelines
We have collected 44 datasets from 10 different data repositories and we are planning to complete their analysis by the end of August 2022. We also are in the last stage (signature of data user agreements) to obtain a further 25 datasets from the 6 other data repositories.

Potential Relevance and Impact
To our knowledge, there are no studies directly using the proposed methods of calculating the re-identification risk scores across a range of publicly available clinical trial datasets. Therefore the results of this study could help improve the current methods used for de-identification/anonymisation of clinical trial datasets.

Funding
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PS8A-02

Developing a prototype tool to aid mapping trial data to CDISC standards for Data Sharing

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Introduction
CDISC stands for "Clinical Data Interchange Standards Consortium" and is commonly used to refer to a set of data standards primarily used in the pharmaceutical industry. CDISC Provides a standardised way of presenting clinical trial data and Harmonisation for data sharing.
A key dataset definition provided by Clinical Data Interchange Standards Consortium (CDISC) is the Study Data Tabulation Model (SDTM).
Mapping existing clinical trial data from sources not designed for SDTM from the outset to the SDTM standard is achievable but can be resource intensive. The aim of the project was to create a prototype software that would assist in the mapping of existing clinical trial data to the SDTM standard.

Methods
This project provides an early-stage prototype software that guides the flow and provides functionality to aid in the processes of mapping an existing clinical trial dataset not designed for SDTM into a SDTM standard dataset.
It was envisioned at the outset that the prototype software would be able to use text matching functionality to provide quality recommendations for mappings greatly reducing the time taken to identify suitable mappings for data.

Results
Our prototype software provides an experience that does help guide users along the process of mapping a dataset from a data dictionary to an SDTM format.
However, the desired gains in automation from mapping fields in the data dictionary to SDTM items automatically proved much more difficult than expected.

Discussion
Ultimately it would be beneficial for data capture tools to be built with consideration of SDTM from the outset and therefore avoid the need for mapping activities after the fact.
The uptake of SDTM within academic clinical trial units is low and a considerable barrier is familiarity with the standards and cost of training. Mapping allows development of familiarity in a less pressured timeframe than that experienced during trial setup.
Our prototype demonstrates a mechanism for supporting the conversion of existing dataset to SDTM. The prototype needs to be extended across SDTM domains and piloted. Further work is needed to demonstrate to CDISC how this may support their ambitions within academic clinical trial units. Additional work on automation would increase efficiency however the mapping process itself benefits those unfamiliar with the SDTM requirements.

PS8A-03

Generating High-Utility Synthetic Clinical Trial Data Using Non-Parametric Data-Augmented Multiple Imputation

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Introduction
Generating and releasing synthetic clinical trial datasets allows researchers to replicate or reanalyse published studies whilst protecting trial participants from the disclosure of their sensitive information. However, because clinical trial datasets often have complex structures and limited sample sizes, the potential information loss from data synthesis tends to be great, which may make the analysis given by the synthetic datasets substantially different from those achieved using the original datasets. To improve the usefulness of synthetic datasets for statistical replication and reanalysis, a novel framework, Data-Augmented Multiple Imputation (DA-MI), has been developed. However, DA-MI can only be used in parametric settings, while non-parametric synthesis methods may have better performance at capturing the complex nonlinear relationships between the clinical variables. Thus, we extend the original DA-MI framework to include non-parametric methods and allow us to synthesize complex datasets from a clinical trial.

Methods
Traditionally, synthetic data has been generated by first fitting regression models to the original data and then simulating samples from these fitted models to create synthetic data. The DA-MI approach improves accuracy by generating some `noisy observations' of the original data and uses these `noisy observations' and the original data to fit regression models. However, the DA-MI method can currently only use parametric regression methods. To allow the use of non-parametric regression models, we adapt the DA-MI methodology by simulating synthetic data using Sampling Importance Resampling algorithm. This is also more computationally efficient than Monte Carlo Markov Chain algorithm proposed for the previous DA-MI approach. Furthermore, we extend the DA-MI approach to preserve the missingness structure in the original data. We implement a non-parametric DA-MI method, Data-Augmented Categorical and Regression Tree (DA-CART), and use it to generate synthetic data for the Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST). The usefulness and disclosure risk of sensitive information due to the release of synthetic CanBEST datasets are measured by utility and disclosure risk metrics respectively.

Results
Compared to conventional synthesis methods, the synthetic CanBEST datasets generated by DA-CART have a higher utility with a moderate increase in the disclosure risk of sensitive information. The utility is similar to that obtained with parametric DA-MI but using flexible non-parametric regression.

Conclusions
Our DA-CART method can generate high-utility synthetic trial datasets with acceptable disclosure risk. DA-CART method can be implemented within standard software for synthetic data generation, facilitating the

dissemination of trial evidence and encouraging the republication and reanalysis of the published clinical trials.

PS8A-04

The End of Clinical Trials As We Know Them? The Role of In Silico Modelling in Surgical Trials

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Introduction
In Silico Clinical Trial (ISCT) are defined as 'the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/medical intervention'. ISCT modelling is reported in the regulatory evaluation of biomedical products specifically vaccine therapies. FDA have guidance for computational modelling in medical device submissions.

Methods
To provide a framework for ISCT research and assess opportunities in prospective surgical trials research, acknowledging requirements to simulate effects that are realistic, plausible and accurate at the individual level.

Results
Our framework consists of three ISCT classifications:
1. Virtual Systems Simulations: computational models of anatomy or physiology to simulate known biological systems, making explicit (mechanistic) or data-driven (phenomenological) assumptions on causal biological-interventional relationships with outcomes. In intervention development, simulations could explore opportunities to optimise patient selection to individualised interventions, could assist in refining enrolment criteria for trials and could overcome design constraints of conventional trials (e.g. blinding). An understanding of background biology is required.
2. Virtual Subject-Specific Interventions: builds on individualised computer modelling combining imaging and device sensing technologies to derive markers not directly measurable, simulating patient level biological variability. This could be used to track biological systems to personalise device intervention development and has potential in refining and optimising device design. In this classification it is essential to explicitly model uncertainty, establish variability, safety and reproducibility.
3. Virtual Patient Populations: generative models simulating virtual patients with specified characteristics (and known variability) and augmenting them with real clinical trial patients to predict treatment outcomes. This may aid early phase research identifying potential interventions to take forward to conventional later phase trials; optimise interventions to sub-populations; inform adaptive designs; mimic rare disease populations. These simulations require an existing cohort of evidence; modelling assumptions may not be realised and models may be over simplified.

Discussion
Adoption of ISCT in surgical research is limited. Clinical trials conclude safety and efficacy but can be limited in explaining why interventions fail. ISCTs could provide insights into the impact of surgical / device modifications on outcomes. ISCTs could have an early phase intervention development role in informing, de-risking and complementing late phase clinical trials.
Prospective, pragmatic clinical trial evaluations designed in context, addressing uncertainty and patient diversity, are still required to change standard clinical practice. Clinical trialists should embrace the

opportunities that ISCT simulation and modelling brings, recognising this is not the end of clinical trials as we know them.

PS8A-05

Developing and evaluating a tool for detecting problematic RCTs in health systematic reviews

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Introduction (covering aims/objectives/settings)
Systematic reviews of health interventions synthesise evidence from all RCTs published on a given topic. They are frequently influential, and are included in clinical guidelines. Unfortunately, it is now clear that some RCTs included in systematic reviews are actually fabricated, with ivermectin for treatment of COVID-19 providing a recent example. However, there are no established ways for systematic review authors to identify these problematic trials, and usually no checks are done at all.

Methods/Approach
We are developing a tool for detecting problematic RCTs in health systematic reviews. We are assembling a long list of items which could be included in a checklist to be applied when undertaking a systematic review. Each of these items will be applied to a large sample of systematic reviews to obtain evidence of their feasibility and impact on review results and conclusions. They will simultaneously be entered into a Delphi process including relevant stakeholders (methodologists, systematic reviewers, editors, publishing professionals) to establish which items are backed by expert opinion. A consensus meeting will be held, and participants will be presented with results of both the application to systematic reviews and Delphi survey. This meeting will be used to agree on the items to be included in the tool. We will then prospectively test the tool in the production of new reviews, and will gather user feedback in order to make amendments.

Results Structure and Timelines (what form would the results takes)
We will present an overview of the project, deliver interim results, and provide information about how to participate in the development of the tool.

Potential Relevance and Impact
A tool for detecting problematic RCTs in the production of systematic reviews of interventions, backed by empirical evidence of feasibility and impact, as well as expert consensus, will be developed. This will prevent these trials from contributing to the conclusions of systematic reviews, which would otherwise serve as a platform for fabricated data to influence patient care.

PS8B-01

Perceptions of need and the decision to participate: a qualitative investigation of the experiences and perspectives of patients asked to take part in 3 RCTs

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Introduction

Recruitment to randomised controlled trials (RCTs) is known to be challenging. Several studies have examined patients' and recruiters' perspectives of recruitment, and how communication plays out during the recruitment encounter. The interplay between what recruiters communicate and how patients interpret and use this information is less well understood. This study aimed to address this evidence gap by linking audio-recorded recruitment consultations with interviews from patients approached to take part in 3 'case study' RCTs.

Methods

42 interviews were conducted with 41 patients, all who gave informed consent. Patients were purposively sampled and recruited for this qualitative study from three secondary care RCTs (one renal, one oncology based and one surgical trial) which were all anticipated to have recruitment challenges from the outset. 20 patients had declined and 21 had agreed to RCT participation. Where possible, (17 patients) interviews were analysed alongside audio-recordings of recruitment consultations. Interviews were analysed thematically, using the constant comparison approach.

Results

Across the RCTs, consultation audio-recordings revealed that although healthcare professionals (HCPs) tended to express uncertainty in patient consultations, this was often undermined through suggestions that patients may benefit from one treatment pathway or another. Interviews suggested that throughout their pathway patients perceived that they had been offered treatment recommendations, and often did not recognise that there was uncertainty as to which treatment option was best. Instead, patients framed their decisions about RCT participation around perceptions of treatment necessity, with clear indications that these perceptions were shaped by discussions with HCPs. Many of those who rejected randomisation did so because they felt it could prevent them from receiving treatment they needed, or expose them to treatment that was unnecessary for them. Conversely, many of those consenting to the RCTs believed participation offered the opportunity to receive a treatment that would be beneficial, or even necessary. These perceptions were established based on conversations with HCPs across their pathways, included those recorded.

Discussion

Throughout their pathway, patients often constructed perceptions of needing or benefitting from specific treatments. Perceptions of need were often shaped by HCPs that patients encountered, many of whom did not consistently convey uncertainty. These findings indicate further work is required to integrate RCTs into

standard care and improve how all HCPs, not just recruiters, communicate uncertainty to patients. It also highlights opportunities for future recruitment interventions to support both recruiting and non-recruiting HCPS throughout a patient's clinical pathway.

PS8B-02

Co-produced resources to support patient and public involvement in developing core outcome sets – an e-toolkit and animation

Ms Heather Barrington[1], Dr. Nicola Louise Harman[1], Mr John Turner MBE[4], Mrs Maureen Smith[5], Mrs Deborah Morris[4], Professor Christopher Morris[2], Dr Adele Jayne Horobin[3], Dr Sarah Louise Gorst[1], Professor Paula Ruth Williamson[1], Professor Bridget Young[1]

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Introduction

This work links to the international Core Outcome Measures in Effectiveness Trials (COMET) Initiative. Core Outcome Sets (COS) can reduce research waste by promoting consistency in outcome reporting. Over 400 COS have been published; another 300 COS are in development. COS should be relevant to all research stakeholders, including patients, carers and the public. Patient and Public Involvement (PPI) in COS research helps to ensure that COS studies are accessible and acceptable to all stakeholders, but PPI in COS studies is not undertaken consistently, is often of limited scope, and its impact is rarely documented. This may partly reflect a lack of tools and training for COS teams. We aim to address this gap in resources using a COS specific PPI toolkit that will help COS developers to consider the range of ways that PPI could help in their study and provide practical support on how to achieve this.

Method

The toolkit has been co-created with patient research partners. It is designed to follow the timeline of a COS study. COS developers are provided with questions to consider with their public research partners at each stage. Specifically designed PPI resources at key COS development stages are included and we provide links to relevant resources from other organisations. The toolkit also includes a template for documenting PPI activity and impacts throughout the study.

Reflection on the tools required for effective PPI in COS has also identified the need for other resources. COMET has addressed one of these by working with public research partners to -co-produce an animation explaining PPI in COS and the range of ways to achieve PPI.

Results structure and timeline

The PPI in COS animation is available on the COMET website. It has been promoted in the COMET Initiative newsletter and through social media. Development of the PPI in COS toolkit is underway and will be available in Summer 2022. The animation will be presented and the toolkit showcased.

Relevance and impact

The toolkit and associated resources, including the animation, will be highlighted in the next revision of the COMET Handbook - a key resource for COS developers. By providing a PPI reporting and impact tool it is envisaged that COS developers will begin publishing about their PPI, which will further inform the work of future COS developers.

PS8B-03

Patient and public involvement prior to trial initiation: lessons learnt for rapid partnership in the COVID-19 era

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Introduction
Clinical trials have and continue to play a critical role in the global public health response to the COVID-19 pandemic. Despite the increasing recognition of the value of Patient and Public Involvement (PPI) in clinical trials, just 22% of the COVID-19 research proposals reviewed by Research Ethics Committees in the UK at the start of the pandemic reported PPI. There is a perception that PPI might result in delays in delivering research and therefore delays in obtaining important results. Here we report our experience of rapid PPI for a COVID-19 clinical trial.

Methods
RAPID-19 is a COVID-19 clinical trial which was planned to be submitted for fast-track ethics review in the United Kingdom. During the development of the trial protocol, the PPI Panel at the London School of Hygiene & Tropical Medicine Clinical Trials Unit was involved in the design of the study. The meeting with the PPI Panel lasted just over 1 h and was conducted by teleconference.

Results
Although we only had a short period of time to explore the study with the PPI Panel, we were able to gain valuable insight into how the trial would be perceived by potential trial participants. Substantive changes were made to the trial to improve the acceptability of the research without compromising the study timelines. Having access to public contributors with relevant lived experience is an important resource for a Clinical Trials Unit and is critical for rapid PPI. The move to remote working due to lockdown required virtual discussions which helped to overcome some of the barriers to organising face-to-face meetings at short notice.

Discussion
PPI for clinical trials can be conducted in a time-efficient manner within the pressured environment of a pandemic. Involving PPI contributors at an early stage in protocol development maximised the opportunity to shape and influence the trial as well as limited potential delays which could occur if changes to the protocol had to be made at a later stage.

PS8B-04

Patient and public involvement in numerical aspects of trials (PoINT): exploring patient and public partners' experiences and identifying stakeholder priorities

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Introduction
Patient and public involvement (PPI) is increasingly common in trials, but its quality remains variable in a lot of settings. Many key decisions in trials involve numbers, but patients are rarely involved in those discussions. We aimed to understand patient and public partners' experiences and opinions regarding their involvement in numerical aspects of research; and discuss and identify priorities, according to multiple stakeholders, around the most important numerical aspects in trials to involve patients and the public in.

Methods
The study had two stages: 1) Online focus groups with patient and public partners recruited via online platforms and analysed using inductive thematic analysis; 2) Online priority setting meeting with UK and Ireland based stakeholders and following James Lind Alliance methodology. Pre-selected numerical aspects were introduced prior to the meeting and discussed and prioritised based on a voting system.

Results
In Stage 1, we held two focus groups with patient and public partners (n=9). We identified four themes in the analysis: "Determinants of PPI in numerical aspects", "Identity and roles", "Impact of involving patients and the public in numerical aspects". Public partners believed being involved in numerical aspects of research is important and should be facilitated, but communication about these aspects needs to be clearer. An environment and relationship with researchers that facilitates that will include time for discussion; support to improve knowledge and confidence; clear language and definitions; trust. Public partners perceive their role as bringing an outsider perspective and were mainly interested in involvement in assumptions and dissemination of quantitative research. They believed this can lead to more transparency and improve their experience. In Stage 2, we identified twelve numerical aspects of trials to be prioritised. We held a priority setting meeting with 14 stakeholders, which led to the selection of three priority numerical aspects in patient and public involvement: target differences, interpretation of results, cost-effectiveness.

Discussion
This is the first research project taking a participatory, multi-stakeholder approach to explore PPI in key (numerical) aspects of trial design, conduct, and dissemination. We found public partners and researchers believe PPI in numerical aspects is important, and it has potential to make trials more relevant, and transparent contributing to reduce research waste. We provide a platform for future efforts to improve patient and public involvement in trials and a prioritised set of future research foci.

PS8B-05

Would you be happy to be contacted about research?

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Introduction
Recruitment of research participants from primary care has been notoriously challenging. Although, a recent NIHR survey conducted in 2021 indicted a positive increase in the public's attitude to health research. Since the pandemic, the way in which heath research is now delivered, has also changed. Patient-centred research, enabled by digital tools, is part of a vision set out by the government (2021), 'The Future of UK Clinical Research Delivery'. A brief research study to investigate the use of SMS to invite research participation was initiated by Keele CTU.

Method
A randomised study (The Who) examined the utility of a text message (SMS), sent from participating General Practices (GPs), to collect brief research data. People registered with participating GPs, ≥18 years, with a recorded mobile phone number, were sent a SMS containing a link URL to an online questionnaire. 18 GPs were stratified by list size and deprivation, then allocated to two groups (A&B). GPs in Group A sent eligible people a pre-notification SMS informing of their imminent invitation to participate in The Who. Two days later, the GPs sent the SMS invitation. GPs in Group B sent eligible people an SMS inviting them to participate in The Who. All GPs sent a reminder SMS 7 days later.
In 2019, Keele University undertook a research study (Automated Check-in Data Collection (AC DC) Study) which found that 47% of primary care consulters would be happy to be contacted by their general practice, about research of relevance to them. The same research question was asked again in this study, "Would you be happy for [PRACTICE] to contact you about any future research studies which are relevant to your health, to improve care for patients in the NHS?"

Results
Whilst data collected is currently in analysis, early findings show an approximate 15% response rate and with little variation by Group A and B GPs. Almost 90% of people indicated a willingness to be contacted by their GP about any future research studies of relevance to them.

Discussion
Response rates to SMS invitations to participate in research, capture data quickly and efficiently, potentially without need of any pre-notification. However, low response rates may result in response bias. Whilst the mode of asking the same research question may not be comparable, the results of The Who potentially concur, that since the pandemic, there has been a positive increase in the public's attitude to health research.

PS8C-01

Agreement and completeness of routine versus trial-specific patient outcome data : a systematic review

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There is growing interest in enhancing the conduct of randomised controlled trials (RCTs) by using routinely-collected healthcare data (RCHD). However, few studies have formally compared the suitability of these healthcare systems datasets, collected through interactions between patient and the health service. This review identified studies that compared RCHD to trial-specific data collection to assess the quality, challenges, and suitability for use by trialists. It provides an overview of the outcomes that have been investigated and the conclusions drawn whilst identifying key gaps in the evidence.

The review searched MEDLINE and EMBASE for papers published between January 2017 – April 2021. The search strategy follows on a previous unpublished review by G. Powell (University of Liverpool). A manual search was also performed in conference proceedings of the International Clinical Trials Methodology Conference and Society for Clinical Trials. A study was considered eligible if at least one routine data source (e.g. hospital episode statistics (HES) or data from a national data provider) was compared to trial-specific data collection in the UK. The review protocol was prospectively registered on PROSPERO (CRD42020186048).

1977 records were identified of which 1945 were excluded on title and abstract screening. Of 32 papers considered in more detail for eligibility, 26 papers were excluded. The 6 eligible papers represent 6 studies that compared RCHD between 2002-2015 to trial-specific data. Data assessments varied from comparing outcomes of interest to trialists, such as incidence of hospital admission and overall survival, with comparisons of clinical characteristics. Authors' methods used to assess agreement varied, with half the studies using Kappa statistics and the remainder using a combination of frequency, proportions, sensitivity, and specificity. Two studies assessed death data: one reported no evidence of a difference in 5-year and 8-year survival rates and the other reported substantial agreement however, highlighted some disagreement of confirmed deaths between both sources. Two studies assessed hospital admission: one reported better sensitivity and specificity of HES compared to a reference and the other reported an underestimation of events by HES.

Surprisingly, few studies have presented formal assessment of the relationship between trial-specific data collection and RCHD. Recent publications represent older assessments with limited recent evidence of the suitability of current RCHD that are available through national data providers like NHS Digital. This highlights the need of carrying out these data assessments within ongoing clinical trials to map the potential of RCHD and utilise effectively in clinical trials.

PS8C-02

Leveraging Real-World Data for Time-to-Event Endpoints in Clinical Trials

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Introduction
Use of Real-World Data (RWD) to augment evidence in clinical trials is often constrained by the type of endpoints considered. Particular limitations arise for Time-to-Event (TTE) endpoints where there are differences in missing events between trial data and RWD, definition of "time zero", reporting bias, immortal time bias, among others. This research focuses on the problems of differences compared to trial data in missing events and time zero in RWD, reviews current methods to address these challenges, and makes recommendations.

Methods
Absence of events of interest versus missing events require careful evaluation depending on whether we are working with clinical trial data or RWD; appropriate management of (structured) missing events is needed in a real-world context. Uncertainty in defining time zero arises when it is unclear whether baseline of therapy initiation is the same for subjects in the clinical trial versus those in RWD, especially the control arm; or when working with two comparator groups in a RWD setting. Not knowing the common baseline makes comparison of events difficult, and subsequent results less reliable.

Results and Discussion
Drawing upon experience of TTE endpoints across therapeutic areas, we (Methodology Team of PSI Special Interest Group on Real-World Data) propose recommendations to mitigate the (structured) missing events in RWD by leveraging on 'softer' endpoints (e.g. time to treatment change / escalation / discontinuation), and for the "time-zero" uncertainty, allowing 'multiple' baseline within patients, adjusting for patients' differences (e.g. propensity matching, IPTW). Examples of applications in different therapeutic areas / diseases (e.g. multiple sclerosis, respiratory, infectious diseases, atopic dermatitis, oncology) are provided. Furthermore, experiences from a CPRD-HES linked study are described, and practical issues needing consideration while emulating a target trial highlighted.

PS8C-03

Development of routine data based heart failure outcome ascertainment methods and application to the ASCEND trial

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Introduction

Heart failure (HF) is an important cause of morbidity and mortality. Ascertainment of HF hospitalisations in trials involves identifying potential events, gathering supporting evidence and clinical adjudication. Using routinely collected healthcare data (RCD) may reduce the cost and complexity of this process. A systematic review showed that RCD algorithms for acute HF outcomes have high specificity but lack sensitivity, missing around a third of events. We used a broad list of HF diagnostic codes, combined with a clinician review of the RCD record to reduce false positives, using data from two large randomised trials.

Methods

Potential HF events were identified among SHARP (Study of Heart and Renal Protection) and ASCEND (A Study of Cardiovascular Events in Diabetes) participants with linked RCD, using relevant diagnostic codes, or a study-reported HF event in the trial follow-up. A method involving clinician review of RCD records was developed in SHARP.

A further refined RCD adjudication process was applied to ASCEND. The outcome assessed was hospitalisation where HF was the primary reason for admission or a significant complication prolonging it. ASCEND HF events were adjudicated using clinical documents obtained from primary care physicians (clinical adjudication) where possible, and through clinician review of the RCD record (RCD adjudication). The diagnostic accuracy of outcomes ascertained using RCD-reporting, study-reporting, or both, with and without RCD adjudication, was compared to gold standard (GS) clinically adjudicated study reported outcomes in SHARP. In ASCEND, the GS includes both study and RCD reported events which have undergone clinical adjudication.

Results

1574 participants had data linkage in SHARP. 38/50 participants with study reported events were clinically adjudicated as a HF hospitalisation (GS). 79/154 participants with RCD reported events were RCD adjudicated as definite or possible HF. The sensitivity of RCD-reporting and RCD adjudication (both sources) was 76.3% (95% confidence interval [CI] 59.8-88.6) and 60.5% (95% CI 43.4-76) respectively, while specificity was 91.9% (95% CI; 90.4-93.2) and 96.4% (95% CI; 95.3-97.2) respectively. Results of a similar process in ASCEND including >200 study reported and >1800 RCD reported events in 928 participants will be presented.

Discussion

RCD-based HF outcome ascertainment has moderate sensitivity and high specificity in a trial population with chronic kidney disease. The utility of this process in a trial population with diabetes will be presented. Broadening the diagnostic codes used to capture HF and using RCD-based adjudication may provide an ascertainment method suitable for streamlined studies.

PS8C-04

Can we use routinely collected data for trial outcomes? Benefits, challenges and recommendations- a case study using the ISCOMAT cluster randomised trial among heart-failure patients

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Introduction

Routinely collected data (RCD) are increasingly being used in randomised controlled trials due to their potential for improving trial conduct and reducing costs. RCD can be used to underpin trial design, identify participants for trial recruitment, and support participant follow-up (data collection and outcome assessment). Despite obvious appeal and advantages, there remain: concerns around data validity and accuracy; difficulties identifying, accessing, and extracting relevant data. Concerns can vary depending on the source and type of RCD, and the purpose and manner of their use within a trial.

ISCOMAT, a cluster randomised trial, evaluates a complex intervention to improve the safety and continuity of medicines management at NHS care transition in 1641 heart failure patients recruited from 43 cardiology services. The primary outcome (binary composite endpoint of all-cause mortality and heart failure-related hospitalisation) and key secondary outcome (prescribed at least one cardiovascular recommended medicine) are derived from RCD at 12 months post-hospital discharge.

Methods/Approach

The primary outcome will be derived via NHS Digital using: mortality data, obtained from the Civil Registrations (Deaths) Secondary Care Cut (ONS); and hospitalisation data from Hospital Episode Statistics (HES) admitted patient care (APC) dataset. Medicines Dispensed in Primary Care (NHSBSA), now available via NHS Digital, will be used to derive the key secondary outcome, with ISCOMAT one of the first trials to use this data source for deriving trial outcomes.

Results Structure and Timelines

Follow-up is complete and analysis is ongoing. We will report on our experience of these RCD to derive our trial outcomes: including benefits, challenges, and methodological considerations. Specifically, we consider: data linkage; data quality and completeness; opportunities for addressing missing data in the main RCT; comparisons with patient reported outcomes; the level of data used for analysis; rules for generating spells and complete inpatient spells; determining admission type and reason; measuring costs for economic evaluation and the benefits and limitations of the prescription/dispensing data.

Potential Relevance and Impact

Whilst it is feasible to obtain NHS Digital data to support data collection and outcome assessment, considerable time is required to access the data, understand the data, and derive the outcomes. The latter requires multidisciplinary input: clinical, statistical, health economics and pharmacological. We report the unique characteristics of RCD and address its problems to increase transparency and facilitate further learning from trials that have used routine data.

PS8C-05

Use of routine healthcare data in randomised implementation trials: a methodological systematic review

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Introduction

Routine healthcare data are increasingly used in randomised controlled trials evaluating health interventions in participant identification, outcome assessment and intervention delivery. Some trials that evaluate the effect of strategies designed to improve the uptake of evidence-based practice are referred to as implementation trials. However, little is known about how routine healthcare data have been used in randomised implementation trials. This review aims to describe the methodological characteristics, reported rationales, barriers and facilitators of randomised implementation trials conducted using routine data.

Methods

We searched MEDLINE (Ovid), Cochrane Methodology Registry and Cochrane Central Register of Controlled Trials from Jan 2000 to Dec 2021, and manually searched protocols from trial registers. We included implementation trials and type II and type III hybrid effectiveness-implementation trials conducted using routine healthcare data. We extracted quantitative and qualitative data and performed a narrative synthesis to summarise the findings.

Results

We included 80 implementation trials, the majority of which were cluster designs (53.8%), conducted in North America (63.8%) and in primary care settings (81.3%). Multicomponent implementation strategies were commonly evaluated (70.0%), as opposed to single strategies. The most frequently implemented evidence-based interventions were clinical guidelines (22.5%). Most trials assessed adoption as the implementation outcome (65.0%). The majority of trials used data from electronic health records (EHRs) (62.5%), routine data were predominantly used in a combination of participant identification, intervention delivery and outcome assessment (58.8%). More than half of the trials specified the name of databases (61.3%), and few trials performed data linkage (16.3%). Seven themes of reported rationales for using routine data were offering validation of results, increasing efficiency, assessing outcomes, reducing research burden, improving quality of care, identifying study samples, and assessing representativeness. Four themes of barriers and facilitators were data quality, EHR systems, research governance and external factors.

Discussion

Identifying the implementation trials was difficult due to poor trial reporting. Further work is required to enhance the adoption of and adherence to existing guidelines on designing and reporting implementation studies. Additional work is needed to harmonise the language used in describing implementation strategies and implementation outcomes. Routine healthcare data are promising in supporting the implementation of evidence-based interventions. Particularly, data derived from EHRs have been widely used for participant identification, outcome assessment and intervention delivery. However, barriers exist that prevent routine data from achieving its full potential. Future research should focus on improving research governance, data quality and data delivery and optimising healthcare data systems.

PS8D - Spotlight Session: HRB TMRN, Public communication about randomised trials

Public communication about randomised trials

Sandra Galvin[1], Simone Lepage[1], Tom Conway[1], Sinéad Hynes[1], Declan Devane[1]
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Background
These are exciting and challenging times for clinical trials. The number and variety of treatments continue to grow, increasing pressures on researchers to determine how these compare to current treatments while rising costs and regulation can make trials expensive and complex. However, as pressure on resources grows, there is more demand for reliable and robust evidence on the benefits, harms and costs of health care so that people can make informed choices.

Alongside this, there is wider recognition of the importance of involving service users, practitioners, policymakers, and the public in health and social care decisions and the prioritisation of research. The need for and importance of patient and public involvement in health (and social) care research is now well established across many jurisdictions, and there is an increasing evidence base supporting its value. However, evidence suggests that the general public understanding of clinical research is limited.

Aim
This workshop will share examples of initiatives that seek to increase public understanding of and involvement in randomised trials and why they matter. This will include examples of completed and ongoing initiatives.

Session 1: *Schools Teaching Awareness of Randomised Trials (START)*
Sandra Galvin
START is an outreach initiative that invites primary school children (8-12 years old) (and their teachers) to design, conduct, analyse and report their 'very own randomised trial'. START encourages primary school children to think critically about science and the world around them. START has been recognised by primary school teachers as a "unique teaching tool" and by children as a 'fun way to learn about science.

Session 2: *The People's Trial*
Declan Devane
The *People's Trial* aimed to help the public learn about randomised trials, understand why they matter and be better equipped to think critically about health claims. *The People's Trial* embraced the concept of 'learning by doing'. It sought to enhance understanding of randomised trials by facilitating the involvement of the public in the trial research process from question identification and prioritisation to helping decide how the findings of the trial would be shared.

Session 3: *The Kid's Trial*
Simone LePage
We are currently developing *The Kid's Trial.* The Kid's Trial aims to create an online randomised controlled trial with children as the co-creators and participants. Although building from the work of The People's Trial, The Kid's Trial has some unique challenges. Engagement and recruitment of children into trials, and an online trial in particular, poses its own practical and ethical challenges. In this presentation, we will highlight some of the critical factors in the planning and design of the trial.

Session 4: *The COB-MS feasibility trial*
Sinéad Hynes
As part of a feasibility trial of cognitive rehabilitation for people with multiple sclerosis (the COB-MS), we conducted a study within a trial (SWAT) focused on the impact of patient involvement in recruitment. We compared

recruitment material (participant information sheets) created by an embedded patient researcher (a person living with MS) with those created by an experienced researcher. The SWAT looked at the effects on recruitment, retention, and understanding. The presentation will report on the key findings and lessons learned from the SWAT.

PS9A-01

An innovative design tool for clinical trials with continuous monitoring of efficacy outcomes in rare diseases: efficacy transition pathways

Ms Laura Kirton[1], Dr Matthew Murray[2,3], Dr John Apps[1], Mrs Anna Lawson[1], Prof Andrew Peet[1], Prof Theodoros N. Arvanitis[4], Dr Lorna Fern[5], Dr Dipayan Mitra[6], Prof Nicholas Coleman[2], Dr Thankamma Ajithkumar[3], Dr Brigitte Bison[7], Prof Gareth Veal[8], Prof Daniel Stark[9], Prof Giovanni Morana[10], Dr James Nicholson[2,3], Prof Lucinda Billingham[1]

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Clinical trials in rare diseases generally recruit slowly providing an opportunity for continuous monitoring of an efficacy outcome, minimising the number of patients exposed to a potentially ineffective treatment. The efficacy transition pathways (ETP) is an innovative visual tool introduced to aid determination of trial design parameters, and is an extension of the dose transition pathways (DTP) concept, introduced for dose-finding trials by Yap and colleagues (Clinical Cancer Research 2017). Here we demonstrate the practicality of ETP in designing the MonoGerm trial, a proof-of-principal, phase II trial with a Bayesian design.

MonoGerm is a de-escalation trial for patients with intracranial germinoma cell tumours. The current standard-of-care (SOC) for these patients is highly toxic multi-agent chemotherapy followed by potentially curative radiotherapy. The aim of the trial is to evaluate single-agents (monotherapies) as alternative treatments to SOC to reduce toxicity, such that complete response (CR) rate is non-inferior to SOC. Not observing a response to monotherapy within an acceptable timeframe may necessitate delivery of SOC as rescue medication and jeopardise the curative ability of radiotherapy. Thus, continuous monitoring of efficacy of such monotherapies with built-in stopping rules will prevent unnecessary harm to this predominantly paediatric population.

The trial includes two monotherapies, and each single arm will recruit six cohorts of three patients, with an interim assessment after each recruited cohort and final analysis at 18. Posterior probability distributions will be generated using a beta-binomial conjugate analysis, combining the observed trial data as realisations from a binomial distribution with a minimally informative Beta(1,1) prior. Decision criteria to allow early stopping at interim analyses and go/no-go decisions at final analysis are based on probabilities from these posterior distributions.

ETP visually maps out the parameters used to assert decisions after each interim assessment in the form of a pyramid decision tree. For each recruited cohort and every possible CR outcome, estimates of the true CR rate and probabilities with associated decisions are mapped out.

MonoGerm is a proven example where continuous monitoring of efficacy is imperative and ETP acted as an effective visual tool to explore and refine the trial design parameters. It allowed for clear communication between statisticians, clinical investigators and readily enabled Patient and Public Involvement (PPI). All parties were able to make informed decisions, resulting in an efficient and realistic trial design.

PS9A-02

Visualising the impact of continuous covariates on time-to-event outcomes, an approach using weighted kernel estimators

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Introduction
Associating a continuous covariate against a time-to-event outcome often occurs with some form of categorisation. This can lead to bias, loss of information and a poor representation of any underlying relationship. Understanding these associations often begins with a visual representation of the data but the traditional Kaplan Meier approach is not well suited to this.

Methods/Approach
We develop two methods to visualise the relationship between a continuous covariate and a time-to-event endpoint. Both approaches are based on a kernel estimator for the underlying hazard function with weights applied to account for patterns of censoring in the data. The first approach applies a second weight so that at any point along a covariate x, a hazard function can be estimates. The second approach attempts to estimate both the covariate and the outcome in a bivariate fashion.

Results
Both approaches provide a visualisations in the form of surface plots that show the effects of a covariate without any need for categorisation. The surface plots have some similarities with the traditional Kaplan Meier plots and are accessible by clinicians. They can also be used to visually assess the fit of models and inform whether any transformations of the continuous covariates may be required. We have applied these graphs in practice to aid interpretation of predictive biomarkers in pancreatic cancer

Discussion
Surface plots provide an alternative to Kaplan Meier plots when assessing continuous covariates and can be a useful tool in aiding the analysis and interpretation of their impact on time-to-event endpoints.

PS9A-03

Point estimation in exact two-stage group-sequential two-arm trial designs for binary outcome data

Dr Michael Grayling[1]
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Introduction
An increasing number of trials are now leveraging a group-sequential design to improve trial efficiency in terms of the number of patients expected to be required. When a group-sequential design is used, a naïve approach to point estimation that ignores the sequential nature of the trial may result in a biased estimate. A large body of literature therefore exists on methodology for determining 'adjusted' point estimates that can help remove such bias. This literature has paid little attention though to the case of two-stage 'exact' two-arm designs for binary response data, which are e.g. of growing interest in phase II oncology.

Methods
Formulae for several adjusted estimators of the response rate difference are derived, including the uniform minimum variance unbiased estimator (UMVUE), the conditional uniform minimum variance unbiased estimator (CUMVUE), the conditional maximum likelihood estimator, and two mean adjusted estimators. These estimators are applicable to a broad class of exact two-stage designs. Through analytical formulae for the conditional and unconditional bias and root mean square error (RMSE), the performance of the adjusted estimators along with the naïve (unadjusted) maximum likelihood estimator are compared. The comparisons are performed assuming design parameters motivated by a recent oncology trial that used an exact two-stage design.

Results
The UMVUE is shown to have potentially large conditional bias, though its performance in terms of the RMSE does not appear as poor as for group-sequential designs with normally distributed data. The mean adjusted estimators provide strong performance across all considered statistical criteria and many possible values of the true response rates in the treatment arms. Conditional maximum likelihood estimation appears to result in comparatively very poor unconditional bias and RMSE.

Discussion
The difference in the performance of the unadjusted and adjusted estimators is arguably more limited in the case of exact two-stage designs for binary data when contrasted against existing results for normal data. However, the UMVUE, CUMVUE, and one mean adjusted estimator can be determined easily through analytical formulae and in some settings provide a clear advantage over the naïve unadjusted approach to point estimation. Their use therefore requires minimal effort and may help improve inference for this class of trial design.

PS9A-04

Point estimation for adaptive trial designs: practical considerations and guidance

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Introduction: In adaptive clinical trials, the conventional end-of-trial point estimate of a treatment effect is prone to bias, that is, a systematic tendency to deviate from its true value. As stated in recent FDA guidance on adaptive designs, it is desirable to report estimates of treatment effects that reduce or remove this bias. However, it may be unclear which of the available estimators are preferable, and their use remains rare in practice.

Methods/Approach: We discuss how bias can affect standard estimators and assess the negative impact this can have. We then carry out a review of current practice for reporting point estimates in adaptive clinical trials. We illustrate the computation of different estimators using a real adaptive trial example, which we use as a basis for a simulation study. Finally, we propose guidelines for researchers around the choice of estimators and the reporting of estimates following an adaptive design.

Results: Our review of current practice shows that the use of adjusted estimators remains rare. Through our trial illustration and simulation study, we show that while on average the values of different estimators can be similar, for a particular trial realisation they can give noticeably different values for the estimated treatment effect.

Discussion: The issue of bias should be considered throughout the whole lifecycle of an adaptive design, with the estimation strategy pre-specified in the statistical analysis plan. When available, unbiased or bias-reduced estimates are to be preferred.

PS9B-01

Developing a core outcome set for hand fractures and joint injuries in adults

Mr Sandeep Rajiv Deshmukh[1], Dr Paul Leighton[2], Professor Alan A Montgomery[2], Professor Jamie Kirkham[3], Mr Ryan Trickett[4], Professor Christina Jerosch-Herold[5], Mr Jeremy N Rodrigues[6,7], Professor Xavier Griffin[7], Professor Matthew Costa[7], Miss Alexia Karantana[1]

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Introduction

Hand fractures and joint injuries are common, with significant impact for patients and wider society. Lack of consistency in outcome selection in clinical research on these injuries makes interpretation of the available evidence challenging. We aimed to develop a core outcome set on hand fractures and joint injuries in adults; a baseline set of agreed upon outcomes to be used in all future clinical research on these injuries.

Methods

Through systematic review of treatment outcomes and in-depth qualitative work exploring the patient perspective we synthesised a longlist of outcome domains deemed relevant for these injuries by key stakeholders. The longlist underwent a consensus prioritisation process in an international three-round Delphi survey involving patients, hand therapists and surgeons. Participants rated each domain for importance on a 9-point Likert scale, with feedback of each stakeholder groups' ratings from the previous round provided in Rounds 2 and 3. Final round results were analysed based on pre-determined consensus criteria.

Subsequently, representatives from key stakeholder groups engaged in an international online consensus meeting based on an adapted nominal group technique. Through discussion and prioritisation steps using pre-determined consensus criteria, a final core outcome set was determined.

Results

Synthesis of the outputs of the systematic review and qualitative research generated a total of 37 outcome domains. Four more were added as a result of participant suggestions at the end of Delphi Round 1. Over 94% (144/152) of participants completed all three rounds (54 patients, 55 surgeons, 35 hand therapists). Twenty domains reached consensus as 'very important'.

All outcome domains were discussed at the final consensus meeting, which had 27 participants (12 patients, seven surgeons, six hand therapists, a health economist and a trial manager). After iterative prioritisation steps, a final vote selected seven outcome domains for inclusion in the core outcome set: fine hand use; pain / discomfort at rest; pain / discomfort with activity; self-hygiene / personal care; return to usual work / job; range of movement; and patient satisfaction with outcome / result.

Discussion

The development process arrived at a final set of seven core outcome domains. These touched upon several areas including functional tasks (basic aspects and working life role), patient comfort, abstract/physiological function (range of motion) and patient satisfaction. They are recommended as the baseline domains to be measured in future clinical research on these injuries, with the optimum way to measure the domains being the subject of future work.

PS9B-02

Development of a core outcome set with measurement instruments for research and clinical practice for Post COVID-19 condition (Long COVID)

Dr Sarah Gorst[1], Dr Timothy Nicholson[2], Dr Daniel Munblit[3], Dr Nina Seylanova[4], Dr Nicola Harman[1], Professor Dale Needham[5], Professor Paula Williamson[1], on behalf of the PC-COS Steering Committee
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Introduction
Post COVID-19 condition (PCC), also known as Long COVID, is a major health problem. Existing studies and clinical practices are evaluating PCC using a wide range of outcomes and measurement instruments, resulting in substantial heterogeneity. Given substantial research funding for evaluating PCC, there is an urgent need to develop a core outcome set (COS) to ensure that critically important outcomes are evaluated, measured and reported in a consistent manner. The aim of this study was to develop a COS, including recommended measurement instruments, for use in both research and clinical care for PCC in adults.

Methods
The PC-COS study (https://www.pc-cos.org/), which was conducted in collaboration with the World Health Organization, followed the COMET Initiative guidelines for COS development. The first stage involved a multi-step process to reach consensus, amongst people with PCC, their family members, health professionals and researchers, on a core set of outcome domains, including a thorough review of outcomes reported in previous studies, a two-round international modified Delphi consensus process (in English, French, Chinese, Russian and Spanish), and then an online consensus meeting to finalise the COS. The second stage focuses on reaching consensus on how to measure the core outcome domains from stage one. For each of the core outcome domains, we identified instruments used in published and ongoing PCC studies, along with others specifically designed for PCC. Information for each instrument, including description, costs and administration information, was summarised in a standardized 1–2-page sheet, including a non-technical “lay summary”. Thereafter, a three-round online Delphi process (in English) will be completed to reach consensus on a recommended measurement instrument for each core outcome domain.

Results
In the first stage of this study, 1535 participants from 71 countries, representing six continents, participated in the online Delphi process, with 1148 participating in both rounds (75% completion rate). The results of the Delphi were finalised at an online interactive consensus meeting, where agreement was reached on the inclusion of 12 outcome domains: cardiovascular, respiratory, nervous system, cognitive, physical, and mental physical functioning; fatigue; pain; post-exertion; work/occupational; survival; and recovery. The process for stage 2 is ongoing.

Discussion
A COS for PCC was developed using a rigorous methodology. Identifying which instruments are best to measure these outcomes is underway. This minimum set of consensus-based core outcomes and measurement instruments is recommended to be used in all clinical research and practice settings for adults with PCC.

PS9B-03

Ethical considerations for the inclusion of patient-reported outcomes in clinical research: The PRO ethics guidelines

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Background

Patient-reported outcomes (PROs) are used in clinical research to provide evidence of the benefits and risk of therapies from a patient perspective. PRO trial data have the potential to inform regulatory approvals, health policy and clinical practice. In observational studies and routine clinical care, PRO data provides information on disease burden and real-world evidence of treatment safety and effectiveness. However, ethical concerns have been raised regarding PRO use.

Aim

To develop an international, consensus-based, PRO-specific ethical guidelines for clinical research.

Methods

The PRO ethics guidelines were developed following the EQUATOR Network's guideline development toolkit. This included (1) a systematic review of the ethical implications of PROs in clinical research, supplemented by the SPIRIT-PRO Extension; (2) a two-round international Delphi exercise (n=96

stakeholders); and (3) a consensus meeting (n=25 international stakeholders) with input from six additional stakeholders. Prior to voting, consensus participants received a summary of the Delphi results and information on whether the items aligned with existing ethical guidance.

Results
Twenty-three items were considered in round 1 of the Delphi: six candidate items from the systematic review and seventeen from the SPIRIT-PRO Extension. Ninety-six stakeholders voted on the importance of each item for inclusion and twelve additional items were recommended for voting in round 2 of the Delphi (n=35 items). Fourteen items were recommended for inclusion at the consensus meeting (n=25 participants). The final wording of the PRO ethical guidelines was agreed by consensus participants. Included items focused on PRO-specific ethical concerns relating to research rationale, objectives, eligibility requirements, PRO concepts/domains, PRO assessment schedules, sample size, PRO data monitoring, barriers to PRO completion, participant acceptability and burden, administration of PRO questionnaires for participants who are unable to self-report PRO data, input on PRO strategy by patient partners and/or members of the public, avoiding missing data and dissemination plans.

Conclusion
The PRO ethics guidelines provide recommendations for ethical concerns that should be addressed in PRO clinical research. Addressing ethical concerns of PRO clinical research has the potential to ensure high-quality PRO data whilst minimising participant risk, burden and harm, empowering research participants and protecting participant and researcher welfare.

PS9B-04

Development of core outcome sets for clinical trials of organisational and service level interventions: the RoboCOS study

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Introduction

Core outcome sets have been developed to ensure that clinical trials measure outcomes that are relevant to all key stakeholders. To date, core outcome sets have primarily focussed on clinical interventions applied at the patient level. Little attention has been paid to the development of core outcome sets for the evaluation of organisational or service-level interventions. This presentation will describe the development of a core outcome set for the evaluation of a service level intervention and highlight generalisable learning. It will use the RoboCOS study, which developed a core outcome set for the evaluation of the introduction of robotic assisted surgery as part of a clinical service, as a case study.

Methods

The development of the core outcome set followed international COS-STAD (Core Outcome Set – Standards for Development) best practice guidelines. However, each phase had to be extended to ensure organisational perspectives were included. Key adaptations included: extension of search strategies to encompass national and international policy documents and health technology assessment (eg NICE) reports to ensure organisational and policy outcomes important for service delivery were identified (routine clinical trials tended to focus on patient-level outcomes); the need to expand the structure of the core outcome set to reflect the multi-level nature of outcomes of potential importance (to reflect the more complex structure and impacts of organisational interventions); and the requirement to adjust the pre-determined consensus definitions to ensure consideration of each system level separately.

Results

In RoboCOS, the expanded literature review and interviews identified that the introduction of robot assisted surgery to a service could have impacts at four system levels – patient, surgeon, organisation and population level – and that any core outcome set had to reflect this multi-dimensional nature. The consensus process was thus adapted to ensure that at least one outcome be included under each system level - standard consensus thresholds were adapted to enable this. The final COS included 10 outcomes: four at patient level; two at surgeon level; three at organisational level and one at population/policy level. These include outcomes not routinely seen in patient-level core outcome sets such as surgeon visualisation and equity of access.

Discussion/conclusion

Core outcome sets for the evaluation of service/organisational level interventions can be complex. They impact at multiple levels and these need to be taken into account. Search criteria have to be expanded and the outcome development process needs to ensure that all levels are included.

PS9C-01

A hybrid approach to comparing parallel-group and stepped-wedge cluster randomized trials with a continuous primary outcome when there is uncertainty in the intra-cluster correlation.

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Objective
To evaluate how uncertainty in the intra-cluster correlation (ICC) impacts whether a parallel-group (PG) or stepped-wedge (SW) cluster randomized trial (CRT) design is more efficient in terms of the required sample size, in the case of cross-sectional SW-CRTs and continuous outcome data.

Study Design and Setting
We motivate our work by reviewing how the ICC and standard deviation (SD) were justified in 54 Health Technology Assessment (HTA) reports on CRTs. To enable uncertainty at the design stage to be incorporated into the design specification, we then describe how sample size calculation can be performed for CRTs in the 'hybrid' framework, which places priors on design parameters and controls the expected power in place of the conventional frequentist power. Comparison of the PG- and SW-CRT designs is conducted by placing Beta and truncated Normal priors on the ICC, and a Gamma prior on the SD.

Results
Many HTA reports did not adhere to the CONSORT guideline of indicating the uncertainty around the assumed ICC, while others did not justify the assumed ICC or SD. Even for a prior ICC distribution with a small mode, moderate prior densities on high ICC values can lead to a SW-CRT being more efficient because of the degree to which a SW-CRT is more efficient for high ICCs. With careful specification of the priors, the designs in the hybrid framework can become more robust to, for example, an unexpectedly large value of the outcome variance.

Conclusion
When there is difficulty obtaining a reliable value for the ICC to assume at the design stage, the proposed methodology offers an appealing approach to sample size calculation. Often, uncertainty in the ICC will mean a SW-CRT is more efficient than a PG-CRT design.

PS9C-02

The non-inferiority complex - a review and assessment of UK publicly funded non-inferiority trials.

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Introduction
Non-inferiority trials aim to show that a new treatment is "no worse than" the comparison whilst having an additional benefit, such as reduced side effects, which make the new treatment potentially worthwhile. A key design feature of non-inferiority trials is the non-inferiority margin (NIM) which determines how similar the treatments must be in order to be declared non inferior. This work aims to explore the design features in non-inferiority trials, especially the selection of the NIM, focussing specifically on UK publicly funded trials. An additional objective is to assume the information provided around the anticipated benefit (superiority) of the new treatment.

Methods
A review was conducted to identify publicly funded non-inferiority trials through the ISRCTN trial registry and the National Institute for Health Research database from 1970 to 2021 inclusive. Inclusion criteria were the requirement to be: a randomised controlled trial including a non-inferiority comparison, publicly funded and a UK funder. This identified 123 non-inferiority trials and their key design features were extracted from any available documentation.

Results
From the 123 records identified, nine represented a pilot/feasibility trial which have not been included in the summary due to differences in design aspects. The primary outcome was most often (51%) a clinical outcome with the benefit (i.e. superiority aspect) of the trial most commonly being safety (e.g. adverse events) followed by patient reported outcome measures. When assessing this benefit, the review found in 62% of cases it was a direct benefit to the patient receiving the treatment, other less common benefits were to the health service (e.g. costs) or public health (e.g. reduced antibiotic use).
The non-inferiority margin was found to be most commonly based on a difference in proportions between the treatment groups with the median NIM being 8%. The justification for how the margin was selected was available in 55% of trials with the most common rationale being clinical judgement. However, the basis of this judgement varied greatly from the opinion of one/two clinicians to a more comprehensive survey.

Discussion
The NIM chosen has a huge impact on the success of the trial, however the justification for this chosen value is not always well defined. Researchers should make clear how the NIM has been set and endeavour to be as comprehensive as possible when eliciting opinions to ensure appropriateness of the NIM chosen and subsequent success of the trial.

PS9C-03

The Trials Communication Wheel: stakeholders to consider in the lifecycle of the trial

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Introduction

Communication is a crucial aspect of the clinical trials lifecycle. It transcends all clinical trial stages, from decisions over research priorities, and all aspects of trial design, analysis and reporting, right through to dissemination. Unsurprisingly, communication was identified as one of six key priorities within the Trial Conduct Working Group of the Trials Methodology Research Partnership, TMRP, in the UK. A sub-working group (SWG) was established in April 2020 to refine and progress the communication research agenda, i.e., best methods (including who, what, where, when, how) for communicating with patients and the public, trial participants (potential and enrolled), trial sites, collaborators, funders, healthcare workers and research governance organisations. Initial SWG conversations led to two key initial priorities for our working group: 1) who the key communication stakeholders are; 2) at which stage of the clinical trial cycle interaction with each should take place.

Methods/Approach

The Communication SWG meets quarterly. At the initial meeting, members were asked to consider communication research priority areas and communication stakeholders relevant to clinical trials. In December 2020, based on our discussion, one member, RS, drafted an initial diagram of communication across the trial lifecycle incorporating ideas discussed using the NIHR Involve Research Cycle guidance. This was refined at subsequent meetings and presented to a graphic designer, VR.

Results

V1 of the Trials Communication Wheel was produced in June 2021 and detailed discussion of the wheel took place at the SWG meetings. We went through eight iterations to produce the final working version. Key stakeholders were identified and classified into seven groups: patients and the public; trial participants; health and social care professionals; funders; industry; scientific community; policymakers. Trial development, conduct and results phases were identified and the stakeholders to consider at each phase detailed. The wheel colour and contrast combinations adhere to the Web Content Accessibility Guideline standards. The wheel was presented to the MRCCTU at UCL PPI group and all feedback was incorporated.

Discussion

We believe the Communications wheel is a useful resource for trialists to refer to when developing and refining communication plans for their research. Using this resource should promote more in-depth consideration of the varying complexities of communication within clinical trials, including the need for deployment of different strategies, resources and knowledge to effectively engage with a diverse group of stakeholders with varying needs of communication. An iterative evaluation process will be implemented once the Trials Communication Wheel is launched.

PS9C-04

Designs for parallel-group cluster-randomised trials, where the clusters are institutions: a classification system to aid identification, with six proposed sub-types

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Introduction

Designs of cluster-randomised trials (CRTs) are often not reported in sufficient detail. Moreover, when a design is not explicitly reported, there is limited guidance available on how to identify a design based on its components. Whilst closed-cohort (CC) and (repeated) cross-sectional (R-CS) designs are well-established, previous definitions of an open-cohort (OC) design have been inconsistent, and no other broad design types are recognised to exist despite the vast range of designs used in practice.

Methods

Drawing on a similar framework for stepped-wedge CRTs, a classification system for parallel-group CRTs was developed where the clusters are institutions.

As part of a User Engagement work-package in OPIS-CRTs, trialists working in CRTs across a range of roles used the classification system to classify their own trials, firstly in an in-person workshop, and subsequently in an online survey. Trialists provided feedback on each component and overall, and the classification system was revised to remove ambiguity and to ensure wide applicability.

The survey also asked trialists to provide examples of CRTs with a possible OC design; these were classified using the system.

Results

The classification system consists of six core design indicators, and five additional design considerations. Five design sub-types are presented with illustrative examples: CC, non-standard CC, R-CS, open-cohort with discrete recruitment (OC-D) and new admission continuous recruitment (NACR). Open-cohort with continuous recruitment (OC-C) is suggested as a possible sixth design sub-type, but no examples of this were found. These new definitions of OC designs clarify the ambiguity surrounding this design in the literature to date.

The level of intervention delivery (individual- or cluster-level) is highly influential on design choice, and timescales are highlighted as an integral design component.

Respondents provided 46 examples of CRTs with a possible OC design. Using the classification system, only 7/46 (15%) had a possible OC design. The most common reasons for exclusion were that the provided design was actually CC (46%), NACR (15%) or R-CS (13%).

Discussion

Trials provided by survey respondents indicated that even amongst CRT experts, there is lack of clarity surrounding CRT designs and their components.

Whilst this system can be used retrospectively to assess unclear CRT designs, it could also be used prospectively by trialists at the planning stage to consider the range of design options and prompt consideration of potential associated statistical issues.
This framework provides opportunities for more design-specific research to be carried out in the future, including associated analyses.

PS9D-01

Learning from COVID-19 related trial adaptations to inform efficient trial design - a sequential mixed methods study

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Background
The COVID-19 pandemic has resulted in many adaptations to clinical trial procedures to enable trials to continue. This study explored whether the adaptations made to clinical trials by UK Clinical Trials Units (CTUs) during the pandemic have potential to improve the efficiency of trials.

Methods
We conducted a mixed methods study. We carried out an online survey of all registered UK CTUs to identify studies that had made adaptations due to the pandemic. We purposively selected studies for inclusion and interviewed relevant CTU staff to explore the adaptations and their potential to improve the efficiency of future trials. We undertook a literature review of published evidence concerning the identified adaptations, and conducted a workshop in which CTU and patient representatives reviewed the findings from the interviews focusing on the potential of the adaptations to improve the efficiency of future trials.

Results
The survey identified forty studies. We selected fourteen studies and fifteen CTU staff were interviewed. The workshop included 15 CTU and 3 patient representatives. Adaptations were not seen as leading to direct efficiency savings for CTUs. However, three adaptations may have the potential to directly improve efficiencies for trial sites and participants: a split remote-first eligibility assessment (where, instead of undertaking eligibility assessment in person, those elements that can be undertaken remotely are done so prior to an in-person appointment), recruitment outside the NHS via a charity, and remote consent. We found a lack of published evidence to support the former two adaptations, however, remote consent is widely supported in the literature. Other identified adaptations may benefit by improving flexibility for the participant. Barriers to using these adaptations include the impact on scientific validity, limitations in the role of the CTU, and participant's access to technology.

Conclusions
Only three adaptations of those undertaken by CTUs to progress clinical trials during the pandemic have the potential to improve clinical trials long term:- a split remote-first eligibility assessment; recruitment outside the NHS via a charity; and remote consent. Some of the other adaptations could jeopardise the scientific integrity of trials. The effectiveness of adaptations could be tested in 'studies within a trial' (SWAT). Researchers should report the use of novel trial techniques clearly when disseminating the results of a study to ensure other can learn from their experiences.

PS9D-02

Covid-19 experiences in Vietnam, Indonesia and Nepal translated into evidence based, consolidated learning in clinical research

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Introduction

The Oxford University Clinical Research Unit (OUCRU) is a large-scale research programme with units in Vietnam, Nepal and Indonesia focused on having local, regional and global impact on health by leading a locally driven research programme on infectious diseases in Southeast Asia.

The COVID-19 pandemic substantially impacted OUCRU's research conduct by exacerbating existing operational, institutional and regulatory challenges. The OUCRU Clinical Trials Unit (CTU) aims to consolidate lessons learned over the past 2 years and rethink the clinical research operations, enabling a better response to future pandemics and ensure lessons learned are translated into evidence based best practices.

Method

We developed a multicenter survey to investigate the impact of Covid-19 and local Covid-19 related policy responses on the management of the different Units, the conduct of the trials, as well as on patients follow-up and care. Using both open-ended and close-ended questions, we interviewed a wide range of teammembers including CTU managers, study coordinators, pharmacists, medical staff and laboratory technicians, to capture information related to (1) the challenges faced by each Unit to ensure adherence to protocols, regulatory requirements, and GCP standards in all ongoing trials, (2) the methods adopted to accommodate to an everchanging environment and respond to emergency situations, (3) the lessons learned during this pandemic and (4) the structural and methodological changes implemented to adapt timely and efficiently in case of a novel pandemic situation.

Results structure

Results of the survey, which is currently ongoing, will be categorized into 3 themes including (1) Timeline and detailed global community policy responses to the COVID pandemic in Vietnam, Indonesia and Nepal, (2) Impact of the COVID restrictions on the general conduct of trials and studies (governance, operations, infrastructures, human resources, and study participants) and (3) solutions developed for immediate and long term responses to a pandemic situation.

Relevance and impact of the report

OUCRU is a unique programme, running across three Low- and Middle-income countries in Southeast Asia, where clinical research has significantly grown over the last decade. When Covid-19 emerged, the programme was running over 20 trials. The survey data will be published and provide information to other academic centers managing clinical trials during pandemics. It will inform authorities and sponsors worldwide about the operational, regulatory and human challenges in these countries during a pandemic

but will also demonstrate that the local responses and expertise exist to both protect clinical research participants and ensure high quality research.

PS9D-03

Conducting UK clinical trials during and post the Covid-19 pandemic: impact, challenges and solutions

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Introduction
The Covid-19 pandemic has had a major impact on (non-Covid-19) clinical trials globally, particularly participant and site recruitment and trial success/stoppage. Trials with anticipated recruitment challenges may have integrated support such as the QuinteT Recruitment Intervention (QRI) to help to identify and understand the sources of the challenges.

Methods
This paper reports on 13 UK clinical trials which anticipated recruitment challenges and included a QRI . The QRI continued to identify the sources of recruitment challenges during the pandemic, with a view to informing solutions, using methods of data collection including screening and recruitment logs, observational data from trial and site meetings, site surveys and qualitative interviews.

Results
In all but one of the 13 trials, recruitment was lower than even the lowest expected rates. The QRI helped to identify recruitment challenges in all trials: delays opening sites (particular issue for trials set-up during the pandemic), lack of capacity of trial recruitment staff and fewer eligible patients or difficulty accessing patients (due to treatment changes, risk of Covid-19 or impact of the pandemic). Almost all trials reported pandemic-related staffing issues due to redeployment, prioritisation of Covid-19 care and research, and Covid-19-related staff sickness/isolation/stress, particularly for research nurses. Trials of elective procedures were particularly impacted by the pandemic, including long waiting lists , changes to pathways, deprioritisation and limited clinical capacity. S ome trials' outcome measurement was affected. Some trials implemented changes to their protocol including remote consent/data collection, some of which were in response to QRI findings. Most of the challenges identified by the QRIs were logistical pandemic-related challenges beyond the control of site or central trial teams. In addition, these challenges limited the ability of the QRI to identify 'hidden' challenges such as issues with equipoise or information given to patients.

Discussion
The flexibility of the QRI facilitated rapid data collection to understand and document , and in some instances respond to, pandemic-related challenges, highlighting the value of embedding qualitative work and stakeholder consultation into trials likely to face difficulties .
This paper highlights the extensive and consistent pandemic-related challenges face by clinical trials, in the UK, and, given that many challenges are insurmountable at individual study, or even CTU level, this underscores the need for clear guidance from central bodies on how to overcome them.

PS9D-04

Hibernation or rapid set-up: lessons from three pandemic trials

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Introduction
An urgent public health (UPH) crisis, rapid in progression and unpredictable in nature, creates a challenging environment for delivering research. For a clinical trial to keep pace with the advancement of a health crisis, innovative and agile approaches to design and delivery are needed. A trial may be designed and set up in advance of a crisis or set up rapidly upon the emergence of a crisis.

Methods
We present a narrative comparison of three pandemic trials and reflect on lessons learned for future research in UPH crises.

Results
Set-up pre-UPH crisis (Influenza)
- ASAP (https://www.nctu.ac.uk/trials/respiratory.aspx)

Routine HRA approvals. Placebo-controlled. Resource commitment (trial hibernated for a decade, annual checks to maintain readiness, rapid activation evidenced through mock activations). Not activated for COVID-19. Intervention (dexamethasone) adopted by RECOVERY trial.
Set-up during UPH crisis (COVID-19)
- RECOVERY (https://www.recoverytrial.net/)

Open-label, platform. Strong support through NIHR UPH badging e.g., the Chief Medical Officers of England, Wales, Scotland and Northern Ireland, and the NHS Medical Director, encouraged participation. Expedited site opening and recruitment. 10 treatments (4 effective) assessed to date.
- PROTECT-CH (https://www.protect-trial.net/)

Fast-tracked approvals. Open label, platform. Barriers to trial set-up (lack of research infrastructure in care home setting, difficulties securing insurance, contract delays with drug manufacturers). Abandoned due to no longer being feasible following successful vaccination programme.

Setting up a trial in advance of a crisis may enable rapid recruitment but requires ongoing resources to maintain readiness. It was decided at the outset of the pandemic that a single-arm placebo-controlled trial (ASAP) was not commensurate to the need for multiple evaluations in response to COVID-19; instead, the intervention (dexamethasone) was evaluated as the first arm of a platform trial (RECOVERY). RECOVERY showed that an adequately resourced and supported platform trial can be successfully set up at pace to evaluate multiple treatments. PROTECT-CH unveiled the inadequacies of the existing infrastructure for rapid set up of a clinical trial in the social care setting, specifically care homes.

Discussion

Delivering an open-label clinical trial in a secondary healthcare care setting might be optimally accomplished through rapid trial set-up at the start of a UPH crisis. To achieve this, however, requires significant research capacity and co-operation between multiple stakeholders. Setting up a hibernating trial in advance of a crisis might be more appropriate in other settings where the necessary infrastructure or resources for re-deployment are lacking or when a placebo-controlled design is necessary.

P-001

Application of an adaptive design with sample size re-estimation and early stopping in a diabetic foot ulcer trial.

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Introduction
The diagnosis of Diabetic Foot Ulcer (DFU) related Osteomyelitis (OM) is complex, with no universally accepted definition and poor reliability of common diagnostic tests. The poor prognosis of OM vs Soft Tissue Infection (STI) means that faced with clinical uncertainty, clinicians are likely to over rather than under-diagnose OM. RCTs enrolling participants where STI needs to be distinguished from OM are therefore difficult.

Methods/Approach
In an ongoing HTA trial enrolling DFUs complicated by STI, the most common reason for screen failure (up to 50%) is clinical suspicion of OM.
We, therefore, proposed as part of an NIHR HTA funding application, an adaptive trial design including both populations (STI & OM) to avoid the need for absolute clinical distinction at screening and mitigating the risk of excluding participants. This will result in efficient recruitment strategy. A single infrastructure team will enable answering the primary research question for both populations within one trial.
The adaptive feature included an interim analysis to facilitate an efficient decision-making by allowing the recruitment to either the STI or OM groups to stop earlier for efficacy/futility. Quickly evaluable endpoints made the choice of an adaptive design feasible and favourable. Given the uncertainty on the response in the STI group identified in the literature and recent trials, we have included a sample size re-estimation at the time of the interim to allow for the reduced sample size if the underlying assumptions were too conservative. We evaluated several design options by simulations and assessed the robustness of these options to the assumption on the response rate in the control group.

Timing of Results
The funding application is under review, and if successful, we are expecting the research to start within 2023, and the results to be available in 2028. However, we would like to present the process of choosing an adaptive design for a trial outside the cancer area and the potential benefits such an innovative design could provide.

Potential Relevance & Impact
An adaptive design can allow for a more efficient decision-making in a trial. However, it requires a closer collaboration and constant communication between statisticians and clinicians from the planning stage. Sharing our experience on why an adaptive design was chosen for a diabetic ulcer trial, and how the application with an adaptive design was prepared, increase the awareness of innovative designs in practice and encourage the audience to consider an adaptive design for their trials.

P-002

Running an Adaptive Cluster RCT in the NHS during the COVID-19 Pandemic: the challenges of the COVID-Nurse Complex Intervention Trial

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Background

COVID-19 presented health services with unprecedented challenges: how to care for patients with COVID-19 in the face of substantial barriers to care, when best practices were unknown. The ISRCTN registered COVID-Nurse trial evaluated a pandemic-specific fundamental nursing care complex intervention. This abstract focuses on issues faced, revisions to our trial design and methods required to deliver the trial.

Methods

We planned COVID-Nurse as a two-arm, rapid-cycle adaptive cluster RCT evaluating a pandemic-specific fundamental nursing care complex intervention for healthcare workers on COVID wards, on patient experience of care, compared to usual care.

We aimed to recruit 18 clusters in three cycles, matching sites on research intensity and population ethnicity, adapting the intervention following feedback between cycles.

Results

Competition for site recruitment: COVID-Nurse was not badged as an urgent public health (UPH) study; clinical research departments prioritised UPH and pharmaceutical trials; consequently we were unable to recruit sufficient sites to undertake matching. Revisions: we redesigned the trial as a standard cluster RCT, abandoning our adaptive design; we recalculated the sample size, reducing recruitment targets.

Dynamic nature of the pandemic: hospital admissions fluctuated significantly. When cases were high (winter 2020/21), sites declined participation due to clinical pressures and staff shortages; when cases were low (summer 2021) sites declined due to insufficient patients. Revisions: we required two extensions, doubling trial duration.

Clinical and managerial engagement: some nursing teams were reluctant to participate in a trial requiring behavioural change and staff training; wards could be COVID 'decommissioned' at short notice, requiring new teams to be trained at intervention sites; consequently, we recruited fewer clusters than intended and observed variable rates of implementation of the intervention. Revisions: we allowed sites to implement specific elements of the intervention.

Discussion

Cluster trials of behavioural interventions are challenging to implement, compounded in our case by exceptional COVID-related recruitment, epidemiological, clinical and managerial factors. We were unable to recruit to time and target, had severe operational issues managing the ebb and flow of the pandemic, and despite strong patient and public involvement, struggled to persuade some clinical nurses of the value of a pandemic-specific intervention. Even though we abandoned our adaptive design for a traditional cluster RCT due to the factors cited above, our revisions ensured we delivered the trial, recruiting almost 1000 patient and nurse participants.

P-003

Delivering Value for Money in Clinical Trials: Value-Adaptive Designs for Efficient Delivery of Publicly Funded Trials

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Introduction

Value-adaptive designs are a set of emerging methods for efficient clinical trial design that aim to maximise expected population health for the money spent. These designs involve adaptive data collection processes that consider the costs of the research process itself in relation to the precision of the estimated effectiveness of a treatment and health technology assessment decisions around cost-effectiveness. These designs have the potential to deliver more efficient and innovative studies that give robust evidence to inform practice and policy.

Methods

As part of the EcoNomics of Adaptive Trials project (https://www.sheffield.ac.uk/scharr/research/centres/ctru/enact), we engaged with key stakeholders from across the NIHR on the potential use and implementation of value-adaptive methods in NIHR research. We also applied value-adaptive methods to two retrospective case studies to explore the estimated health and economic value provided by the designs. These results were used in turn to assess the opportunities value-adaptive designs offer for improving the efficiency of publicly funded trials. In addition, points to be considered by the public, funders, clinicians, researchers and healthcare decision makers to deploy these methods successfully were explored.

Results

Opportunities identified included: the use of resources to more efficiently learn which health technologies are most cost-effective; incorporation of the costs and benefits of the research process itself, and mechanisms to inform the choice of which research to pursue to maximize expected health economic benefit. Applying this approach in practice will involve addressing the perceived learning curve of stakeholders regarding the value-adaptive approach when applying for research funding and disseminating trial results. Additionally, the potential impact of the designs on the financial administration of funder budgets and staff in clinical trial units when the trial delivery period is not fixed (eg. may be shortened or lengthened) may require careful thought. It was highlighted how, practically, researchers must ensure that they have access to appropriate expertise in the value-adaptive methods, can calculate the costs of conducting the trial accurately, and are able set up appropriate computing and management processes to implement the design successfully.

Discussions

Challenges to the deployment of value-adaptive designs remain, but we hope they can be implemented with increased experience and application of these approaches. Where appropriate, it may only require small changes beyond current practices. With careful implementation and further discussion, the future use of value-adaptive designs holds promise for more efficient publicly funded health research.

P-004

Considering 'Non-Promising' Treatment Effects at Interim Analyses: Futility of the Treatment, Rather than Futility of the Trial.

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Introduction
It is increasingly common to include one or more pre-planned interim analysis/es during a clinical trial. When there is concern that the treatment under consideration may not show efficacy, futility analyses are used. Current methods of assessing futility at an interim analysis focus on whether the trial's final analysis will likely demonstrate a statistically significant effect compared with control. While at first this appears to test whether a treatment is clinically useful, assessing whether the trial's final analysis is statistically significant is an assessment of whether the trial is futile, rather than the treatment itself. Current methods may also allow trials which have excluded clinically meaningful effects at interim to continue.

We propose an alternative futility interim analyses which stops trials when the interim estimate excludes treatment effects deemed potentially clinically useful, considering the treatment under assessment therefore 'non-promising'. We contend that this approach has more desirable operating characteristics, as it directly selects for treatments which, at interim, may show clinically meaningful treatment effects. This results in either trials that stop at interim with interval estimates clearly demonstrating a lack of evidence of efficacy, or they continue to final analysis.

Methods
Taking 8 different scenarios with varying effect sizes and variances (4 null at final analysis, 4 which treatment effects at final analysis) from a fictional randomised controlled trial of a novel therapy compared against a control with a single pre-planned interim analysis, we simulated the operating characteristics of 4 existing interim futility analysis methods (group sequential O'Brien-Fleming/Pocock designs; conditional power; and a Bayesian approach using the posterior probability of the interval intersecting the Region of Practical Equivalence, ROPE) and 3 different implementations of the 'non-promising region' approach (O'Brien-Fleming/Pocock, and a Bayesian implementation). We ran 1,000 iterations of each approach/scenario, and compared the percentage of trials stopped at interim (the primary metric of interest).

Results
Broadly, all approaches show useful stopping behaviour. However, the frequentist O'Brien-Fleming method appeared more likely to stop trials at interim when estimates are less precise, regardless of whether useful treatment effects are included in the interim estimate. The 'non-promising region' approaches generally allow trials which have interim estimates including useful treatment effects to proceed regardless of precision.

Discussion

The ‘non-promising region’ approach bases stopping decisions on the magnitude of the interim estimate, rather than its precision. We suggest that this is a desirable property for treatment selection in clinical trials.

P-005

Confidence intervals for the treatment effects in adaptive enrichment designs

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Targeted therapeutics have an increasing market share in modern medicines. There may be uncertainty around which subset of patients will benefit from a treatment under development. Consequently, adaptive enrichment group sequential designs have been proposed in Phase II/III trials. Such designs incorporate an interim decision as to whether to proceed recruitment with the whole population or restrict recruitment to the more promising subgroup. The second-stage sample size may also be dependent on the first-stage data. Hence they can increase the efficiency of trials and maximize power by concentrating limited sample sizes on responsive subgroups. While these designs are devised to ensure Type I error is controlled, accounting for multiplicity, CONSORT guidelines on trial reporting also require treatment effect estimates and corresponding confidence intervals. However, the adaptive nature of the procedure complicates estimation of the treatment effects and makes quantification of uncertainty in treatment effects challenging. In particular, confidence intervals based on the naive maximum likelihood estimate and corresponding Fisher information will tend to have incorrect coverage. Hence, we consider method for constructing confidence intervals for the treatment effect for subgroups at the end of an adaptive enrichment trial. Focusing on a two-stage design with two disjoint subgroups, we develop a general method based upon devising an appropriate p-value function. Initially, the entire sample space is partitioned into several disjoint subspaces by using a predetermined selection rule. Then our p-value functions integrate over certain subspaces based on score space ordering method. We consider both the case of constructing a confidence interval for the treatment effect in the chosen subgroup conditional on selection, and also unconditional confidence intervals for a given subgroup. By inverting the relevant p-value functions, we obtain confidence intervals with exact asymptotically coverage probabilities. The approach is illustrated through application to two specific adaptive enrichment designs.

P-006

REFRACT: A randomised, sequential phase II adaptive platform trial utilising a Bayesian approach to sharing control data through the application of power priors

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Introduction
Follicular lymphoma (FL) is a common subtype of non-Hodgkin lymphoma with an estimated 10-year UK prevalence of 16,000 cases. Most patients have incurable, advanced stage disease and frequent relapses. Treatment resistance, early progression, and poor survival occurs in ~25% of patients, whilst increasing numbers experience treatment resistance, and eventually exhaust treatment options, underpinning the need for novel therapies. There are currently no standard treatment pathways or randomised trials comparing experimental with current therapies, and outcome data from current therapy in relapsed/refractory FL (rrFL) are limited. We have designed a study that allows for rapid evaluation of multiple novel therapies whilst simultaneously minimising patient recruitment.

Methods/Approach
This trial is designed as a prospective, sequentially randomised phase II adaptive platform trial utilising a Bayesian approach to sharing control data. There are three planned treatment arms, each with a control group of investigator choice therapy (ICT) and a novel experimental arm. Patients in Round 1 will be randomised using a 1:1 allocation, with Rounds 2 and 3 randomised using a 4:1 allocation, in favour of experimental treatment. The change in allocation ratio will be accounted for using power priors, allowing for borrowing of previous control data.

Results
The main objective of this randomised trial is to compare novel therapies against ICT in order to identify treatments with superior activity based upon the primary outcome of post-induction complete metabolic response, assessed using the Deauville 5-point scale and Lugano 2014 criteria at 24 weeks. Secondary outcomes include overall metabolic response, progression free survival, overall survival, time-to-next treatment as well as assessments of safety and quality of life.
284 patients will be recruited across three rounds, with 189 receiving an experimental treatment. To allow for the most efficient use of patients in the analysis and reduction in the number of control patients required, we will incorporate control arm data from previous rounds into the current round using power priors. Previous control patients will be weighted at 75% of an active control patient within the prior, with opportunity for adjustment should control treatments change over time. Extensive simulations have been conducted to assess operating characteristics across a range of response rates and weightings.

Discussion
With the use of power priors and an adaptive design this trial can evaluate three novel treatments in a disease that urgently requires further options. REFRACT has received funding and plans to open in early 2023.

P-007

Adapting the Time-to-Event Continual Reassessment Method to incorporate consolidation immunotherapy treatment in a Phase I platform study (CONCORDE) testing novel drug-radiotherapy combinations

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Introduction

CONCORDE is the first phase I drug-radiotherapy combination platform study in non-small cell lung cancer, designed to identify the Recommended Phase II Dose of different DNA Damage Response inhibitors (DDRi) in combination with radical thoracic radiotherapy (RT). Time-To-Event Continual Reassessment Method (TiTE-CRM) methodology informs the dose escalation individually for each DDRi-RT combination, and a randomised calibration arm receiving RT-alone aids the attribution of toxicities. Two experimental arms A and B (PARP and ATR inhibitors) are currently recruiting. The addition of the immune checkpoint inhibitor durvalumab as consolidation treatment following RT will be included in future arms of the CONCORDE platform, adjusting to the changing treatment landscape. However not all participants will be able to receive consolidation durvalumab after RT, for reasons such as progression or persistent toxicity from treatment. This raises the question as to how a single TiTE-CRM model for this arm can accommodate both groups of DDRi-RT participants (with and without consolidation treatment), which will potentially have different toxicity profiles.

Methods

We report the novel statistical design and implementation of the TiTE-CRM in CONCORDE. We detail the considerations, development and the selected adaptations to the TiTE-CRM design for CONCORDE-C, along with the simulation work conducted to assess the robustness of these adaptations. Statistical parameters of the TiTE-CRM were calibrated following recommendations by Lee and Cheung (2009). Simulations were performed in which two separate populations (with and without consolidation treatment) were evaluated across a variety of scenarios with different toxicity profiles, and then combined in the same adapted TiTE-CRM model. Utilising modified code from the R package 'dfcrm', these simulations were performed to assess the operating characteristics and robustness of the adapted model.

Results

Results of our simulation work showed that the statistical model we have proposed for CONCORDE-C (ATR inhibitor) can answer the research question under a wide range of potential scenarios. It performs well under varying levels of recruitment and recommends the closure of arms where excessive levels of toxicity are observed. However model performance decreases when the observed toxicity in participants receiving consolidation treatment is different from our initial assumptions.

Discussion

The results demonstrate how TiTE-CRM methodology may be used in practice in a complex dose finding RT-drug combination platform study and adapted to incorporate consolidation immunotherapy treatment. This work also highlights the importance of a randomised calibration arm for this study, to inform attribution of toxicities and toxicity assumptions in this population.

P-008

Identifying optimal adaptive design methods in critical care: a simulation study

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Background
Adaptive designs are increasing in popularity as they offer more efficiency than traditional fixed designs, allowing for early stopping for efficacy or futility. This can be particularly beneficial for large late-phase trials with binary endpoints in critical care. However, there is an array of design parameters and statistical methods to choose from and the evidence to select between them is limited. We were motivated by two real-life trials (ADRENAL and NICE-SUGAR) to compare the performance of five statistical methods for interim monitoring. We examined the impact of the number of interims via an extensive simulation study to determine the optimal design.

Methods
We constructed three group sequential designs using the Haybittle-Peto, O'Brien-Flemming and Hwang-Shih-DeCani approaches and two Bayesian adaptive designs based on the posterior probability and predictive probability, examining one, two, four, and nine equally spaced interim analyses. Datasets were simulated 10,000 times under the null and alternative scenarios, based on the same assumptions made for the two-arm ADRENAL and NICE-SUGRA trials. The trial operating characteristics evaluated were: type-I and type-II error rates; probability of making an early correct and incorrect decision; expected sample size; and bias of treatment effect estimate. An unadjusted logistic regression was performed with the 90-day mortality as the outcome and the randomised arm as the covariate. The null hypothesis for no between-arm treatment difference used a two-sided significance level (α) at 0.05.

Results
Under the null scenario, the type-I error rate was well maintained with an increasing number of interims using group sequential designs, but it was inflated using the Bayesian Posterior Probability approach beyond one interim. The expected sample size was reduced on average by over 30% for nine interims, with no bias observed in the treatment effect estimate for all designs. The O'Brien-Flemming and Bayesian Predictive Probability approaches achieved the highest overall probability of stopping for futility. Under the alternative scenario, the two Bayesian approaches showed the highest overall probability of stopping for efficacy for the ADRENAL trial, whereas the Haybittle-Peto approach obtained the greatest power for the NICE-SUGAR trial. The estimate became more negatively biased as the number of interims increases.

Conclusions
This simulation study demonstrates that with the right design, the correct conclusion can be reached with a significantly reduced sample size. Triallists should consider increasing the number of interim analyses as the saving in sample size as well as the chance of reaching the correct answer early increases substantially.

P-010

Decision making under uncertainty in PI-II dose finding trials in Oncology

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Introduction
There is increased interest in dose finding methods in oncology using both toxicity and efficacy endpoints with targeted therapies. Patients typically seek treatment benefit from entering a trial. It is therefore unethical to put patients at undue risk of toxicity or treat at doses where evidence suggests alternatives may be more beneficial. A phase I trial design proceeds in stages with a decision as which dose to give the next group of patients made after every stage. The success of a trial is measured by its ability to locate an optimal dose and its tendency to suggest treatment at undesirable doses. Bayesian decision theoretical approaches have previously been found to be in theory ethically and scientifically sound. In practice however, it is challenging to specify a utility function capturing clinical preferences while maintaining good operating characteristics sensitive to utility specification.

Methods
Outcomes from treatments are not deterministic; utilities are a measure of preference when facing an uncertain outcome. We propose a design where attributes for utilities are defined for probabilities associated with binary efficacy and toxicity events. In doing so, clinicians can account for individual patient risk while meeting wider trial objectives, i.e. identifying a recommended phase II dose. The two attributes are shown to be utility independent; allowing evaluation of more easily assessed single attribute utility functions. We argue attitudes to risk for univariate utility functions follow heuristics from prospect theory. Namely they are framed from the perspective of a reference point, with a risk averse attitude for perceived gains, and risk seeking for losses. Additionally, with loss aversion it is ethical to avoid losses more so than to pursue gains.

Results
We outline why using heuristics from prospect theory to structure utilities around outcome probabilities is justified in this setting. The design is compared for a range of scenarios to an alternative design not accounting for uncertainty in terms of the percentage of correct selection and numbers of patients treated at each dose. The design in general gives comparable operating characteristics but excels in difficult scenarios when the optimal dose and/or unsuitable doses are close to stopping boundaries.

Discussion
The specification of a utility function can be challenging with two continuous attributes as it can involve evaluation at an infeasible number of points. We propose a structure to simplify this and in doing so can improve upon operating characteristics.

P-011

Application of a Bayesian value-based sequential design to the HERO trial

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Introduction
Efficiency is often cited as a key motivation for the development of sequential trial designs. However, many proposals feature stopping rules that do not incorporate explicit consideration of the trade-off between the expected benefits and costs of stopping/continuing recruitment. We consider a Bayesian decision-theoretic model of a value-based sequential trial that aims to maximise the overall value generated by the trial (i.e. the expected benefits accruing to patients from better-informed decision making, minus the costs of the health technology and the trial). We investigate the potential advantages and disadvantages of this approach via retrospective application of this design to data from the Hydroxychloroquine Effectiveness in Reducing symptoms of hand Osteoarthritis (HERO) trial.

Methods
We used the data from HERO, together with sequential applications of multiple imputation, to reconstruct what might have happened had the trial been run according to the value-based sequential design. We used resampling to investigate the operating characteristics of this design, and estimate the additional value delivered over a fixed design for two maximum sample sizes: 248 ('Case A', the same as the original trial) and 496 ('Case B').

Results
Recruitment to HERO would not have stopped early had it been run according to the value-based sequential design. For Case A, the mean sample size of the resampled trials was 247, saving around £800 of the trial budget. For Case B, the mean sample size was 469, saving around £22,400. In both cases, 55-57% of the resampled trials resulted in a final estimate favouring placebo, meaning 45-43% resulted in an adoption decision at odds with the results of the original trial.

Discussion
For this case study, the value-based sequential design delivered limited additional value compared with the fixed design (less than 0.5% for both sample sizes). This limited benefit was driven by two factors. Firstly, the equivocal cost-effectiveness data observed in HERO meant the signal was rarely extreme enough to indicate early stopping. Secondly, the speed of accrual and delay between recruitment and observation of outcomes meant there was limited opportunity for the value-based sequential design to stop early. The results of this case study provide insight into how the value-based design might be practically implemented and highlight a number of key elements of a clinical trial's design that trial teams may wish to consider before applying this approach prospectively (for example, the delay between randomisation and observation of outcomes relative to the length of recruitment).

P-012

Should RECOVERY have used Response Adaptive Randomization? Evidence from a simulation study

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Background
The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is aimed at addressing the urgent need to find effective treatments for patients hospitalised with suspected or confirmed COVID-19. The trial has had many successes, including discovering that dexamethasone is effective at reducing COVID-19 mortality, the first treatment to reach this milestone in a randomised controlled trial. Despite this, it continues to use standard or `fixed' randomization (FR) to allocate patients to treatments. We assessed the impact of implementing response adaptive randomization (RAR) within RECOVERY using an array of performance measures, to learn if it could be beneficial going forward. This design feature has recently been implemented within the REMAP-CAP trial.

Methods
Trial data was simulated to closely match the data for patients allocated to either standard care or dexamethasone in the RECOVERY trial from March-June 2020, representing two out of five arms tested throughout this period. Two forms of FR and two forms of RAR were tested. Randomization strategies were performed at the whole trial level as well as within three pre-specified patient subgroups defined by patients' respiratory support level.

Results
RAR strategies led to more patients being given dexamethasone and a lower mortality rate in the trial. Subgroup specific RAR reduced mortality rates even further. RAR did not induce any meaningful bias in treatment effect estimates, but reduced statistical power compared to FR, with subgroup level adaptive randomizations exhibiting the largest power reduction.

Conclusions
Using RAR within RECOVERY could have resulted in fewer deaths in the trial. However, a larger trial would have been needed to attain the same study power. This could potentially have prolonged the time to full approval of the drug, unless RAR itself led to an increased recruitment rate. Deciding how to balance the needs of patients within a trial and future patients who have yet to fall ill is an important ethical question of our time. RAR deserves to be considered as a design feature in future trials of COVID-19 and other diseases.

P-013

PATHOS: A Phase III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human papillomavirus (HPV)-positive oropharyngeal cancer

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Introduction

Current treatment protocols for Human Papillomavirus Positive Oropharyngeal Squamous Cell Carcinoma (HPV+ OPSCC) cause significant acute and late toxicities, including swallowing dysfunction affecting quality of life (QOL). The PATHOS study aims to assess whether swallowing function can be improved following transoral resection of HPV+ OPSCC by reducing the intensity of adjuvant treatment, without resulting in inferior survival outcomes.

Methods

PATHOS is an international, multicentre, parallel group randomised controlled trial enrolling patients with HPV+ OPSCC staged T1-3 +/- ipsilateral nodes, suitable for transoral surgery and neck dissection.
Following surgery and histopathological assessment of surgical specimens, participants are risk-stratified into 3 groups:
Group A: No further adjuvant treatment as per standard of care
Group B: Participants with T3 tumours or T1-2 with close (1-5mm) margins, perineural or vascular invasion or >1 ipsilateral lymph nodes, randomised to RT 60Gy in 30# over 6 weeks (Control Arm B1) or 50Gy in 25# over 5 weeks (Test Arm B2).
Group C: Participants with high risk pathological features, <1mm margins or Extracapsular Spread (ECS), randomised to RT 60Gy in 30# over 6 weeks with (Control Arm C1) or without (Test Arm C2) concurrent Cisplatin.

Progress

PATHOS Phase II showed feasibility of recruitment and safety of the approach, enrolling 242 participants across 20 UK sites by October 2018. With oversight from the Funder, Sponsors and Independent Data Monitoring Committee, PATHOS was adapted into a Phase III study, increasing the sample size to 1100 and combining the primary endpoint of 12-month MDADI superiority with overall survival.
As a result of close partnerships between the UK, and international Investigators, Funders and Coordinating Bodies, PATHOS has opened in 15 more UK sites and in 4 other countries (USA, Australia, France, Germany). Currently a total of 698 participants are registered and 424 randomised in either Group B or C. Recruitment will continue until the end of 2023.

Conclusions

The PATHOS study is powered to prove survival non-inferiority in the de-intensified adjuvant treatment arms. However, through the development and strengthening of UK and international collaborations, we are able to utilise the data that is being collected to maximise study outputs without compromising the co-primary endpoints. These collaborations include the validation of artificial intelligence radiotherapy planning tools, impact and economic assessments and translational research sub-studies and programmes including genome sequencing.

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P-014

ABA-feed: The effectiveness and cost-effectiveness of Assets-based feeding help Before and After birth for improving breastfeeding initiation and continuation

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Introduction
As a trial initially recruiting and implementing an intervention in a predominantly face to face setting, ABA-feed made essential revisions to training, recruitment and delivery moving to a become an remote enabled trial. These are reviewed here to inform on a practical approach post-pandemic public health multi-centre trials.

Methods/Approach
The aim to recruit 2,730 nulliparous women from scanning and antenatal clinics from 10-15 sites around the UK was adapted due to the COVID-19 pandemic, lockdown measures, and the restricted access to clinical settings moving forwards. The trial design for ABA-feed was modified to cover not only multiple recruitment options (face to face and remote) but also the training of peer supporters and the delivery of the intervention.
The new trial design enabled; remote consent, randomisation and baseline data completion directly onto the trial database while speaking with the participant via telephone or video conference. The database was also designed so that these processes could take place in person when clinics were accessible. To obtain maximum recruitment an ABA-feed participant website was developed (and advertised through social media) where women could register their interest in the trial. The complexity of the variety of recruitment sites and locations also required individual solutions to recruitment. The remote option was beneficial to the more rural areas in Wales and Scotland. It also enabled recruitment to continue when NHS sites did not have the capacity to dedicate research staff to recruitment. The training of approx.100 peer supporters took place completely remotely via video conference using video clips and presentations with an accompanying training handbook. The intervention itself was originally designed so that the peer supporters could meet in person with the expectant mothers at around 30 week's gestation. Due to social distancing and potential reluctance to meet face to face this could be done via video-conferencing facility or over the telephone if women prefer. Follow-up data is being collected via completion of questionnaires through a link sent directly to women's email addresses.

Results Structure and Timelines
As of May 2022 the trial has recruited 450+ women across 15 sites. The 6 month internal pilot is due to end mid-July 2022.

Potential relevance and Impact: Adaptations to the ABA-feed trial processes improved flexibility of trial delivery, for central and site staff, and participants. This pragmatic approach should be implemented in trials in the future.

P-015

Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART): a phase III randomised, double-blind, placebo-controlled, multi-arm, multi-stage, adaptive platform trial

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Introduction

Motor neuron disease (MND) is a rapidly fatal neurodegenerative disease. Despite decades of research and clinical trials there remains no cure and only one globally approved drug, riluzole that prolongs survival by 2-3 months. Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART) aims to evaluate the efficacy of drugs efficiently and definitively in a multi-arm, multi-stage, adaptive trial. The first two drugs selected for evaluation in MND-SMART are trazodone and memantine.

Methods and proposed analysis

Initially, up to 531 participants (177/arm) will be randomised 1:1:1 to oral liquid trazodone, memantine or placebo using the minimisation variables: riluzole, gastrostomy, non-invasive ventilation and long survivor status (>8 years since diagnosis at baseline). The co-primary outcome measures are the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) and survival. Most trial assessments can be completed remotely supported by telehealth, and treatments are liquids due to potential swallowing difficulties highlighted by the patient advisory group. This is a 4 stage trial with 3 interim analyses. The decision to continue randomising to arms after each interim analysis will be made by the Trial Steering committee who receive recommendations from the Independent Data Monitoring Committee. The primary analysis of ALSFRS-R will be conducted when 150 participants/arm, excluding long survivors, have completed at least 18 months of treatment giving 83% power to detect a 25% reduction in rate of decline of ALSFRS-R compared to placebo (one-sided 2.5% significance level). Participants will continue to take their allocated treatment for arms continuing to the last stage until 113 deaths have been observed in the placebo group, at which point analysis of survival will have 90% power to detect a hazard ratio of 0.65 (at a one-sided 2.5% significance level). The trial design ensures other promising drugs can be added for evaluation in planned trial adaptations. Using this novel design reduces time, cost, and number of participants required to evaluate drugs and reduces exposure of participants to potentially ineffective treatments.

To date the trial has 17 recruiting sites across the UK and has randomised 340 participants. Interim analysis 1 for memantine and trazodone was completed in March 2022 and will be presented at the meeting.

Ethics and dissemination
MND-SMART was approved by the West of Scotland Research Ethics Committee on 2 October 2019. (REC reference: 19/WS/0123). Results of the study will be submitted for publication in a peer-reviewed journal and a summary provided to participants.

ClinicalTrials.gov Identifier: NCT043028

P-016

Designing a Bayesian interim analysis with an ordinal outcome for efficacy, harm and futility in FOxTROT 3 (A phase III trial in The FOxTROT Platform)

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Introduction

Bayesian adaptive designs are increasingly used in confirmatory randomised, controlled trials (RCTs). However, they are more common in early phase trials or those with a simple binary endpoint and methods for implementation are often opaque, therefore uptake remains limited. This work explores designing a Bayesian interim analysis for efficacy, harm and futility in the FOXTROT 3 trial, a phase III, frequentist-designed RCT for patients with colon cancer suitable for surgery. The primary endpoint is tumour regression grade (TRG), an ordinal pathology outcome, categorised as no, poor, partial, moderate and complete response, assessed at surgery. An odds ratio (OR) <1 for TRG indicates benefit for the experimental group compared to control.

Methods

Simulations were conducted where a range of priors and stopping boundaries were explored for the interim analysis. The following priors were specified: flat and sceptical priors for analysis of efficacy, flat and optimistic priors for analysis of harm and a flat prior only for futility analysis. Trials with a range of true treatment effects as represented by ORs ranging from 0.2-2.0 were simulated, where the maximum trial sample size (nMax) was 714 patients and the interim analysis occurs when 300 patients have reached the primary outcome (nInterim). Priors and associated stopping rules were then applied in the simulated trials. The following stopping rules were explored for each analysis: for efficacy, a posterior probability (PP) of efficacy >0.95 and 0.99 at nInterim; for harm, a PP of harm >0.7 and 0.8 at nInterim; For futility, a probability <0.05, 0.1 and 0.2 that the PP of efficacy will be >0.95 at nMax, given the results at nInterim. Bayesian power and type I error were estimated for each scenario.

Results: The outcome of simulations showing the probability of stopping for efficacy, harm or futility at nInterim for each scenario based on the OR, priors and stopping boundaries specified will be presented. Bayesian power was not significantly decreased when stopping for futility was permitted compared to when it was not, and type I error could be controlled. Interim analysis stopping guidelines based on these results are to be discussed with the trial team and oversight committees before formalisation into the trial (expected August 2022).

Conclusions

Bayesian methods can be applied to frequentist designed trials with ordinal outcomes and operating characteristics can be obtained. These methods are an intuitive way to provide evidence for the questions asked at interim analyses, particularly for futility.

P-017

Sample size for a cluster trial with co-primary outcomes and superiority and non-inferiority hypotheses: the PROMPPT study

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Introduction

Sample size calculations in randomised controlled trials (RCTs) are commonly based on a single primary outcome and use a superiority design to test for treatment effectiveness. For some trials, however, evaluating treatment effectiveness is more complex, requiring multiple outcomes to be considered on a superiority and non-inferiority basis, with randomisation not at the patient level. Our aim is to describe the sample size calculation for one such cluster trial (the PROMPPT study).

Methods/Approach

The PROMPPT study aims to evaluate whether a new pharmacist-led intervention is more likely to reduce opioid pain medication use than usual care in patients prescribed long-term opioids for persistent non-cancer pain. Achieving a reduction in opioid use is desirable, as, for many, such medication does not reduce pain, but causes unwanted side-effects. Therefore, for the intervention to be successful, we required that: (1) opioid use be reduced, and (2) pain severity/interference not be increased. This defined our co-primary outcomes, tested as superiority and non-inferiority hypotheses respectively, at 12-month follow-up. Sample size was calculated in four stages: (1) evaluation of medical record data, current literature and clinical knowledge to inform calculation parameters and likely recruitment rates; (2) calculating the sample size for each outcome as if independent outcomes in an individually-randomised RCT (alpha = 0.05; power = 0.90); (3) taking the largest sample size in stage two, and using the intersection-union test to evaluate power for a range of plausible co-primary outcome correlations; and (4) inflating the sample size for the clustered design (GP practice-level randomisation) and loss-to-follow-up.

Results

Sample sizes of 260 and 468 patients were calculated at stage two. Taking the largest (n=468), assuming independent outcomes (a worst-case-scenario for power), gave 99% power, superiority hypothesis; 90% power, non-inferiority hypothesis; and 89% (0.90*0.99) power, co-primary hypothesis. As 89% approximated our desired power, the stage 3 sample size was not inflated further. We did, however, inflate the sample size for clustering and loss-to-follow-up, giving a planned sample size of 896 patients to recruit from 30 practices; a feasible sample size when judged against likely patient eligibility and recruitment rates in medical record data.

Discussion

The sample size for the PROMPPT study was derived accounting for hypothesis type, co-primary outcomes, clustered design, and loss-to-follow-up. It is important to consider these factors when planning sample sizes for trials of this nature.

P-018

Parent views on Cluster Randomised Trials: considerations from two trial feasibility studies

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Introduction
The majority of literature and guidance on recruitment and conduct of Cluster Randomised Trials (CRT) has been derived from 'expert' opinion. There is a lack of empirical research exploring the views of the public to inform the acceptability, design and conduct of CRT's. Without such insight there is a risk that current recruitment and consent processes may not consider the needs and perspectives of patients and families. This study aimed to synthesise parent data from two trial feasibility studies in neonatal and paediatric settings.

Methods
Qualitative synthesis, comparing and contrasting parent interviews from the GASTRIC study, which explored feasibility and design (e.g. Cluster/ Individual randomisation) of a clinical trial of no routine measurement of stomach contents to guide feeding in preterm or sick neonates and ventilated children, and the PICNIC pilot study to determine the feasibility of a CRT comparing different models of infection control in critically ill children.

Results
We thematically analysed 54 interview transcripts including GASTRIC n= 31 parents (22 mothers, nine fathers) of children with relevant experience and PICNIC n= 23 parents (15 mothers, eight fathers) of children involved in the pilot CRT.

Parents in both studies found the cluster design acceptable and preferable to an individual randomisation approach for what were viewed as low risk studies. The main reason provided was the acceptability of the proposed trial arms. However, some parents in PICNIC had a misconception that their child would have received one of the treatments anyway. Parents cited the trust they have in medical staff to make decisions regarding the care of their child in an ethical manner. Also stating that a cluster design prevents concerns about children receiving different care within the same ward. Views on seeking prospective consent differed between the two studies but all valued a conversation about the study with clinicians. How these conversations are conducted needs careful consideration to avoid miscommunication of study aims and 'usual care'. In addition there is a need to clarify what withdrawal of consent for a CRT means.

Conclusions
Our findings suggest that parents found a CRT design acceptable for these neonatal and paediatric trials, yet there is a need to carefully consider how we communicate CRT's to parents at the pre-trial stage. Further work is needed to explore the views of the public on approaches to recruitment and consent in CRT's.

P-019

Accounting for the uncertainty in the ICC estimate when calculating the sample size for cluster-randomised trials with continuous outcomes

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Introduction
Calculating the sample size for cluster-randomised controlled trials (cRCTs) requires an inflation factor to account for the intra-cluster correlation coefficient (ICC), a value that quantifies the degree of dependence within clusters. Estimates of the ICC are often taken from pilot or preliminary trials and are estimated with uncertainty. This uncertainty can have a marked impact on the resulting power of the trial being designed. We aimed to develop an approach to account for the uncertainty in the ICC estimate when calculating the sample size for a cRCT with a continuous outcome.

Methods
This was a methodological study using simulated data.
We developed an approach to account for the imprecision in the ICC estimate using numerical methods to integrate the sample size for a cRCT over plausible values of the ICC. This gives a sample size which is the average over all these plausible values.
We simulated 4 hypothetical scenarios which take an ICC estimate from pilot cRCTs of differing sizes. For each, we generated distributions of plausible values for the ICC estimated using Searle's, Swiger's and Fisher's methods. Finally, we calculated the sample size for a main cRCT using our integrative adjustment over the plausible ICC values provided by the three different methods. We compared these with two other common approaches.
A sensitivity analysis explored the impact of this approach on the main trial power in a realistic scenario.

Results
In each case the main trial sample size using our integrative adjustment was greater than using the point estimate for the ICC which does not account for its imprecision. The overall sample size also depended on the number of clusters in the main trial. We found that this approach consistently preserved main trial power at 10% or more above using a simple ICC point estimate for realistic conservative scenarios.

Discussion
The proposed method estimates the sample size for a cRCT that accounts for the imprecision in the ICC and thus can help mitigate potential power loss that can result from using an uncertain point ICC estimate. This method can be used with any means of estimating distributions of plausible values for the ICC, allowing broad applicability. This work has been published in Statistical Methods in Medical Research and R code for the calculation of the adjusted cRCT sample size is available.

Resources
Paper: doi.org/10.1177/09622802211037073
R code: journals.sagepub.com/doi/suppl/10.1177/09622802211037073/suppl_file/sj-R-4-smm-10.1177_09622802211037073.R

P-020

Intra-cluster correlation for patient reported outcome measures in individually randomised cluster trials

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Introduction
Many trials that are individually randomised have some form of clustering, for example hospital sites/centre or therapist. Ignoring clustering in a cluster randomised controlled trial (C-RCT) can cause the standard error to be incorrectly estimated, which leads to incorrect type I error rates. To account for this, the sample size for a C-RCT is inflated by a design effect (DE) based on the intra-cluster correlation (ICC) and cluster size. However, often for an individually randomised cluster trial, this level of clustering is not taken into account when calculating the sample size.
Our aim was to calculate the ICCs from a number of individually randomised trials that had a patient reported outcome measure (PROM) as an outcome and clustering in the trial design. This analysis aims to inform how much sample sizes should be inflated in the design of future individually randomised cluster trials.

Methods
We calculated the ICC using ANOVA from 12 different individually randomised trials which had clustering in at least one-arm. For those with clustering in one-arm, we calculated the ICC in that arm. Across those 12 trials, there were 31 different PROMs, measured at various times post randomisation (range 0.25-18 months). Clustering was either at therapist level, centre level, or both. The DE was calculated for the ICC of the most popular PROM in our trials, EQ-5D.

Results
We calculated 278 (171 two-arm, 107 one-arm) ICCs across the 12 trials. For two-arm clustering, the median average cluster size for centre level was 28.6 (range: 8 – 120) and for therapist level was 21.3 (range: 11.4 - 76.7). For centre level, the median ICC was 0.000 (max: 0.238) and for therapist level, the median ICC was 0.000 (max: 0.053). The DE for the median average cluster size and the median ICC was 1.00 for both centre and therapist level. For one-arm clustering (therapist level only), the median average cluster size was 7.8 (range: 3.5 – 22.7). The median ICC was 0.007 (max: 0.291). The DE was 1.05.

Discussion
Overall, the ICCs for individually randomised cluster trials with PROMs are small. When clustering in one-arm is of concern, in the absence of any trial population specific outcome data or information, an assumed ICC of around 0.01 would not be unreasonable for sample size estimation. For two-arm trials, in the absence of any trial population specific outcome data or information, an assumed ICC of around 0.01 would be conservative.

P-021

A Bayesian Power Prior Approach for Incorporating Pilot Data into Cluster Randomised Controlled Trial Analysis: A Simulation Study

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Introduction
In Cluster Randomised Controlled Trials (CRCTs), randomisation occurs at a group level, which has methodological implications that make design, conduct and analysis more complicated. Typically, CRCTs are analysed using mixed-effects regression. The Power Prior is a Bayesian analysis technique in which historical data is parameterised as an informative prior distribution, then discounted according to the similarity between the historical and current datasets. A Normalised Power Prior (NPP) approach has been proposed which accounts for the clustered structure of CRCT data, enabling incorporation of evidence from historical data (e.g. pilot study) into the definitive trial analysis whilst allowing for potential differences between the two datasets, where greater differences result in less information borrowing. A simulation study is presented which aimed to: (i) verify that the NPP appropriately discounts historical data according to the similarity between datasets, (ii) assess the performance of the NPP approach compared to the frequentist mixed-effects model and simple dataset pooling.

Methods
A simulation study was undertaken generating two datasets at each iteration: historical data (with which to construct the power prior) and current data. A range of scenarios was considered, with varying treatment effects, intracluster correlation coefficients and sample sizes (number of clusters) for each of the two simulated datasets.
Properties of both the treatment effect estimator and corresponding interval were calculated to assess the performance of the NPP analysis. Specifically, the bias, mean squared error (MSE) and empirical standard error are presented, as well as the coverage and average width of the 95% intervals.

Results
The results of the simulation study verify the sensitivity of the NPP method in appropriately discounting evidence from historical data when there is dissimilarity between the datasets. Furthermore, the results indicate an increase in bias when using the NPP approach compared to the more traditional mixed-effects model (but a reduction compared to simple pooling), and a reduction in MSE and empirical standard error. In terms of properties of the interval, coverage was reduced under certain scenarios, and interval widths were consistently narrower in comparison with the frequentist mixed-effects approach.

Discussion
The NPP approach offers a principled means of specifying an informative prior distribution for analysis of CRCT data given relevant historical data. Under certain scenarios, estimates may be biased, but estimation is also more precise and therefore there may be potential to facilitate more efficient CRCT design.

P-022

Strategies to minimise and monitor biases and imbalances by arm in surgical cluster randomised trials: evidence from ChEETAh, trial in seven low- and middle-income countries

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Background
Cluster randomised controlled trials (cRCT) present challenges regarding risks of bias and chance imbalances by arm. This paper reports strategies to minimise and monitor biases and imbalances in the ChEETAh cRCT.

Methods
ChEETAh was an international cRCT (hospitals as clusters) evaluating whether changing sterile gloves and instruments prior to abdominal wound closure reduces surgical site infection at 30 days postoperative. ChEETAh planned to recruit 12,800 consecutive patients from 64 hospitals in seven low-middle income countries. Eight strategies to minimise and monitor bias were pre-specified: (1) minimum of 4 hospitals per country; (2) pre-randomisation identification of units of exposure (operating theatres, lists, teams or sessions) within clusters; (3) minimisation of randomisation by country and hospital type; (4) site training delivered after randomisation; (5) dedicated 'warm-up week' to train teams; (6) trial specific sticker and patient register to monitor consecutive patient identification; (7) monitoring characteristics of patients and units of exposure; (8) low-burden outcome-assessment.

Results
This analysis includes 10,686 patients from 70 clusters. The results aligned to the eight strategies were: (1) 6 out of 7 countries included >4 hospitals; (2) 87.1% (61/70) of hospitals maintained their planned operating theatres (82% [27/33] and 92% [34/37] in the intervention and control arms); (3) minimisation maintained balance of key factors in both arms; (4) post-randomisation training was conducted for all hospitals; (5) the 'warm-up week' was conducted at all sites, and feedback used to refine processes; (6) the sticker and trial register were maintained, with an overall inclusion of 98.1% (10686/10894) of eligible patients; (7) monitoring allowed swift identification of problems in patients inclusion and key patient characteristics were reported: malignancy (20.3% intervention vs 12.6% control), midline incisions (68.4% vs 58.9%), elective surgery (52.4% vs 42.6%); (8) 0.4% (41/9187) of patients refused consent for outcome assessment.

Conclusion
cRCTs in surgery have several potential sources of bias that include varying units of exposure and the need for consecutive inclusion of all eligible patients across complex settings. We report a system that monitored and minimised risks of bias and imbalances by arm, with important lessons for future cRCTs within hospitals.

P-023

Estimating Intra-cluster Correlation Coefficients for Neonatal Cluster Trials from Routinely Recorded National Data

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Background
Neonatal data have natural clusters: multiple birth sets clustered by mother and the neonatal unit administering care. It is well established that accounting for clustering needs to be considered when conducting randomised controlled trials. There are few published intra-cluster correlation coefficients (ICC) for neonatal outcomes for any level of clustering. Furthermore, there is a lack of neonatal cluster randomised trials with large sample sizes in the literature. Using routinely recorded data can be a convenient, quick and cost-effective way to estimate ICC which are essential for neonatal study design.

Methods
Routinely recorded data held in the National Neonatal Research Database from all neonatal admissions in England, Scotland and Wales between January 2016 and January 2020 were analysed. ICC and their 95% confidence intervals were calculated for core neonatal outcomes and others commonly used in trials, at the level of both the neonatal unit and mother. Results were stratified by gestational age group and neonatal level of care, which were chosen to represent typical neonatal trial populations. The design effects of a hypothetical neonatal cluster trial were calculated for all outcomes to illustrate the impact of clustering on sample size considerations.

Results
Overall, mother level ICC estimates were larger than neonatal unit level estimates. ICC varied from 0.0008 to 0.0642 for neonatal unit clusters (N=184 clusters) and 0 to 0.5957 for mother clusters. Neonatal unit level ICC were low for mortality (0.0054, 95% CI 0.0039, 0.0068) and other core outcomes (severe necrotising enterocolitis 0.0042, 95% CI 0.0020, 0.0063) and were higher for outcomes related to care delivery (duration of intensive care in days 0.0237, 95% CI 0.0177, 0.0298; days receiving parenteral nutrition 0.0265, 95% CI 0.0197, 0.0332). The stratification groups revealed lower gestational age groups tended to have high neonatal unit level ICC estimates whereas the opposite was generally seen for mother level ICC estimates. The design effects for the combined effect of both clustering levels ranged from 1.10 to 3.78. Design effects varied widely between outcomes and stratification levels.

Conclusions
Clustering at the level of the neonatal unit and the mother can be estimated easily and precisely for key neonatal outcomes using routinely recorded national neonatal data. As these estimates vary across outcomes and trial populations, they are an important application to inform the design of neonatal studies and calculate sample sizes for neonatal trials to improve their rigour.

P-024

Get help with the Intra-cluster correlation coefficient (ICC): a Shiny app for Cluster Randomized Trials

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Introduction
In Cluster Randomized Trials (CRT) participants are randomized as groups (clusters) rather than individually. The intra-cluster correlation coefficient (ICC) is a measure of between-cluster variability and it is crucial to take this parameter into account when calculating the sample size of a CRT. Although reporting ICCs in trial reports is considered good practice and recommended by the CONSORT statement for CRTs, this is something that is not done systematically. Due to this and other uncertainties, obtaining adequate ICC estimates is often difficult. A Shiny app could help researchers without deep methodological knowledge to choose appropriate ICCs before a trial and assist with its estimation during or after a trial.

Methods/Approach
I developed a Shiny app that helps to estimate the ICC in different scenarios with a variety of methods for binary and continuous outcomes. 1) A Bayesian approach can be used to derive a posterior distribution for the ICC based on a selection of ICCs from relevant sources, and the 95th percentile of this posterior distribution can be used for the sample size calculation. 2) If the proportions of the outcome are known for all the clusters before a trial with routine data, then the ICC can be estimated by a method based on the assumption of a beta distribution for binary outcomes. 3) The ICC can also be estimated for continuous or binary outcomes from a dataset provided by the user a) during the trial to check the assumptions of the original sample size calculation, or b) to estimate the ICC(s) at the end of the trial. For this method, the user has also the possibility to adjust for the effect of the intervention if the clusters are in different arms in the dataset.

Results and Discussion
The aim of the “Get help with the ICC” application is to help users in the design of a CRT and/or the communication of results. The Shiny app allows data to be imported easily for estimation and provides a range of data visualizations in addition to various types of ICC estimates (from Mixed models, Generalized Estimating Equation, ANOVA, etc.). Further innovative methods will be added to the app in the future such as meta-analysis of ICCs or methods accounting for uncertainty in a single ICC estimate.

P-025

Factorial clinical trials: Insights from a Design of Experiments Perspective

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Introduction

Factorial clinical trials have been used to simultaneously evaluate more than one treatment factor when it is safe to assume no interactions between the factors or the trial has been powered to detect realistic interactions: a 2x2 factorial trial is then widely understood to give "two independent answers for the price of one". This tradition grew from including treatment factors as dummy variables in a regression model. From a Design of Experiments perspective, factorial designs are used to optimise "complex" interventions, which contain several potentially interacting components. Here, factors are generally included in an analysis-of-variance.

Methods

Outside of medicine, a distinction is made between simple and main effects. Simple effects are estimates of pairwise comparisons "inside-the-table", while main effects are estimates of marginal comparisons "outside-the-table". In a regression model, simple effects are estimated using dummy-coding (1,0), and their estimates are correlated; main effects are estimated using effect-coding (1,-1), and their estimates are independent or orthogonal. We performed a simulation study to confirm which parameters (or estimands) are estimated using a range of analysis options for 2x2 factorial trials, providing empirical estimates of standard errors under a variety of scenarios.

Results

Where dummy-coding is used, models with and without the combined effect of factors A and B estimate different parameters for the effects of A and B – neither are biased. When effect-coding is used, both models estimate the main effects; power to detect these effects is independent of the size of the AB interaction; and the AB interaction is measured on the same scale as the main effects. Effect coding redefines the main effects to be half what they are with dummy-coding. In the 2x2 case, the simple effect of factors A and B combined is four times the size of the AB interaction from the effect-coded model.

Discussion

Clinical trialists have traditionally been interested in estimating the simple effects of factors A and B. If interactions are plausible, these effects must be estimated by including the simple effect of A and B combined in the model, which is precisely equivalent to a four-arm analysis. Where factors A and B represent components of a complex intervention, interest turns to estimating main and interaction effects. These should be estimated using effect-coding, where sample size calculations for the main effects are unaffected by the size of the interaction and all effects of the same size can be estimated with equal power.

P-026

Typologies to standardise the reporting of anaesthetic interventions in clinical trials.

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Introduction

Evaluation of anaesthetic interventions through randomised controlled trials (RCTs) is fundamentally important for evidence-based anaesthesia care. Anaesthetic interventions are complex, often comprising multiple interacting components, and there is significant variation in how these are defined and reported. These issues, however, are not unique to anaesthesia. To address similar issues in surgical trials, a framework or 'typology' was developed to help standardise and monitor the delivery of surgical interventions. A similar approach in anaesthesia is needed. This study aimed to develop typologies (i.e. frameworks) to help triallists and clinicians approach standardisation of anaesthetic interventions in RCTs.

Methods

Separate typologies were developed for each main mode of anaesthesia: 1) General (GA), 2) Regional (RA), and 3) Sedation. Trial reports and associated protocols identified in a recent systematic review (SR) of anaesthesia RCTs provided the data for development of the provisional typologies. The Methods sections of the papers were scrutinized for text describing delivery of anaesthetic interventions. A framework approach to thematic analysis of qualitative data was used to code and categorise text into components of anaesthetic interventions. Initial coding frameworks were developed using six exemplar RCTs. Further RCTs were purposefully selected from the SR to ensure a range of foci and interventions were represented in the emerging typologies. An iterative process of selecting papers and amending the coding framework was repeated until data saturation was reached – the point at which the research team agreed no new categories were being identified with inclusion of additional papers.

Results

Data saturation of categories within the typologies was reached after inclusion of 15 RCTs each for GA and RA, and 13 RCTs for sedation. Each typology is structured into three main sections: 1) Expertise of the administrator of the anaesthetic intervention, 2) Setting/location of the anaesthetic procedure, and 3) Intervention components, including those taking place before, during and in the recovery from anaesthesia. The main area of difference between the three typologies are the intervention components that take place during the anaesthetic intervention, which are specific to each mode of anaesthesia.

Discussion

Initial typologies of the main components of anaesthetic interventions have been developed using qualitative analysis of trial reports identified in a recent SR of anaesthetic interventions. A mixed methods study with key stakeholders is now being undertaken to further refine the typologies to ensure they are acceptable and feasible for use by professionals conducting anaesthetic and peri-operative trials.

P-027

Building a dynamic randomisation system to allocate therapists within complex intervention trials: experiences and recommendations from the FReSH START and SAFE-PIT trials

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Introduction
In many clinical trials of complex interventions, the intervention, or components of an intervention may be delivered by individuals, such as psychological therapists, physiotherapists, or surgeons. Random allocation of the person delivering the intervention to participants, can reduce selection bias and confounding. For example, with non-random allocation, one person may always deliver the intervention to participants with more severe symptoms, so it may be difficult to separate the effect of the person delivering the intervention from the participants' characteristics.
However, randomising intervention deliverers can be problematic in practice, if only certain people are available to deliver the intervention or if participants exhibit strong needs about who they wish to see (such as needing to be treated by a therapist of particular gender).

Methods
FReSH START and SafePIT are randomised controlled trials of psychological therapy for adults who self-harm, where the intervention therapy is delivered by healthcare professionals. We present our experience of implementing a dynamic randomisation system to allocate therapists to participants and discuss its advantages and disadvantages.

Results
We developed a bespoke system to randomly select a primary therapist to deliver the intervention to each participant. This system uses a live list of available therapists each of whom can be marked as active or inactive, which is frequently updated. For example, therapists can be marked as inactive during parental or medical leave, and they can then be marked as active once they return.
In addition to the primary allocated therapist, a randomly ordered list of the remaining possible therapists at the corresponding site is provided. In cases where the primary therapist cannot deliver the intervention (for reasons such as short-term sick leave or participant need), the site team are advised to move systematically through the list of therapists to select the next suitable and available therapist to deliver therapy to the participant.

Discussion
The bespoke system required initial resource for development and ongoing resource to maintain the list of active therapists. The dynamic system allows us to reduce potential bias through therapists selecting participants to treat whilst incorporating flexibility in the system with respect to therapist capacity and participant need. However, to work optimally, it relies on good communication with sites regarding therapist availability.

P-028

Hospital at Home: A causal mediation analysis investigating the mechanism of action of an admission avoidance intervention

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As the number of older people increases rapidly, health and social care systems have to deal with a growing number of unplanned admissions. Hospital at Home (HAH) is an admission avoidance intervention, supported by a growing evidence base, allowing people to receive acute care in their own homes instead of in hospital, managed by a multi-disciplinary team. A UK clinical trial of HAH vs. Hospital care was recently published, the largest of its kind, providing new opportunities to explore factors that mediate the success of this multi-component intervention.

Methods
The trial randomised 1055 patients to HAH or Hospital care following an acute health event. The primary outcome was 'Living at home' at 6 months follow up (binary). Delirium was measured at baseline, 3 days, 5 days and 1 month. Readmission to hospital after initial treatment within 1 month was also measured. We use counterfactual arguments and logistic models, estimated using simulation methods, to estimate the Natural Indirect Effect (NIE) of HAH on risk of Long-Term Residential Care (LTRC), via the binary mediators Delirium and Readmission in the first month. The mediators will also be considered in a joint analysis where they form separate causal pathways.

Results structure
On average 3.5% fewer patients in the HAH group were in residential care at 6 or 12 months, compared with the Hospital group (95% CI [1%, 7.9%]). In a mediation analysis of Delirium only, the NIE was 0.006, meaning that around 0.6% (95% CI [0%, 1.6%]) of the treatment effect acted through delirium, with 2.9% a direct effect of HAH, as shown in the figure. Conversely, people randomised to HAH had a higher rate of readmissions, so that the effect mediated by Readmission acted in the opposite direction to the total effect on LTRC. Further analysis will consider the indirect treatment effects of Delirium and Readmission simultaneously.

Potential relevance
Exploring the mechanism of a complex intervention can provide guidance on more effective targeting. There is evidence that HAH is as effective as Hospital care, and so it is important to break down how it achieves this and when it may be superior. The current study provides some evidence that HAH may partly work by reducing incident delirium, allowing patients to maintain independence and avoid LTRC. Further analysis will explore the role of Delirium and Readmission together, investigating the mechanism of HAH and how it can be used to improve healthcare for elderly patients.

P-029

The effectiveness of nurse-led Information-Motivation-Behavioural skills model-based diabetes self-management education among patients with Type 2 Diabetes (IMB-DSME): randomised controlled trial

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Introduction
Diabetes self-management education can improve outcomes for people with T2DM but has not yet been tested in the Eastern Mediterranean Region, where the prevalence of diabetes is rapidly rising. The aim was to develop and examine the effectiveness of 'Information Motivational Behavioural Model-based Diabetes Self-Management Education intervention' (IMB-DSME) on self-care activities, quality of life and glycaemic control in people with T2DM attending outpatient clinics in hospitals in Jordan, a lower middle-income country.

Methods
This was a two-arm parallel group randomised controlled trial. 151 participants were recruited from two hospital sites (80.8% of 187 approached: Site 1, n=106; Site 2, n=45; mean age 55 ± (7.58); 57% female). Participants were randomised to either 12-week IMB-DSME intervention (n=77) or treatment as usual (TAU) control group (n=71) with outcomes assessed at baseline, 3 months (3m) and 6 months (6m) in both groups. IMB-DSME was developed using intervention mapping, and an Arabic translated version of PRIDE educational toolkit. Delivery was nurse-led, using motivational interviewing and brief action planning, through two face-to-face sessions (~20-30 mins at baseline/3m), weekly logs, and follow-up phone calls (~30 mins) at participant referred frequency over the 12 weeks. Primary outcomes were diabetes self-care behaviour score (DSCB: dietary modification, physical activity, medications management) measured by the Summary of Diabetes Self-Care Activities Scale sub-scales (SDSCA) and the Medication Adherence Rating Scale (MARS). Secondary outcomes were IMB main determinants: knowledge, motivation and behavioural skills, quality of life and glycaemic control (HbA1c). Analysis was by intention-to-treat, undertaken using STATA version 15.0.

Results
Mean score of the total of three self-care behaviours for IMB-DSME participants increased statistically significantly by 1.71 (95% CI, 0.84 – 2.59) and 1.61 (95% CI, 0.76 – 2.46) at 3m and 6m respectively compared to participants in the TAU group. Specifically, there was a statistically significant improvement in dietary modifications and medications management, and a non-significant trend towards increased physical activity. All IMB determinants of self-care (knowledge, motivation and behavioural skills) improved in the intervention group at 3m and 6m, as did quality of life. HbA1a improved in the IMB-DSME group at 3m for those who attended Site 1 only, although trial sites differed in treatment regimens. Attrition was low, 6.6% loss to follow-up.

Conclusion
IMB diabetes education for people with T2DM in Jordan improves diabetes knowledge, motivation and behavioural skills for self-care, self-care behaviours and quality of life over 6 months. Short-term improvements were observed in glycaemic control.

P-030

Aggregating prior distributions from experts for sample size calculations

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Introduction
When eliciting prior distributions from experts, it is often desirable to combine them into a single group prior. There are many methods of prior aggregation, which can roughly be categorised into two types. Mathematical aggregation methods combine prior distributions using a mathematical rule, while behavioural aggregation methods assist the group of experts to come to a consensus prior through discussion. As many commonly used aggregation methods have different requirements in the elicitation stage, there are few, if any, comparisons between them.

Methods
In order to choose a sample size for a randomised controlled trial into a novel diagnostic test for Motor Neuron Disease, we elicited a number of prior distributions from a group of experts directly involved in the trial and an independent group of experts. We then aggregated these prior distributions using a range of mathematical aggregation methods, including Equal Weights linear pooling, the Classical Method, and a Bayesian aggregation method. We also undertook an in-person behavioural aggregation with the trial experts, using the Sheffield Elicitation Framework, or SHELF. In this presentation, using expert answers to seed questions, for which the elicitors know the true values, we compare and contrast the different aggregation methods and their performance.

Results
We found that experts involved in designing the study were no more confident than the independent experts. We demonstrated that all aggregation methods outperformed the individual experts and that SHELF and the Classical Method performed best among them. Although we only completed SHELF with one group of experts, results show that SHELF was the best-performing aggregation method.

Discussion
SHELF is a good first choice of method if you are able to bring experts together in the same room, or virtual platform, for the elicitation. The Classical Method is a suitable alternative if you can develop appropriate seed questions, and can be used when the experts cannot be brought together. If external factors prevent more accurate methods being used, Equal Weights aggregation is typically more accurate than using the priors from individual experts.

P-031

Development and preliminary validation of a brief participant-reported questionnaire to measure the use of informal care, social care and personal expenses

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Introduction
Resource-use measurement is an integral part of assessing cost-effectiveness within trial-based economic evaluations. Typically, questionnaires are produced on an ad hoc basis and rarely validated. ModRUM, a generic, modular resource-use measure designed for collecting self-report healthcare resource-utilisation data has recently been rigorously developed and extensively tested in the UK (bristol.ac.uk/modrum). We aimed to develop bolt-on modules covering the use of informal care (i.e. unpaid care provided by relatives, friends or the community), social care and personal expenses.

Methods/approach
A rapid review was conducted to identify potential items, and supplemented by an online survey of social-care professionals to identify obvious omissions. A long-list of potential items was drawn up. Two focus groups were held (one with academic health economists, the other with people who access social care). Prior to the health economist focus group, participants were asked to prioritise appropriate items from the long-list for inclusion in brief modules; the results were used to guide discussions in both focus groups. Following qualitative analysis drawing on methods of constant comparison, items were selected and the health economists were asked to confirm agreement. Draft bolt-on modules were developed using similar phrasing and question structure as in the existing healthcare module. The draft modules are now undergoing face and content validity testing with health economists, and think-aloud testing with people who access social care.

Timing of potential results
Results are complete for the rapid review (which identified a list of ≈200 suitable items), the survey (24 social care professionals responded and one item was renamed as a result) and the focus groups (involving 5 health economists and 4 people who access social care). The focus groups shaped the social care and informal care modules, but suggested that the scope of personal expenses was unlikely to lend itself to a generic format. However, aids and adaptations came up as personal expenses that were very costly when they were relevant; the focus of the personal expenses module was therefore changed to explicitly cover aids and adaptations.
The health economist interviews and cognitive interviews for the drafted modules are in progress, and we anticipate results by the end of July.

Potential relevance and impact
Three new modules (covering informal care, social care and aids/adaptations) have been developed for use alongside ModRUM, a rigorously developed standardised healthcare-utilisation questionnaire. These modules extend the use of ModRUM to studies undertaking analyses from broader perspectives than healthcare.

P-032

Bayesian Mapping approaches from the EQ-5D-5L to two condition specific measures in Vitiligo patients: the VITIQOL and the VNS: Results from the Hi-Light trial.

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Introduction
Vitiligo presents a significant health related quality of life (HRQoL) burden. The Viti-QoL is a 16-item condition specific measure. The Vitiligo Noticeability Scale (VNS) is a 5-point clinical measure of vitiligo. Neither instruments are suitable for economic evaluation. No mapping algorithm to convert between EQ-5D-5L and these instruments exist, at present. We present new mapping algorithms that can be used to convert responses into utilities using data from the HI-Light randomized control trial using frequentist and Bayesian approaches.

Methods
Data from 181 patients were collected at two timepoints for each instrument; at screening and at 6 months for Viti-QoL and at 3 and 6 months for VNS. For Viti-QoL, a linear mixed effects model as well as Beta Binomial (BB) regression models were used for the total score across all 16 items . For VNS, a discrete 'U' shaped, non-linear 4-parameter model was used to model mean utility over each VNS category. The model was of the form EQ-5D = $\alpha + \beta*VNS + \gamma*\log(VNS+\delta)$. Several other model forms were also used. We used varying prior distributions for the parameters.

Results
For the Viti-QoL , the model selected was : 0.9736 -0.00216*Total VitiQoL score. The AIC was -583 and predicted vs observed mean (SD) utilities were 0.896 (0.158) vs 0.884 (0.029), respectively. For the VNS, the notable 'U shape' of the mean utilities resulted in a poor linear fit with an AIC of -9.1 and mean predicted vs observed utilities of 0.904 (0.153) vs 0.896 (0.050) respectively. The non-linear model was of the form: 0.91 +0.0566*VNS - 0.112*log(VNS+0.9). The 95% CI for each of the parameters α, β and γ were (0.82,1.19); (-0.052,0.164) , (-0.584,0.192) respectively. The predicted vs observed mean (SD) utilities were 0.918 (0.015) vs 0.917(0.014) respectively with an AIC of -25.6.

Conclusion
We have shown the feasibility of mapping between EQ-5D-5L and VITI-QOL and VNS for the first time. There remain challenges in modelling EQ-5D utilities with VNS due to the discrete nature of the distribution. Bayesian approaches may improve the model choice.

P-033

Economic evaluation on constrained resources: a case study of model development within a feasibility trial of weight loss intervention for the severely obese

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Introduction
In recent years there has been a rising demand by funders, like NIHR and MRC, for feasibility studies to utilise health economic modelling as a framework for exploring uncertainties in the evidence base and linking intermediate trial outcomes to policy relevant endpoints. However, there is little consensus regarding reporting standards for the health economic aspects of pilot/feasibility trials, resulting in inconsistency in approaches, methods and results. The resource and time constraints of feasibility trials often result in relatively simple analyses that do not capture population heterogeneity or equity considerations as a precursor to the main trial. The model development process is often insufficiently documented to ensure replicability. Given the range of approaches and reported results, many trials do not include these results in their progression criteria. The aim of this study is to address these limitations by exploring key steps and pragmatic approaches for development of health economic models within the context of a constrained resource environment. We illustrate this approach using a case study.

Methods
Case study: ImPROving GROUP treatment for people with severe obesity (PROGROUP) is a group-based behavioural intervention, designed as the core intervention for patients referred to Tier 3 weight management services in England. A feasibility trial is currently being undertaken, incorporating economic analyses to provide initial evaluations of the cost-effectiveness of PROGROUP versus 'usual care'. The initial model development framework was established through discussion between health economists, clinical trial specialists, clinicians, statisticians, and patient representatives.

Results
Four core steps in the development of the PROGROUP cost-effectiveness model were identified: 1) deciding whether a de novo model was required; 2) identifying a published model structure to replicate; 3) identifying limitations associated with the model structure in the context of the analysis population and objectives; 4) addressing these limitations. Identified limitations included the potential to include additional obesity-related clinical events, the ability of data sources to represent the severely obese patient population, uncertainty around weight-loss/gain trajectories, and requirements to update cost/utility data. Multiple approaches to addressing each limitation were outlined and discussed, before being formally included in the framework.

Discussion
In the discussion we highlight the strengths and limitations of the approach and discuss the potential adaptability to other settings, including those defined by disease area, health care system and intervention type. These processes can be used to inform reporting guidelines for feasibility studies and provide scope for resources to focus upon the incorporation patient heterogeneity.

P-034

The WHiTE Platform: Using REDCap to run surgical studies and minimise burden.

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Background
The WHiTE Platform is a framework of hip-fracture clinical trials in those aged 60 and over. It is designed to deliver multiple randomised comparisons of interventions by sharing the same infrastructure across different studies (comparisons) with a common underlying dataset. The Platform is coherent with a single set of ethical and regulatory approvals with an explicit legal basis and processing purpose for the use of patient-level data.

Methods
The Research Electronic Data Capture (REDCap) tool as the basis of the data collection system for the Platform. A single instance of REDCap was set up with four projects to manage "Site feasibility", "Screening & Consent", "Data Collection" and the "Delegation log"; access to these projects is determined by role within the study.
The base installation of REDCap was enhanced using several locally written External Modules, the installation of modules from the REDCap repository and the use of the REDCap "Data Entry Trigger" and API to seamlessly link to external randomisation systems. These additions facilitate the data flow through the screening, consent, and data collection processes, ensuring that sites can only access comparisons to which they are participating in, that the correct consent forms (and clauses) are displayed to the participant and only the data collection forms applicable to the consented studies are made available once for data entry.
The WHiTE Platform REDCap Project is configured to allow randomisation into both Clinical Trial of an Investigational Medicinal Product (CTIMP) and non-CTIMP studies. Using a method that considers the type of study, the country within the United Kingdom and the mental capacity of the patient, the appropriate consent form is displayed.

Results
Currently, there are two studies (one CTIMP and one non-CTIMP) utilising the WHiTE Platform infrastructure, with three more that will open by the end of the year. Just over 6000 patients have been screened by 25 sites, with 143 participants recruited into the two open studies. The implementation of the Platform methodology has simplified the process for both patients and research staff, facilitating improved monitoring by the study team, eliminated the use of incorrect consent forms and minimised the use of paper.

Summary
Using REDCap as the infrastructure for The WHiTE Platform is facilitating the screening, consent of patients and the subsequent data collection into multiple comparisons in a more efficient and long-term sustainable way.

P-035

Comparing Time Critical Randomisation Methods in Emergency Care Randomised Control Trials

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Introduction
In most emergency situations, treatment must be given urgently for best outcomes and any delays could cause further harm. This is why the deferred consent model is used in many emergency care trials, as it is likely potential participants may lack capacity to give consent themselves, and consulting others is not reasonably practicable.
Different randomisation methods are used in emergency care to try and fulfil the need for randomisation that is fast, easily accessible and reliable.

Methods
We will be comparing two methods of randomisation in an emergency care setting: sealed envelopes and a progressive web application (PWA).
Sealed envelopes are a traditional method of randomisation in emergency care trials, and are currently used in PARAMEDIC-3, an RCT comparing drug delivery systems in out of hospital cardiac arrests that began recruitment in November 2021. Envelopes have been used in a variety of trials in the past, but are they the best way to randomise in emergency care?
A progressive web application (PWA) is being developed to find a new way to randomise participants in emergency care, to ensure these are quick, reliable and accessible to staff. AIRWAYS-3, an RCT comparing airway management techniques in in-hospital cardiac arrests, and SIS, an RCT on the management of spinal injuries by paramedics, will use a specifically designed PWA to randomise via an electronic device in the hope to change randomisation practice in emergency care. These trials are both in set up and plan to start recruitment in September 2022 and November 2022 respectively.

Results, Structure and Timelines
We will compare the process of each randomisation method, and run small focus groups and discussions within each trial for feedback on each process. We will also be comparing cost, benefits and challenges, and the impact on patient safety and research integrity each method has.

Potential Relevance and Impact
In situations like a cardiac arrest or other high pressure emergency situations, any loss of time to treatment could cause irreparable harm to the patient. If the randomisation methods take any longer than 5 seconds or are not trusted by the clinicians, it will not be used and the trial will not succeed. Participant safety must always be the priority and therefore, fast and reliable randomisation methods are crucial to the success of randomised control trials in emergency care.

P-036

How low can you go? A novel trial design for optimising thresholds for intervention and identifying which patients will benefit from an established treatment

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Introduction
Optimising current clinical practice offers as much scope for patient benefit as developing novel treatments. Indication creep and litigation fear commonly lead to overuse of established treatments that are known to be effective for some patients but may be harmful for others. But how can we inform the optimisation of clinical practice? Traditional trial designs and hypothesis tests are ill-suited to optimisation problems. Thresholds for clinical intervention are often based on laboratory results. For example, a patient's platelet count, if low, can indicate an increased risk of bleeding. Platelet transfusions may prevent bleeding but are also associated with risks such as transfusion reactions and infection. So how low does a patient's platelet count need to be for the benefits of transfusion to outweigh the risks? We developed a trial design for answering this question, with many other potential healthcare applications.

Methods/Approach
Our design identifies the optimum threshold for intervention on a spectrum of patient characteristics—in this case a single biomarker but with scope to include others—by modelling a 'threshold-response curve'. The Threshold for Platelets (T4P) trial will reduce clinical variation in use of platelet transfusions in critically ill patients prior to minor procedures. Patients will be randomised to five platelet count thresholds for transfusion and a threshold-survival curve estimated.
We developed our analytic approach through extensive simulation, informed by routinely collected data, a survey of clinical practice and a clinician focus group. We propose a Bayesian approach which builds on the 'durations' design for establishing optimum duration of treatment. We compare the operating characteristics of fractional polynomials, cubic splines and Gaussian process models.

Results
We found that optimal model choice depends on the functional form of the threshold-response curve but that fractional polynomial models and Gaussian process models were both generally suitable. The trial will be implemented in a fully Bayesian framework, with analysis via Hamiltonian Markov chain Monte Carlo implemented in Stan. Various outputs will be obtained from the analysis, including an optimum threshold for intervention, and a range within which clinical discretion can be empirically justified.

Discussion
This approach represents a paradigm shift in evidence-based care, away from hypothesis-testing and towards continual clinical learning and personalised medicine. The output can be thought of as a model for individualised prediction of patient benefit. The design can be adapted to address many questions about optimising existing clinical practice and has extensive potential application in care decision-making.

P-037

Novel methodologies for large simple trials recruiting from UK primary care

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Introduction
Clinical trials measuring the effect of an intervention on clinical outcomes are more influential than those investigating surrogate measures but are costly. We developed methods to reduce costs substantially by using existing data in primary and secondary care systems, to answer a simple clinical question. The methodology has since been adapted for further studies.

Methods/Approach
- A bespoke web-based trial management system (trial database) is developed for each trial, housed within the secure NHS N3 Data Network
- The database communicates directly with the trial Toolkit software downloaded at participating practices, which issues queries searching entry criteria for GP review of eligibility
- Trial participation is invited using a highly secure automated on-line mail management system (Docmail) that ensures patients receive an invitation within 48 hours, and allows complete version control of trial documents
- Interested patients are contacted once for consent and any relevant trial procedures, with no follow-up visits required
- Events are tracked by upload of accumulating information in the GP database, patient contact, review of national Hospital Episode Statistics and mortality data
- Minimal workload for GP practices

Results and Discussion
- HEAT sent 188,875 invitation letters from 1,208 practices over a period of 5 years, had 30,166 volunteers, and 5,364 H. pylori positive patients randomised to active or placebo treatment. Recruitment was face-to-face, with collection of basic demographic data at the consent visit and a H. pylori breath test
- ATTACK has consented 3,902 patients so far, out of 44,601 invited. Recruitment started in 2019 but was halted in March 2020 due to the COVID pandemic. The trial was adapted to remove face-to-face consent and no sample collection (blood and urine to confirm presence of CKD on the day of consent). Patient eligibility now based on historic values in the patient record. Recruitment re-started in January 2021
- STATIC has been running in secondary care with poor recruitment and has been adapted to run in primary care. Recruitment started in May 2022. Consent is remote, but patients will be sent a kit to enable them to provide a urine sample by post
- Large-scale studies of important clinical outcomes can be conducted simply and at a fraction of the cost of those conducted by industry. This will help to ensure that trials of medical interest can be conducted successfully in the UK

P-038

Bayesian Optimisation for Simulation-based Sample Size (BOSSS): An interactive R package

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Introduction
Simulation offers a simple and flexible way to estimate the statistical power of any proposed clinical trial and determine its optimal sample size. Simulation can, however, be computationally demanding, meaning that finding the optimal sample size can require substantial time and computational resources. Bayesian optimisation offers a potential solution to this challenge by using a Gaussian process model of the power function to guide the search algorithm in an efficient manner. Despite a range of relevant software packages being available, implementing Bayesian optimisation to solve a specific trial design problem is not always straightforward.

Methods
We describe an interactive R package, built using the Shiny framework, which aims to help statisticians apply Bayesian optimisation to solve simulation-based sample size calculations. The package allows the statistician to use their own custom-built simulation routine and can be applied to problems with several design variables and several error rate constraints.

Results
We present a series of examples and show how they can be translated into the BOSSS framework via the graphical user interface. We then demonstrate how the package can be used in an iterative manner to determine optimal sample sizes, and how the results can be displayed and exported.

Discussion
The BOSSS package has the potential to facilitate simulation-based sample size calculations and thus help researchers use complex trial designs where simple analytic power formulae are not available. The general approach used in BOSSS can be applied when any simulation-based metric is used to determine the optimal sample size, and so may be useful in Bayesian or decision-theoretic approaches in addition to the frequentist power-based case.

P-039

Practicalities in the implementation of innovative early phase Bayesian dose-finding designs in an academic clinical trials unit: Enabling high quality and rapid interim statistical analysis

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Introduction

The Continual Reassessment Method (CRM) and the Time-to-event CRM (TiTE-CRM) are two of several innovative early phase dose-finding trial designs estimating the maximum tolerated dose in a phase I clinical trial to inform phase II dosing recommendations. Herein, we present lessons learnt from the implementation of these Bayesian trial designs at The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU).

Methods/Approach

In cooperation with the Drug Development Unit at The Institute of Cancer Research/Royal Marsden Hospital and with external collaborators, the Early Phase and Adaptive Trials Team at ICR-CTSU set up 5 trials employing CRM or TiTE-CRM designs between 08/2019 and 05/2022. To fully realise the efficiency of these designs, interim analyses to inform dose-escalation decisions must be conducted rapidly as time from data receipt to review meetings is short (~3 7 days), with decisions typically made after 1-3 patients. Data management, and monitoring, have to align with this requirement to ensure precise interim decisions. Good communication between key team members is essential to guarantee design familiarity and successful implementation.

Results

We developed standardised R Markdown templates for statistical simulation and analysis plans, as well as for dose recommendation reports, enabling automated reproducible reporting to meet the short turnaround times in CRM/TiTE-CRM trials. Data exchange paths between the team and our collaborators were established and tested upfront. We shared a list of variables that were crucial to run a CRM/TiTE-CRM trial to allow prioritisation of source data verification and data cleaning. We established a training programme for statisticians and trialists new to CRM/TiTE-CRM trials and provided trial-specific inductions for the wider team prior to trial opening. A standardised early phase folder structure, an EndNote library, and forms to document validation of statistical simulation plan as well as dose recommendation reports, facilitate orientation across different trials. Illustrative documentation of other effective tools, processes developed, and lessons learnt, will be presented.

Discussion

The implementation of novel Bayesian, adaptive, dose-escalation trial designs requires close collaboration between clinicians, trial management teams, monitors, pharmacologists, and statisticians to ensure rapid interim analysis, precise dose-decisions, and efficient implementation of trial adaptations. This process requires a robust infrastructure and inter-disciplinary lines of communication to facilitate the successful

delivery of these innovative designs with real-time adaptive decision rules. The recommendations and lessons learnt are highly relevant for trialists who plan to use such designs.

P-041

Implementation of a remote patient pathway and the development of a fully decentralised pathway in a live multi-arm, multi-stage complex intervention trial

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Introduction

COVID-19 had an abrupt and substantial impact upon UK clinical research delivery, but also provided opportunities for rethinking trial processes to better serve the NHS and target populations. It amplified the need to shift from in-person research delivery to remote.

The MODULATE trial (Management of diarrhoea in ulcerative colitis [UC] - a multi-arm multi-stage (MAMS) trial of low FODMAP diet, amitriptyline, ondansetron, or loperamide) responded to these challenges by implementing a remote patient pathway within a pragmatic, multi-centre, efficient, adaptive trial.

Methods

MODULATE seeks to recruit up to 491 participants (396 in phase 2; up to 95 in phase 3) from approximately 26 secondary care settings.

During 2020-21, the team designed and implemented a remote pathway, in collaboration with NHS colleagues and patient representatives, including:

- Self-referral pathway
- Electronic consent (REDCap)
- Trial visits via video-calling or telephone
- Fingerprick blood and stool sample kits posted to participants' homes
- Study IMP posted to participants' homes
- Dietary intervention delivered remotely

These modifications compliment the original remote data capture for trial outcomes. Further modifications planned to enable a fully decentralised trial include:

- Decentralised recruitment pathway utilising a national patient registry
- Central Pharmacy
- Central bank of specialist dietitians

Results Structure and Timelines

MODULATE opened to recruitment in December of 2021. Initial feedback on delivering the remote pathway from our active recruiting teams, alongside a summary of participant uptake on remote aspects of the pathway (vs face-to-face methods) will be presented.

Anticipating further decentralisation will be in place by Autumn 2022, we will reflect on the challenges and solutions to moving to a decentralised pathway while actively recruiting to a live trial.

Potential Relevance/Impact

The integration of e-consent and other remote procedures into a CTIMP, alongside an innovative MAMS design, places MODULATE at the forefront of efficient trial design and trial conduct.

The remote patient pathway reduces burden on both patients and NHS sites through more efficient processes and systems. Many patients with UC continue to shield and this pathway enables participants to take part without leaving their homes. The pathway is flexible and maximises patient choice.

Furthermore, decentralising MODULATE demonstrates how a large, complex trial can adapt to better suit the needs of its participants and setting. The new pathways have the potential to inform design of trials through streamlining processes and maximising efficient recruitment methods, while minimising reliance on the over-stretched secondary care research landscape.

P-042

Using the MOST framework to refine and optimise a behavioural complex intervention to support endocrine therapy adherence: The ROSETA programme

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Introduction

The classical approach to intervention evaluation often involves parallel groups randomised controlled trials. This design cannot easily answer questions about the effectiveness of individual intervention components or mechanisms of effect. The Multiphase Optimisation Strategy (MOST) framework can address these limitations and includes three phases. The preparation and evaluation phases mirror the classical approach, while the second phase (optimisation) uses highly efficient, fully powered experimental designs to refine intervention packages. We will demonstrate how MOST could be used to produce more effective, efficient and scalable interventions using a programme of work to support adjuvant endocrine therapy adherence (AET) in breast cancer survivors. Our objectives are to: 1) use Intervention Mapping to design a conceptual model and develop intervention components to support AET adherence; 2) evaluate the acceptability of the intervention components, and the feasibility of experimentally optimising them; and 3) optimise the intervention package with regard to effectiveness and cost, and undertake a causal pathway analysis to test our conceptual model.

Methods/Approach

We will use expert workshops, public surveys, and qualitative enquiry to design four intervention components (Objective 1). We will randomise 80 women with breast cancer using AET to one of 8 conditions within a 24-1 fractional factorial design with a nested process evaluation (Objective 2). Women will receive usual care, plus a combination of the four intervention components. Progression to Objective 3 will consider consent rates, component adherence, and availability of data. Objective 3 will randomise breast cancer survivors using AET to one of 16 conditions within a 24 factorial design. The planned primary outcome is medication adherence assessed using pharmacy data. The optimal component combination (intervention package) will be chosen according to effects on adherence and per-person cost. A causal pathway analysis will use patient reported outcome data to explore the behavioural mechanisms underpinning the intervention package.

Results Structure and Timelines

Four intervention components targeting medication adherence barriers have been developed: SMS reminders (target: memory); information leaflet (target: beliefs); guided self-help (target: distress); website (target: side-effects). The pilot trial (ISRCTN:10487576) will open in Q2 2022. The decision to progress to the optimisation trial will be made in Q4 2022.

Potential Relevance and Impact

The ROSETA programme is among the first in the UK to use MOST to optimise a complex intervention package and will advance optimisation methodology. ROSETA illustrates how intervention refinement can be operationalised in the context of the NIHR / MRC guidance on complex interventions.

P-043

Use of wearable technologies for evaluation of awake prone positioning effectiveness in moderate to severe COVID-19

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Introduction

In mechanically ventilated patients with acute respiratory failure, placing patients prone reduces mortality. Most benefit is seen with longer periods spent prone. It is less clear whether in patients not requiring mechanical ventilation experience similar benefit from prone position (termed 'Awake prone position (APP)). Differences in compliance and duration of APP are likely reasons for the opposing results, however assessing this is difficult as non-ventilated patients may turn unaided at any time. In the context of COVID-19, where infection control constraints and staff time already limit direct patient observation, this is even more challenging.

Understanding the benefit of APP in COVID-19 remains an important clinical question, with potential to impact outcome in all resource settings across the world. However, to do this, studies need to include robust methods for assessing compliance and quantification of prone position.

Methods

We are currently conducting a randomized controlled trial to determine whether prone positioning of hospitalized Vietnamese patients with moderate to severe COVID-19 for ≥ 8 hours a day reduces the need for escalation of respiratory therapy compared to standard care. To enable more accurate quantification of prone position, we are employing a novel technology, using low-cost wearable sensors. The sensors are simple gyroscope/accelerometers capable of measuring movement and 3-dimensional orientation up to 200 Hz. They store up to 5 days of data which can be subsequently downloaded and analysed.

In pilot work we investigated the most appropriate position to place the sensor to quantify prone position – comparing results obtained from supine, semi-prone and semi-recumbant, and defined cut offs for 'prone' vs 'not prone'. Devices were then introduced into the clinical trial, initially with data downloaded every 24 hours, but subsequently extended to 72 hours to reduce staff time and patient inconvenience.

Expected results

As of May 2022, 20 patients have been enrolled in the study and we aim to present data from 30-40 patients. We will present basic demographic features and duration of prone positions, correlated with manual observations taken 2-8 hourly by study staff. We will report any adverse events and acceptability feedback from patients from a Likeart Scale questionnaire administered at patient discharge.

P-044

Sample size considerations for a definitive trial with correlated multiple primary endpoints

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Introduction
Trials with multiple primary endpoints (MPEs) are considered successful if a significant effect is observed in either endpoint; an effect in both endpoints is required for trials with co-primary endpoints. Whilst methods accounting for multiple testing are well-known, there is limited guidance and few examples of trials incorporating correlation between MPEs into sample size calculations.
STAMINA, a NIHR-funded programme, includes a definitive individually randomised controlled trial. The evaluation of correlated MPEs, cancer-specific quality of life and fatigue, will determine the clinical and cost-effectiveness of the STAMINA Lifestyle Intervention compared to Optimised Usual Care in men with prostate cancer.
Originally cluster randomised, STAMINA was redesigned due to changes in standard practice. We will present the statistical considerations and methodological approach used to determine the sample size for both designs, accounting for correlated endpoints.

Methods/Approach
When multiple hypotheses are tested independently, the risk of Type I error increases. When a positive correlation is assumed between the endpoints, this risk is reduced and the correlation can be used to reduce any over-adjustment.
We compared two approaches to determine the adjustment of the Type I error rate. Firstly, we applied the Bonferroni correction (method 1) which does not incorporate correlation between endpoints. Secondly, we adapted the methods and R-package outlined by Lafaye de Micheaux et al. (2014) which incorporates the correlation into the calculations of the tail probabilities of the error rates for co-primary endpoints (method 2).

Results
Earlier work within the STAMINA programme found a correlation of 0.7 (95% CI: 0.58, 0.78) between the endpoints. We incorporated a conservative correlation of 0.58 into calculations within method 2.
For the cluster randomised design, a sample size of 1150 (adjusted alpha level: 0.025) was calculated for method 1 and a sample size of 1100 (adjusted alpha level: 0.02768) for method 2.
For the individually randomised design, a sample size of 708 (adjusted alpha level: 0.025) was calculated for method 1 and a sample size of 697 (adjusted alpha level: 0.02768) for method 2.

Discussion
Incorporating the correlation between MPEs had a greater impact in the cluster randomised design. Consideration of correlation between MPEs can lead to smaller sample sizes and less stringent alpha levels. The final sample size for the individually randomised STAMINA trial incorporates the correlation between endpoints.

Consideration and incorporation of correlation between endpoints is rarely used in trials. By sharing our approach, we aim to help researchers design more efficient trials.

P-045

Use of Sequential Multiple Assignment Randomized Trials (SMARTs) in oncology: systematic review of published studies

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Introduction

Dynamic Treatment Regimens (DTRs) are a set of sequential decision rules, each one corresponding to a key decision point in the patient's history. The DTR represents a formalization of the multi-stage and dynamic decision process followed by clinicians in their everyday clinical practice. However, providing evidence-based DTRs poses relevant methodological challenges of study design and DTRs' effect estimation. The advent of sequential multiple assignments randomized trials (SMARTs) designs offers new opportunities to develop evidence-based DTRs. The present work investigates the state-of-the-art of the use of SMART designs in oncology, focusing on the discrepancy between the available methodological approaches in the statistical literature and the procedures applied within cancer clinical trials.

Methods/Approach

A systematic review was conducted, searching PubMed, Embase, and CENTRAL (Cochrane Trial Registry) for protocols or reports of results of SMART designs and registrations of SMART designs in clinical trial registries. To be included, the SMART design should be applied to solid tumor research without restrictions on the intervention type.

Results

The search resulted in the inclusion of 14,586 records. After duplicate removal, title/abstract and full-text screening, 33 records were included in the present systematic review. Fifteen were reports of trials' results, four were trials' protocols, and fourteen were trials' registrations. The study design was defined as SMART by only one out of fifteen trial reports. Conversely, except four, all study protocols and trial registrations defined the study design SMART.

Interestingly, despite the primary goal of SMART designs would be to identify the optimal DTR, only six of the records included in the review considered determining the best treatment sequence as the study outcome, and only one as the study's primary outcome. Such an aspect is reflected by the approaches employed for analyzing the studies. With a few exceptions, all the trials made separate analyses for each trial stage using traditional statistical methods, such as regression-based models not taking into account for patient's history throughout the trial and without evaluating the DTRs embedded in the trial.

Discussion

The use of SMART designs in oncology in solid tumors is still limited. Furthermore, study analyses are mainly based on statistical approaches traditionally used in single-stage parallel trial designs, probably because the design and analyses of such trials are challenging, and no formal guidelines are available. Further research in this field is needed to allow for broader use of such designs in oncology.

P-046

A two-stage Bayesian adaptive umbrella trial incorporating changing allocation ratios

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Introduction
Umbrella trials are novel clinical trial designs that evaluate multiple targeted experimental treatments within a single disease setting. Unlike other master protocols (basket and platform trials), there is limited proposed statistical methodology for umbrella designs. As such, these trials are commonly designed and analysed as a series of independent subtrials, each evaluating a unique targeted therapy either as a single-arm or randomised trial. However, there are several ways to exploit the efficiencies of the umbrella design. One such consideration is the randomised umbrella trial with a common control across all subtrials.

Methods
We propose a two-stage Bayesian adaptive design to; i) borrow information across the control arms only; and ii) enable changing of treatment-control allocation ratios at interim in favour of experimental treatment. Allocation ratios are switched if the Bayesian predictive power (BPP) at interim exceeds a pre-specified threshold. Thus, we aim to answer the question whether we can skew allocation in favour of experimental treatment based on interim results and yet maintain the overall desired characteristics (power and type I error). Our Bayesian methodology to enable information sharing is based on the commensurate predictive prior approach and using both a spike and slab prior as well as mixture gamma prior on the parameter of commensurability. We apply this methodology in the context of a phase II randomised umbrella trial with five subtrials, a common continuous endpoint all subgroups and common control. A comprehensive simulation study is done to evaluate the operational characteristics of this design including type I error, power and patients on treatment.

Results & Conclusion
Our findings suggest that it is plausible to skew allocation in favour of experimental treatment and still maintain desired trial characteristics including power. We observe that borrowing information across the control arms leads to increased statistical power (and higher predictive power) compared to compared stand-alone analysis of subtrials, and different decisions on whether to change the allocation ratios or not.

P-047

Advantages of multi-arm non-randomised sequentially allocated adaptive cohort designs for phase II trials

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Introduction

Efficient phase II trial designs are required to rapidly identify promising agents to take forward into larger trials. Adaptive multi-stage trials are examples of such designs, but their efficiency is reduced if there is a delay in assessing patient response to treatment. When researchers wish to evaluate multiple agents at the same time in a non-comparative setting there is further scope to increase efficiency. Here, we discuss the Multi-Arm Sequential Trial with Efficient Recruitment (MASTER) design, which can provide an efficient and rapid assessment of multiple potential therapies within one protocol.

Methods

Motivated by the WIRE trial in renal cell carcinoma (NCT03741426), we compare three approaches to allocating patients to multiple arms in an adaptive phase II trial: 1) single-arm trials with interim analyses conducted in sequence; 2) a parallel multi-arm multi-stage trial; and 3) the MASTER design used in WIRE; in this design recruitment is prioritised to one arm at a time, with a new arm taking priority and opening to recruitment while interim analyses are undertaken. We conduct a simulation study to compare how long the three different designs take to evaluate a number of new treatment arms, focusing on the setting where recruitment is paused to an arm whilst interim analyses are conducted. We investigate how this changes depending on time taken to evaluate the endpoint, the recruitment rate, the number of arms, and number of interim analyses.

Results

The parallel multi-arm multi-stage and the MASTER design are much more efficient than separate single-arm trials. The average time taken is always shorter with the MASTER design, reducing the time taken to evaluate five treatment arms by around 3-4 months compared to a parallel multi-arm multi-stage design under realistic settings. This advantage is maintained as the recruitment rate and endpoint assessment time increases. The MASTER design provides the greatest gain in efficiency when there is a delay in evaluating the endpoint, or where recruitment rates are moderate to high.

Discussion

We recommend the MASTER design as a promising method to efficiently test multiple potential therapies in non-comparative multi-stage phase II trials. The MASTER design minimises the amount of time recruitment is paused whilst awaiting results of interim analyses and offers additional advantages such as generating complete results on individual arms as the trial progresses. We believe the MASTER design provides is a valuable approach to improving the efficiency of early phase trials.

P-048

Use of interventional cohort designs for de-escalation studies with rare outcome events

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Background

Improvements in early breast cancer (BC) treatment have dramatically reduced risk of recurrence (RR) but risk of toxicity remains. For some populations, RR is now sufficiently low that focus has shifted towards de-escalation. For rare events, the sample size required to exclude a small but real potential absolute loss of efficacy in a classic non-inferiority randomised control trial (RCT) is very large with associated challenges. Interventional cohort studies (ICS) offer an alternative to RCTs for such studies.

Methods

In the ICS design, a single cohort is recruited and the RR is assessed against a fixed boundary, rather than a randomised control group.

Several criteria are required for such a design to be appropriate. Firstly, event rates must be sufficiently low such that any deviation from that excellent prognosis paradigm is classed as unsatisfactory. Events must be observed in a timely manner so increased event rates are identified promptly and the endpoint must be objective and specific to avoid the risk of crossing the threshold due to intercurrent events not affected by the intervention. The population entered should reflect the eligible population on whom the standard-of-care (SOC) event rate threshold was defined. We currently have two ICSs aiming to de-escalate treatment in patients with low-risk BC within ICR-CTSU: one in active follow-up and one open to recruitment.

Results

PRIMETIME is a biomarker-directed ICS, investigating safe avoidance of radiotherapy for a subgroup of BC patients deemed to have very low risk of local recurrence. The study is powered to exclude a 5-year ipsilateral breast RR of 5%, which would have required 1000s of patients in an RCT. Rates are monitored using the conditional power of the “final” RR being ≤1% per-year given the “current” interim RR and person-years available. PRIMETIME closed to recruitment in March 2022 with 1623 patients.

HER2-RADiCAL is a response-adaptive trial assessing reduced therapy in HER2+ BC patients who achieved complete pathological response to neo-adjuvant therapy. The study is designed to exclude a 3-year RR of 6.5% requiring 691 patients compared to >2000 for an RCT. Rates will be monitored using a beta-spending function. HER2-RADiCAL opened to recruitment in December 2021.

Involvement of patient representatives was critical for the development and acceptance of both studies.

Discussion

ICSs offer an appropriate alternative to standard RCT for de-escalation studies with rare outcome events. ICSs are acceptable to patients and can provide results to inform clinical practice in a relevant timeframe.

P-049

Implementation of the partial-order time-to-event continual reassessment design, a novel dose-finding methodology, in an early phase oncology trial; theory and practicalities.

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ADePT-DDR is an open label multi-centre platform trial that aims to evaluate the safety and efficacy of different DNA Damage Repair (DDR) agents together with radiotherapy in patients with head and neck squamous cell carcinoma. The initial component of this trial is a single-arm dose-finding phase Ib/IIa trial to evaluate the DDR ATR inhibitor agent, AZD6738, in combination with radiotherapy alone.

This component has been designed using the partial ordering time-to-event continual reassessment method (PO-TITE-CRM) to determine the maximum tolerated dose (MTD) of AZD6738. The PO-TITE-CRM design was introduced in 2013 as an extension to the TITE-CRM design, itself an extension of the original continual reassessment method (CRM), a model-based approach to dose-finding trials. Despite the publication of this novel dose-escalation design its implementation appears to be rare.

One of the key assumptions of the CRM is the monotonicity assumption which is that we assume that as the dosage of a drug increases so does the probability of toxicity. Wages (2011) extended the CRM design to work in the presence of partial orders in which, the order of toxicity probabilities may only be known for a subset of doses. Here the monotonicity assumption does not hold across the entire set of doses. This methodology was then further extended to include a time-to-event (TITE) component that attempts to utilize data from partially observed patients throughout the trial to account for late-onset toxicities. The dose levels under evaluation in the Adept-DDR trial vary not only by dose but by frequency taken. This aspect, alongside the potential later toxicities as a result of the treatment necessitated the implementation of the PO-TITE-CRM design.

Multiple iterations of simulations were utilized to determine the optimal parameterization of the design. Simulation results from the optimal parameterization show the operating characteristics of the design perform well across a variety of scenarios.

We will present an overview of the design methodology and its application in this trial scenario. In addition, we will share some of the challenges that arose when implementing this design and the approaches applied to address these. As the issue of partial ordering may become more frequent with the advent of increasing combination therapy treatments, particularly in oncology, we anticipate this account will be beneficial to those designing trials in the presence of partial orders and encourage other early phase clinical trialists to implement in the future.

P-050

The TIPAL Trial; an example of a decentralised CTIMP and adaptations made during the pandemic

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TIPAL is a multicentre RCT CTIMP investigating the use of Lansoprazole for people with Idiopathic Pulmonary fibrosis (a progressive lung disease with no known cause).

The trial was designed and funded prior to 2020 and received ethical and regulatory approval during the first wave of the Coronavirus pandemic in the UK.

The design initially required clinically vunerable respiratory patients to attend clinic in person and perform aerosol generating procedures (such as lung function tests) as as such was quickly deemed no longer viable.

As a result we extensively redesigned the trial during 2020 to enable participants to take part in the trial entirely remotely.

We updated the method for collecting the primary endpoint (Forced Vital Capacity) through the use of home spirometry kits. These were linked via bluetooth to the 4g enabled tablets which we provided to all participants and enable patients to perform home assessments which are automatically uploaded in to a cloud server which can be reviewed by both the local PI and the central CTU research team.

During 2020 CTU worked with a third party manufacturer to develop an app and platform specifically for the TIPAL trial which collects FVC readings and also gives real time feedback in accordance with the current ATS/ERS guidelines and includes training videos to patients during the trial via the tablet. To ensure these measurements are reliable, flow-volume loop and volume-time curve data is assessed in real time by a central clinical physiologist and additional training can be given to patients on the home spirometry kit via the tablets if needed. A TMG sub-group was established to monitor the quality of this data.

Other measures such as ePROMs are captured by the tablets. Routine follow up visits may be performed via the tablets.

A sub-study uses cough monitors and activity trackers sent to the patients address to measure the cough frequency and patient activity with data analysed centrally. One-to-one training for this is also provided by the central team via the tablets.

Finally we recruited a central pharmacy to enable direct-to-participant dispensing of IMP removing the need for the participant or a family member to attend hospital.

The trial has now started recruitment at 25 NHS trusts in the UK, with more coming on line every day. Feedback has been very positive from sites, specifically as a result of the reduced research burden required of them to undertake this trial.

P-051

Participate From Home - How the use of modern technologies and virtual recruitment sites increase accessibility and recruitment in clinical trials

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Introduction
The COVID-19 pandemic and its disruption to patient care pathways has highlighted the need to stretch the definition of a "site" and develop novel remote recruitment methods within clinical trials. Early in the pandemic, we set up a trial (SG016 Home trial) to explore the use of a inhaled interferon beta-1a formulation (SNG001) for the potential treatment of COVID-19 delivered directly to at-risk patients' homes. Contact was via video link, including vital signs assessments and study medication administration. We set up a virtual site, comprised of a bank of trained heath care professionals (HCP) to remotely screen, recruit and monitor patients throughout their trial involvement. GP sites were set up and also performed these trial tasks remotely. In this talk/poster, we will highlight the benefits and considerations when implementing a virtual site and how this compares to GP sites.

Applications and Implementation
To set up the virtual network, the HRA confirmed that there would be no site details nor a PI. All Investigator responsibilities under ICH GCP fell with the CI and were delegated to a deputy CI, study doctors and nurses. All other responsibilities lay with the sponsor. A clinical responsibilities flow diagram defined the delegation of medical responsibilities. Recruitment was via GP text or social media advert. E-consent was utilised and consent was obtained via sponsor-approved video platforms, following patient identity verification. Other key factors were due diligence and GMC checks for virtual clinicians, assessing medical history, data protection and email correspondence, storage of information at HCP homes' and the logistics of archiving. Lastly, an independant Pharmacy took on central IMP responsibility for all sites.

Results and Discussion
120 participants were recruited, 94 (78%) were recruited via the Virtual Team (VT) and 26 (22%) via GP practices. 329 patients registered to participate in the trial, with 273 (83%) screened by the VT and 52 (17%) by the GP practices. While more patients were recruited to the trial via the VT, the rate of successful screenings was lower (29% for Virtual Team vs 50% for GP practices).
Benefits of virtual site recruitment included the recruitment of patients nationwide and the availability of dedicated research staff for any new registrations. Benefits of GP recruitment included advertising the trial to known at-risk participants, plus increased patient trust in existing NHS networks. Future trials implementing the benefits of both systems could prove the most effective way of incorporating virtual recruitment.

P-052

Methods for delivering Randomised Clinical Trials based on routinely collected health data – Clinical Practice Research Datalink's (CPRD) experience

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Introduction
Clinical Practice Research Datalink (CPRD) facilitates interventional research using routinely collected health data on over 16 million patients from 1 in 4 GP practices across the UK. CPRD has developed an interventional research services platform (IRSP) to support patient recruitment and facilitate trial delivery. This online platform, used in conjunction with the electronic health records (EHR) in the CPRD Primary Care database, is the basis for supporting innovative data enabled trials in the UK. Two NIHR funded trials, DaRe2THINK and AYSMPTOMATIC are currently being delivered.

Methods
Using the CPRD Primary Care database in conjunction with IRSP, enables rapid, targeted recruitment into trials through searches of the coded data, modelled on protocol selection criteria. This list is accessed via IRSP and reviewed by the patient's healthcare providers to ensure only patients who are potentially eligible for the trial are invited to participate. These near real time, modifiable, centralised searches can be regularly updated and the search can be geographically targeted to recruitment sites. This approach promises rapid low-cost targeted recruitment into trials. IRSP is also used to support trial delivery, and provides the platform for initiation, study training, randomisation, enrolment and safety reporting.

Results
CPRD clinical trial related services are in their infancy and focus on increasing recruitment rates and efficiency as a priority. In the past year, this approach has enabled recruitment of 294 patients across 4 studies in a COVID impacted primary care setting. CPRD has undertaken 42 rapid feasibility searches, each taking 5-10 working days and geolocated to target recruitment sites. Searches identify GP practices with high number of eligible patients and enable prioritised practice recruitment. Between 15% and 25% of practices approached agree to participate and the fastest turnaround time from invitation to practice sign up is 24 hours. GP review to invitation rates vary depending upon disease area and inclusion-exclusion complexity, but have been over 80% for some studies (average of 62%) . Patient uptake following invitation for DaRe2THINK is currently 17%. In another example, dynamically modifying the patient selection search resulted in a 27% increase in invitation rates following GP patient review.

Discussion
The combination of CPRD's Primary Care database and IRSP support innovative trial recruitment and delivery, and is supporting the paradigm shift to remote, data enabled trials. CPRD are continuously developing these systems and integration with other systems such as REDCap®, an open-source research data capture platform, will further enhance these capabilities.

P-053

World Hip Trauma Evaluation (WHiTE) Platform: the story behind the set-up of a novel clinical trials framework for clinical trials for fragility hip fracture

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Introduction
WHiTE (World Hip Trauma Evaluation) Platform is a platform trials framework, designed to efficiently deliver multiple randomised comparisons of IMP and non-IMP interventions for patients aged 60 years and over with a hip fracture. It is based upon experience derived from the planning and delivery of a related group of randomised trials of hip fracture interventions. The Platform allows for the simplification of the hip fracture participant's research pathway and capture efficiencies in the reduction of documents and duplication of clinical reporting forms. Interventions may be simple, complex or multimodal e.g. IMPs, surgical interventions or care pathways; delivered at any stage along the diagnostic, treatment and rehabilitation pathway. Our aim was to set in place a research and governance infrastructure for the efficient delivery of a suite of randomised comparisons.

Methods
We prepared a master protocol with a common core dataset and documentation and described within this the research components expected to be consistent between randomised comparisons, such as consenting and data collection procedures. Additional processes specific to a randomised comparison are provided in the comparison-specific protocol appendix. This set-up enabled a single IRAS application which was submitted to the ethical and regulatory bodies.

Results
The Platform encompassing its current randomised comparisons benefits from over-arching MHRA, REC and HRA approvals and an explicit legal basis and processing purpose for the use of patient-level data. Future randomised comparisons can be added to the Platform as substantial amendments, which enables a more efficient process of review and approvals by these bodies. This also provides a more resourceful method for review of capability and capacity at participating sites, an additional benefit to the reduced burden of documentation required during study conduct by the site research staff as well as the participants.

Discussion
The distinctiveness of this Platform has generated a space for discussion regarding the formulaic set-up in aspects of regulatory and registration systems, which are not overtly designed to be Platform-friendly. Overall, we have overcome these following in-depth consultations at each stage with relevant stakeholders to agree the best practice for set-up, such as ISRCTN and CPMS registrations; with each comparison being set up individually on these. The considerations for platform designs are likely to highlight a need for future efficiencies in other aspects of the research system. We hope to see this evolution along with that of our WHiTE Platform and the novel challenges we may face in the future.

P-054

The impact of design adaptations for an innovative biomarker-based strategy (hybrid) RCT - The OUTSMART trial.

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Introduction
The appearance of antibodies against human leukocyte antigens (HLA Ab), particularly if they contain donor specific antibodies against the graft (DSA+), is a validated strong prognostic biomarker of kidney transplant failure. HLA Ab screening is expensive and there is a need to determine its usefulness; preliminary evidence suggested that treatment decisions based on the presence of the biomarker could alter prognosis. A prospective, open-label, randomised, biomarker-based strategy (hybrid) multicentre trial (OUTSMART) assessed whether screening for these prognostic biomarkers combined with optimized immunosuppression for HLA positive participants could prevent kidney graft failure.

Methods/Approach
Participants were randomly allocated (1:1) to either unblinding or double-blinding of their HLA status, and then stratified accordingly (HLA Ab+ DSA+, HLA Ab+ Non-DSA or HLA Ab Negative). The blinded group remained on standard care and the unblinded HLA Ab+ group were treated with a pragmatic optimized immunosuppression protocol. There were three separate hypotheses: i) superiority of biomarker-led care in participants with HLA+ DSA, ii) superiority in participants with HLA+ Non-DSA, and iii) non-inferiority of the overall HLA Ab unblinding strategy.
To enrich the sample of biomarker positive participants, HLA Ab negative participants were re-screened for their HLA status every 8 months; and moved to the relevant HLA positive stratum if they became HLA Ab+. If a participant was initially HLA Negative but became HLA Ab+, their time at risk began at rescreening rather than at randomisation for the primary analysis.
The primary endpoint was originally graft failure (Yes/No) at 36 months follow-up. After lower-than-expected biomarker positivity rates, this was amended to time to graft failure with variable follow-up to increase power. The revised primary analysis used Cox regression.
Later, there was concern that the COVID-19 pandemic might impact the results as excess deaths were expected in this vulnerable population. The end of the primary data collection period was brought forward to March 2020 with additional “post-COVID-19” data collected up to September 2020.
Each adaptation had the potential to affect the results; sensitivity analyses assessed their impact.

Timing of Potential Results
Sensitivity analyses results consistent with the primary analysis. Full results to follow once the primary paper is published.

Potential Relevance & Impact
Adaptations to trial design to improve efficiency should be considered even for complex biomarker-based designs. This applies even after the trial has started, if reported transparently and care is taken to assess the impact of changes on the robustness of the results.

P-055

Developing a systematic framework to identify, evaluate and report evidence for drug selection in motor neuron disease adaptive platform trials.

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Introduction

Despite decades of clinical trials, effective disease modifying treatment options for motor neuron disease (MND) remain limited. There is a pressing need to innovate how we identify and evaluate candidate drugs in clinical trials. Motor Neuron Disease - Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART; ClinicalTrials.gov number: NCT04302870) is an adaptive platform trial aimed at testing a pipeline of candidate drugs in a timely and efficient manner. We aim to develop a systematic and structured framework to identify, evaluate and prioritise candidate drugs for evaluation in MND-SMART, taking into consideration emerging data in different domains and expert opinion.

Methods

We identify and evaluate evidence from these domains: (i) published literature through Repurposing Living Systematic Review-Motor Neuron Disease (ReLiSyR-MND), a machine-learning assisted systematic review evaluating clinical studies of MND and other neurodegenerative diseases which may share similar pathological pathways, animal in vivo MND studies and in vitro MND studies; (ii) unbiased in vitro high throughput drug screening; (iii) pathway and network analysis, and (iv) pharmacological, feasibility and clinical trial data by mining drug, chemical and clinical trial registry databases. We compile an integrated list of candidate drugs including drugs which have been described in at least one clinical publication, positive hits in any of our in-house MND in vitro assays, and drugs which target pathways and networks of interest. For each drug, we obtain predictions on blood brain barrier permeability from admetSAR (http://lmmd.ecust.edu.cn/admetsar2/). Next, we generate a list of prioritised drugs deemed suitable for imminent repurposing in MND-SMART, taking into consideration availability in oral formulation, prescription-only medicine status in the British National Formulary, and evaluation of safety profile by clinical triallists in the context of common comorbidities.

Discussion

We further identify, evaluate, and synthesise evidence across the different domains for prioritised drugs and report these using automated workflows as interactive, curated, living evidence summaries. These summaries can be used to inform expert panel discussions on drug selection for future arms of MND-SMART at trial adaptation epochs.

P-056

A modified nominal group technique to develop a logic model and complex interventions for a randomised controlled trial in children with symptomatic pes planus

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Introduction
Children with symptomatic flat feet (pes planus) frequently present for care but there remains uncertainty about how best to manage the condition. There is considerable variation in practice between and within professions. The Orthotics for Treatment of Symptomatic Flat Feet (OSTRICH) trial was designed to evaluate three frequently used interventions for symptomatic pes planus (exercise and advice, exercise and advice plus prefabricated orthoses, and exercise and advice plus custom made orthoses). Each of these interventions contain multiple interacting components so are considered complex interventions, and required developing prior to starting the trial, as did an overarching logic model to enable assessment of trial fidelity. This paper focusses on the novel development process undertaken to develop the interventions and logic model.

Methods
We used a modified Nominal Group Technique that combined an electronic survey with two face-to-face meetings to achieve consensus on the final logic model and menu of options for each intervention. Using the Nominal Group Technique across consecutive meetings in combination with a questionnaire is novel to our knowledge, and enabled us to develop complex interventions that reflect contemporary clinical practice.

Results
In total 16 healthcare professionals took part in the consensus process. These consisted of 11 podiatrists, two orthotists, two physiotherapists, and one orthopaedic surgeon.
Both meetings endorsed the logic model with amendments to reflect the wider psychosocial impact of pes planus and its treatment, as well as the increasing use of shared decision making in practice. Short lists or 'menus' of options were agreed for prefabricated and custom-made orthoses, anatomical structures to target in stretching and strengthening exercises, and appropriate elements of health education and advice.

Discussion
Our novel modification of the nominal group technique produced a coherent Type 3 logic model and shortlist of options for each of the interventions that explicitly enable adaptability. We formed consensus on the range of what is permissible within each intervention so that their integrity is kept intact, and they can be adapted and pragmatically applied. The process of combining survey data with face-to-face meetings has ensured the interventions mirror contemporary practice and may provide a template for other trials.

P-057

Developing a Core set outcome of exercise intervention for lung cancer patients in perioperative period-a study protocol

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Introduction
Lung cancer is one of the most common malignant tumors in the global population, with the characteristic of high morbidity and mortality. As exercise interventions are effective for lung cancer patients during the perioperative period, a growing number of randomized controlled trials (RCTs) are proposed by researches to exercise the patients. However, a large number of clinical trials are not subsumed in the systematic evaluations to provide the optimal evidence for clinical practice caused by the inconsistent outcomes reported of the RCTs. This study is aimed to develop a core outcome set (COS) to improve the consistency of the RCTs outcomes reported and to synthesize the data across studies in the systematic evaluation.

Method
The development of the COS consists of four steps: (1) A outcomes reported list of registered and published exercise interventions in clinical trials for the perioperative patients with lung cancer will be extracted by literature review. (2) An additional outcome list will be collected by semi-structured interviews to the patients. (3) A two-round Delphi surveys will be performed to prioritize and condense the outcomes. (4) The COS will be proposed through a face-to-face consensus meeting with the key stakeholders, and measurement tools will be recommended for each outcomes.

Results An agreed upon set of minimum outcomes and outcome measures will facilitate the combination and comparison of the results for the future exercise intervention trials.

Conclusions The patients and clinicians will select more effective outcome indexs by using the proposed COS. The quality of trial reporting will be improved, and the research wastage and the incidence of postoperative complications will be reduced significantly.

P-058

A Core Outcome Set for Clinical Trials of Traditional Chinese Medicine for Chronic Pulmonary Heart Disease

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Introduction
Pulmonary heart disease (PHD, also called “cor pulmonale” classically) is right ventricular enlargement secondary to pulmonary hypertension (PH), which may lead with time to right heart failure (RHF). Traditional Chinese medicine (TCM) has major advantages in improving long-term symptoms and life quality of patients with chronic pulmonary heart disease (PHD, also called “cor pulmonale” classically) over oxygen therapy, but there still a lack of consensus-based clinical outcomes for evaluating its therapeutic value for PHD. This study aimed to develop a core outcome set (COS) for clinical trials of TCM on chronic PHD to tackle the outcome issues.

Methods
A steering committee and a working group were established, and the study protocol was registered on the website of COMET network before the study. A systematic literature review through eight literature databases and two clinical trial registration platforms were retrieved to obtain reported outcomes of TCM for chronic PHD. Qualitative interviews with medical professionals and patients with chronic PHD treated using TCM were conducted to generate a set of outcomes. After standardization and classification, a pri were prioritized by stakeholders via two rounds of an online Delphi survey and face-to-face consensus meetings. Following the final consensus meeting, a final COS was generated.

Results
An initial set of 595 outcomes was identified from 1,313 included trials. A preliminary list of 92 outcomes was employed in the Delphi study. Participants from seven stakeholder groups were invited to the Delphi surveys, with 45 completed the first round and 25 completed the second round. Twenty-two participants attended the consensus meeting and agreed on a final core set of outcomes comprising eight items including pulmonary function outcomes (FEV1 and FEV1/FVC), 6-minute walk test distance, NYHA cardiac function class, all-cause mortality, rehospitalization rate, chronic obstructive pulmonary disease assessment test score (CAT), SF -36 and TCM symptom scale.

Discussion
The COS developed in this study provides the minimum requirement for measurement and reporting in future clinical trials of TCM for chronic PDH to reduce heterogeneity across trials and facilitate evidence-based decision-making for stakeholders.

P-059

Development of core outcomes and core measures sets of low back pain

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Background and purpose
Due to the heterogeneity of outcomes or measures reported in clinical trials of low back pain, meta-analyses is hardly conducted for evidence. We aimed to develop core outcome set (COS) and core measures set (CMS) of chronic low back pain (CBP) for all clinical studies.

Methods
The CBP clinical research outcomes and measurement tools lists were established through systematic review of randomized and observational clinical trials in recent 5 years, synthesis meta of qualitative studies on experience or outcome of CBP patients, and interviews of clinicians and CBP patients. And then two rounds Delphi surveys were held among multi-stakeholder representatives to select the important outcomes. The COS-CBP and CMS-CBP were established by experts and patients consensus meeting with nominal group method.

Result
A total of 57 outcomes and 348 measurement tools were pooled. The Delphi surveys selected 10 important outcomes. The consensus was met that the COS-CBP and CMS-CBP were constructed: Pain or Discomfort (Numerical Rating Scale-Pain, NRS-P and Visual Analogue Scale/Score-Pain, VAS-P), Exercise Function (Functional Rating Index, FRI), Daily Activity (Activities day Live, ADL), Lumbar Dysfunction (the Oswestry Disability Index, ODI), Impact on Quality of Life (12-Short Item Survey Form, SF-12), and safety outcomes (self-reporting, no recommended measurement tools). The corresponding measurement time frames included baseline, immediately after treatment course and follow-up of 1 week, 2 weeks, 4 weeks and 8 weeks after treatment.

Conclusion
The COS-CBP and CMS-CBP were determined by patients, physicians and other multi-stakeholder, will be considered and used as outcome and measurements in CBP trials, properties of measurements are warranted for further validation.

P-060

Development of a core outcome set for describing the learning curve in studies of novel invasive procedures

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Introduction
Novel surgical techniques are commonly introduced into clinical practice without robust evaluation, potentially resulting in patient harm. A key part of evaluating novel procedures, as outlined in the IDEAL framework, is acknowledgement of the 'learning curve', where an improvement in surgical performance and outcomes is observed over time. There is currently a lack of standardisation for selecting and reporting outcomes when evaluating the learning curve of novel procedures, which can hinder the next stage of evaluation. We aim to develop a core outcome set to be reported in all studies describing or assessing the learning curve for novel invasive procedures.

Methods/Approach
Methods have been adapted from the Core Outcome Measures in Effectiveness Trials (COMET) guidance. Work will be undertaken in three phases:

Phase 1: A 'long list' of outcomes will be identified by extracting all relevant information from: a) an umbrella review of existing systematic reviews describing the learning curve in surgery, and b) qualitative interviews with key stakeholders. After de-duplication, the 'long list' will be arranged into themes and operationalised into a Delphi questionnaire.

Phase 2: Key stakeholders (patients, surgeons, methodologists, statisticians, journal editors, members of key organisations e.g. IDEAL collaboration) will be invited to complete the Delphi survey and score the importance of including each outcome in a 'core set' in sequential rounds.

Phase 3: Outcomes remaining after the conclusion of the Delphi survey rounds will be discussed in stakeholder consensus meeting(s), to agree on the final core outcome set.

Timing of Potential Results
Initial findings from the review and qualitative work will be presented, and the overall project will be completed in the next year.

Potential Relevance and Impact
The development of a core outcome set for the learning curve in studies of novel invasive procedures will facilitate standardised and efficient reporting in studies of surgical innovation. This can ultimately achieve consistency in describing and evaluating the learning curve and facilitate progression to the next stage of evaluation.

P-061

Low core outcome set use in clinical trials published in major medical journals

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Introduction
To examine current practices in late-phase trials published in major medical journals and examine trialists' views about core outcome set (COS) use.

Methods
A sequential multi-methods study was conducted. We examined late-phase trials published between October 2019 and March 2020 in JAMA, NEJM, The Lancet, BMJ, and Annals of Internal Medicine . The COMET database was searched for COS potentially relevant to trials not reporting using a COS; overlap of trial and COS outcomes was examined. An online survey examined awareness of, and decisions to search for and use a COS.

Results
Ninety-five trials were examined; 93 (98%) did not report using a COS. Relevant COS were identified for 31 trials (33%). Core outcomes were measured in 9 (23%) studies; all trials measured at least one core outcome. Thirty-one trialists (33%) completed our survey. The most common barrier to COS use was trialist's own outcome preferences and choice (68%). The most common perceived facilitator was awareness and knowledge about COS (90%).

Conclusion
COS use in this cohort of trials was low, even when relevant COS were available. Increased use of COS in clinical
trials can improve evaluation of intervention effects and evidence synthesis and reduce research waste.

P-062

Core Outcome Set Methodological research Domains (COSMiD)- The review and categorisation of Core Outcome Set methods research

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Introduction
A core outcome set (COS) represents the minimum set of outcomes that should be measured and reported in all clinical trials in a specific area of health or health care. The use of COS in clinical trials helps to reduce heterogeneity in the choice of outcomes and promotes the measurement and reporting of outcomes most important to stakeholders, thereby reducing waste in research and improving its relevance. COS development is a growing research area, with over 400 published COS and a similar number in progress in mid-2022. These COS use a range of methods and the choice of methods may influence the relevance of the COS and ultimately its uptake.
Research to inform the methods used in COS development, and approaches to increase COS uptake, are growing. As the amount of new information on methods increases, it will become increasingly difficult to navigate.
The aim of the COSMiD study is to review the evidence base on methods used in COS development and to use a categorisation system to summarise this information in order to facilitate searching for methods research in the COMET Initiative database.

Methods/Approach
A classification system has been developed with input from COS developers, methodologists and the COMET People and Patient Participation, Involvement and Engagement (PoPPIE) Group. This classification system of COS methods research has subsequently been used to categorise evidence identified from conference abstracts presented at past COMET Initiative and ICTMC conferences, existing work included in the COMET database, the Study Within a Trial (SWAT) store hosted by the Northern Ireland Methodology Hub and a SCOPUS review up to October 2021.

Timing of Potential Results
The categorisation system includes nine methods domains (recruitment, retention, outcome list development, consensus methods, scope of the COS, study oversight, patient and public involvement, dissemination and uptake, and how outcomes are measured) each with a number of sub-domains. We will present a summary of the research included in each domain and sub-domain including the level of evidence of the studies (e.g. whether it used a randomised or non-randomised evaluation of methods).

Potential Relevance and Impact
This presentation will summarise current knowledge on the methods used in COS development that can be easily identified using the COMET Initiative database. The categorisation of research will also identify gaps in the evidence that may be prioritised for future methods research.

P-063

Defining a Core Outcome Set for Early Phase Trials in Mechanically Ventilated Patients

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Introduction
An early phase trial supplies the initial efficacy estimate for an intervention and a confirmatory, definitive study would be used to confirm this efficacy or show effectiveness. However, many confirmatory studies in critical care fail to prove the promising findings from an early phase trial, which may be because the outcome used for the early phase trial was not appropriate.
Objective
To define a core outcome set (COS) that should be measured in all early phase trials of interventions for mechanically ventilated patients.

Methods
A systematic review of early phase trials of interventions for mechanically ventilated patients published in the six top-ranked critical care journals was done to generate a list of the measured outcomes. All articles published in 2010 were included, along with 10% of articles published in 2014 and 2015. The list of outcomes was used in surveys of critical care clinicians and researchers to prioritise these outcomes. These were done at the UK Critical Care Research Group (UKCCRG) 2018 meeting and via an online survey using Twitter. Participants were given a list of outcomes and a short definition and asked whether results for these outcomes would influence their clinical and research decision-making. They were also asked to score the overall importance of the outcome (0 to 5). The development of this COS was registered on the COMET website.

Results
Data were extracted from 48 articles in the systematic review, and a subset of 22 putative surrogate outcomes were identified as potential early phase outcomes for inclusion in the survey. Among the total of 63 respondents, 50 (79.4%) were medical doctors, 9 (14.3%) were nurses and 26 (41.2%) had experience in leading studies. Organ failure-free days, length of ICU stay, duration of mechanical ventilation (MV), length of hospital stay, Sequential Organ Failure Assessment score (SOFA) and ventilator free days (VFD) were considered as important by at least 50% of the respondents and 63% recommended that mortality should be reported in all early phase critical care studies. Among the physiology outcomes, Oxygenation Index (OI) and PaCO2/FiO2 (PF) ratio was considered as the most important outcomes.

Conclusion
This study identifies the seven most important outcomes to be reported in early phase MV studies. These are mortality, duration of MV, length of stay in ICU and hospital, SOFA, PF ratio and OI.

P-064

Development of a Core Outcome Set in the Clinical Trials of Traditional Chinese Medicine for Stroke: A Study Protocol

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Introduction
Stroke, an acute cerebrovascular disease, is mainly caused by the sudden rupture or occlusion of blood vessels, and is subdivided into ischemic stroke and hemorrhagic stroke. Stroke has become the second leading cause of death worldwide. In Chinese clinical practice, traditional Chinese medicine (TCM)/Integrative Medicine has been widely used for the treatment of stroke. Numerous randomized controlled trials (RCTs) of TCM/integrative medicine for stroke have been conducted to improve the efficacy and safety outcomes of stroke. However, their conclusions should be treated with caution because of the methodological quality defects in RCTs. Pervasive inconsistencies are present in the outcomes collected and reported across these studies, which may lead to the pooling of discrepant data and preclude meta-analysis. The issue could be addressed by developing a core outcome set (COS).

Aims
This study aims to develop a COS in the clinical trials of TCM/Integrative Medicine in the treatment of stroke.

Method and Analysis
A Steering group will be set up to organize and guide the development of this COS. The study contains three phases: (I) we will develop an initial outcome list covering all relevant outcomes, via two steps: (i) systematic reviews of outcomes for clinical trials of TCM/ Integrative Medicine for stroke; (ii) semi-structured interviews with stroke patients; (II) we will conduct three-round Delphi survey with different stakeholder groups to prioritize important outcomes; (III) we will integrate outcomes into a core outcome set by a consensus meeting.

Ethics and Dissemination
This study has been granted by the Ethics Committee of Tianjin University of Traditional Chinese Medicine (TJUTCM-EC20210003). When the COS is completed, we will publish it in an appropriate journal to promote further widespread use.

Registration
This study has been registered at Core Outcome Measures in Effectiveness Trials initiative, COMET database (registration #1678).

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P-066

Considerations when setting up a study investigating electronic patient reported outcomes (ePRO) within clinical trials – the SPRUCE study.

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Introduction
SPRUCE is a study within a trial (SWAT) investigating introducing electronic patient reported outcomes (ePRO) for ICR-CTSU clinical trial participants as an alternative to paper PROs, with a primary endpoint evaluating the difference in return rates between these. This could provide benefit to patients and trial teams at sites, reducing hospital visits and workload. It is important to maintain the option to complete questionnaires on paper to avoid excluding under-served groups.

Methods
We chose a partially randomised study design to prevent participants from being excluded if they had a preference, allowing us to assess the popularity of ePRO, however sample size was based on predicted numbers of randomised patients.
We collected reasons for declining randomisation to assess computer access and literacy within the participant population and ensure implementation of ePRO would be acceptable for our oncology trial participants. Participants can switch questionnaire modality if their chosen or randomised modality is not appropriate for their needs. Participants will be sent a questionnaire at 14 months after enrolment to assess their experience of their modality.
Participants cannot be randomised or choose ePRO without providing an email address, and patients' postal addresses are collected at study entry for prompt administration of questionnaires. ePRO participants are sent a welcome email to validate the email address provided.
Early ICR-CTSU trial PROs are usually administered by sites due to the short timeframe between treatment and PRO collection. The first post-intervention questionnaire is the timepoint of interest in SPRUCE, therefore all questionnaires are administered by the ICR-CTSU. This requires sites to be followed up weekly to determine participants' treatment dates from which the schedule runs to ensure questionnaires are sent on time. This is important because SPRUCE is a SWAT and collects data important to the trials the study is running in; any loss of data would impact these trials in addition to SPRUCE. The documentation for ePRO and paper PRO collection was aligned to minimise bias.

Results
As of 25/05/2022 there have been three participants randomised and ten have chosen their preferred modality (six chose ePRO and four paper).

Discussion
There have been limited studies of the impact of ePRO use in clinical trials and it can be challenging to design and implement a study to robustly assess the effect of ePRO vs paper collection. We hope SPRUCE will provide evidence for the use of ePRO, aspiring to improve patient experience within our trials.

P-067

Formulating a Patient Reported Outcomes strategy in early phase trials

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Background

Early phase clinical trials ascertain how new drugs interact with the human body, indicating preliminary safety profile, side effects, and therapeutic value. Traditionally, drug activity and safety data have been collected using clinical tools. These measures rely on clinician report alone which can lead to under-reporting of symptomatic adverse events better reported directly by patients. Patient-Reported Outcomes (PROs) could facilitate assessment of preliminary evidence of efficacy and tolerability as well as support regulatory review. Feasibility data collected during early trial phases can inform considerations including patient burden, missing data, interpretability and meaningfulness of data in later phases of drug development.

Aim

To formulate a PRO strategy in the context of an early phase clinical trial.

Methods

Through consultation with the Trial Management Group and patient partners; review of available core outcome sets; formulating a PRO proposal and review of available measures and their psychometric properties; and integration of the PRO proposal with wider trial outcomes, a PRO strategy was developed.

Results

A PRO strategy for use in early phase trials based on available evidence, plausible hypotheses, and multi-stakeholder input can be formulated through (1) establishing aims, objectives, and concepts of interest; (2) identifying key outcomes and the rationale for assessment; (3) identifying PROs from outcomes of interest; (4) selecting psychometrically appropriate PRO efficacy and safety measures; (5) formulating schedule of assessment; and (6) specifying PRO-based analyses and endpoints. Measures such as the Patient-Reported Outcome version of the National Cancer Institute Common Terminology Criteria for Adverse Events (PRO-CTCAE) present a potential solution. Feasibility data gathered during early phase trials can enhance future PRO strategy in later phases, promoting efficient use of measures; data completeness; acceptability to trial participants; and inform future analyses and sample size estimation.

Conclusion

PROs in early phase trials can provide preliminary evidence of efficacy and tolerability based on the patient experience; allows alignment with regulatory interest in patient perspective; and provides data that complements traditional outcome data. Use of both clinician and patient-reported AE measurement provides complementary data that can inform more dose selection, improve the identification of symptomatic toxicities, and support protocol-based toxicity management.

P-068

Developing Patient-centred Outcome Measures for Clinical Trials in Drug-resistant Tuberculosis

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Introduction

Drug-resistant tuberculosis (DR-TB) treatment is lengthy and toxic, with a negative impact on adherence in real-world settings. Evaluation of novel regimens should include an assessment of acceptability to patients to help ensure adequate adherence outside clinical trials.

Methods

DR-TB patients and survivors aged 18 years or older were recruited at sites in South Africa, Georgia, and Mongolia through purposive sampling. Focus groups using story stem methodology were used to explore treatment priorities, with story stems drafted to reflect different stages of treatment and the narratives completed by participants. Focus groups recordings were transcribed in English for thematic analysis. A further focus group of DR-TB patients and survivors is planned to review the themes elicited through thematic analysis, ensuring participants agreed no items are missing, and attempt to rank items relating to treatment side effects and symptoms of disease according to importance. An evaluation of existing instruments for measuring quality of life and symptoms reported by participants will be carried out using published criteria to assess potential suitability of each instrument to capture the item of interest. Existing instruments that are identified as candidates will be discussed with a panel of patient representatives. Instruments that are acceptable to these representatives will be presented to a group of stakeholders, including clinical trialists, patient groups, regulators and policymakers.

Results Structure and Timelines

Thematic analysis of the first focus group elicited three “super-themes” of items: 1) treatment experience and the role of good relationships with healthcare providers, 2) mental distress and opportunities for positive well-being, and 3) understanding fear and worry along the treatment journey. In MAY2022, a ranked list of items relating to treatment side effects and effects of disease will be available after a second round of focus groups. Instruments will be identified from a literature search, matched to these patient priorities, and evaluated between MAY2022 and JUL2022. Patient representatives will review the proposed instruments as outcome measures between JUN2022 and AUG2022. A stakeholders meeting will then be arranged to present the proposed outcome measures.

Potential Relevance and Impact

Patient-centred outcome measures will allow DR-TB regimens to be more holistically assessed in clinical trials and treatment recommendations made based on patient acceptability, with improved well-being and adherence. Quantifying acceptability of novel regimens will be particularly important when regimens have similar efficacy. A robust method for capturing additional benefits for novel regimens compared against control would also have application in noninferiority trials.

P-069

PSYCHLOPS – a short patient-generated mental health outcome measure that can be used during any psychotherapeutic intervention.

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Introduction
PSYCHLOPS is a well-established patient-reported outcome measure, first developed in 2005, and now widely used and recommended by the World Health Organisation for use in conflict zones and among refugees around the world.

Methods
It is designed to measure a patient's progress over a course of therapy. The two most important problems are chosen by the participant at the start of therapy, Their severity is recorded on a five-point scale through therapy, together with measures of functioning (one thing that is hard to do) and well-being (how have you felt in yourself). A third problem can be monitored should one develop during the intervention, but this is not used in the scoring.

Results
PSYCHLOPS compares well with conventional instruments. The standardised effect size of treatment (Mean change/standard deviation at baseline) has been shown to be consistently larger: 1.53 (CI 1.30 to 1.76), compared to CORE-OM 1.06 (95% CI 0.90 to 1.23) (Ashworth 2005); and 1.86 (95% CI 1.73–1.99) compared to four other conventional measurement tools with effect sizes ranging from 0.86 to 1.48 (Simpson 2021). This suggests that PSYCHLOPS measures what matters to the patient, but with less background "noise".

Discussion
Another advantage of PSYCHLOPS as a research tool is the wealth of qualitative information that is collected in the free-text description of the patient's problems. In a study of patients with coronary heart disease (Lawton 2014), we identified problems in four social areas (Relationships/Family, Work, Money, Functional), as well as cardiac, non-cardiac & psychological health, and "no problem".
There are versions for children aged 7-13 years old (PSYCHLOPS Kids) and for young people (PSYCHLOPS Teens). The kids are asked for only one problem, score the problem using smiley-faces, encouraged to draw their problems as well as describe them, and given the chance to choose three wishes to help them.

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P-070

Using trial data to estimate minimum important differences in patient reported outcomes via anchor-based and distribution-based methods - Journeying through Dementia case study

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Introduction
The Journeying Through Dementia trial (JtD) compared DEMQOL and DEMQOL-U, measuring dementia specific quality of life, in people with dementia. The aim of this work was to use DEMQOL(-U) data from JtD to elicit the minimum important difference (MID) in DEMQOL in people with dementia. This could then inform future RCT design (i.e. sample size estimation) and aid in interpretation of other RCT results.

Methods/Approach
Anchor-based and distribution-based methods were used to estimate the MID. For the anchor-based method, the global QOL (Q29) item, which asks respondents to "rate your quality of life overall" , from the DEMQOL was chosen as the anchor for DEMQOL and both Q29 and EQ-5D for DEMQOL-U. A one category difference in Q29, and a 0.07 point difference in EQ-5D score, was used to classify improvement and deterioration, and the MID scores were calculated for each category. These results were compared with scores obtained by the distribution-based methods.

Results
A total of 490 people with dementia had baseline DEMQOL data, of these 386 had 8-month data, and 344 had 12-month DEMQOL data. The absolute change in DEMQOL for a combined 1-point increase or decrease in the Q29 anchor was 5.2 at 8 months and 6.0 at 12 months. For the DEMQOL-U the average absolute change at 8 and 12 months was 0.032 and 0.046 for the Q29 anchor and 0.020 and 0.024 for EQ-5D anchor.

Discussion
RCT data can be used to estimate patient reported outcome MID via anchor-based methods providing an anchor has been collected within the trial. The anchor could be a single question, at each assessment, about global QoL or a global rating of change. This presentation will outline the methods and results from this JtD case study. We will discuss more broadly the elicitation and estimation of MID using RCT data via anchor-based and distribution-based methods.

P-071

Patient reported outcomes in randomized clinical trials: Suboptimal planning and poor reporting

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Background

Patient-reported outcomes (PROs) are important patient-centered endpoints in randomized clinical trials (RCT). However, the planning, analysis, and reporting of PROs can be challenging. The aim of this study was to examine the prevalence and characteristics of RCT protocols that have a PRO as primary endpoint, and to evaluate the PRO reporting in the corresponding results publication based on the Consolidated Standards of Reporting Trials – PRO extension (CONSORT-PRO).

Methods

We included 326 RCT protocols approved by ethics committees in the United Kingdom, Switzerland, Germany, and Canada in 2012. In February 2022, we systematically searched for corresponding peer-reviewed results publications in PubMed, Google Scholar, and Scopus. We extracted, independently and in duplicate, RCT and PRO characteristics from the protocols and publications, and assessed the CONSORT-PRO items in the publications.

Results

Out of 326 RCT protocols, 225 published RCT results as peer-reviewed articles and 52/326 (15%) planned a PRO as primary endpoint. The majority of the PRO-RCTs were investigator-initiated (63%, 33/52), parallel design (88%, 46/52), multi-center (60%, 32/52) trials in the area of surgery (19%, 10/52), psychiatry (13%, 7/52) and neurology (11%, 6/52). 38 out of 52 (63%) were published in a peer-reviewed journal. One RCT that had not planned a PRO as primary endpoint added a PRO as primary endpoint in the corresponding publication, resulting in a total of 39 published PRO-RCTs. PROs captured information about symptoms such as pain (48%, 19/39), disease specific outcome measure such as Asthma quality of life questionnaire (41%, 16/39), and mental-emotional functioning (15%, 6/39). Regarding CONSORT-PRO items, the rationale of choosing a specific PRO was documented in 17 (43%), the validation of the used PRO instrument in 24 (61%), the methods of PRO collection in 17 (43%), sample size calculation in 23 (58%), statistical approaches for dealing with missing data in 22 (56%), and PRO-specific limitations for generalizability in 4 (10%).

Discussion

Almost 60 percent of RCTs that planned a PRO as primary endpoint published results in a peer-reviewed journal. The reporting quality of PROs as primary endpoint was poor, especially regarding the rationale, collection methods used, and sample size calculation.

P-072

Blinded outcome assessment of clinical photographs of vitiligo may not reflect the views of patients receiving treatment: validation of the Vitiligo Noticeability Scale (VNS)

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Introduction
Vitiligo is a skin disorder that causes loss of skin colour resulting in white patches on the skin. Validated outcome measures are needed for vitiligo trials. The Vitiligo Noticeability Scale (VNS) was developed to assess patient-reported treatment response.

Objectives
To assess the construct validity, interpretability and reliability of the Vitiligo Noticeability Scale (VNS) - a scale from 1 to 5.

Methods
We used images of vitiligo before and after treatment, plus outcome data, from the HI-Light Vitiligo trial: an observer-blind, randomised controlled trial.
We compared outcome assessments made by trial participants (those who received treatment), with assessments of images by people with vitiligo who were not trial participants (PPI panel), and assessments by clinicians. Psychometric properties of the VNS were assessed, and different binary cut-offs for treatment success were explored.
Three focus groups and two online discussion groups provided insight into use of VNS by people with vitiligo (a mixture of trial participants and other people with vitiligo).

Results
Our hypothesis of a positive association between VNS and participant-reported global treatment success was supported for trial participants (k=0.41 if VNS success defined as ≥ 4; or k=0.71 if VNS success defined as ≥ 3), but not for the blinded PPI panel (k=0.28).
75% of trial participants and 74% of PPI panel assessments valued a VNS of 3 (partial response) as treatment success.
15% of trial participants valued a VNS of 2 (stayed the same) as a treatment success, presumably because participants all had at least one patch of vitiligo that was currently active at baseline. This was not reflected in the scores given by the blinded PPI panel (5% consider a VNS of 2 to be a treatment success).
As hypothesised, the association with participant-reported global success was higher for VNS (k=0.41) than for clinician-reported percentage repigmentation (k=0.17).
Test-retest reliability of the VNS was good: k=0.69 (95% CI 0.63, 0.74). Age and skin phototype did not influence interpretation of the VNS scores.
To people with vitiligo, the VNS is an acceptable and meaningful patient-reported outcome measure.

Conclusion

Trial participants may assess their vitiligo differently compared to blinded assessors. A VNS score of 3 may be more highly valued by people undergoing vitiligo treatment than previously thought.

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P-073

Outcome Measures in Amyotrophic Lateral Sclerosis Clinical Trials of Herbal Medicine

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Introduction

Clinical trials investigating herbal medicines (HMs) for amyotrophic lateral sclerosis (ALS) continue to be conducted in the past twenty years. Clearly defined outcomes in ALS are important to evaluate new HM treatments. We aimed to systematically review the outcome measures used in previous randomised controlled trials (RCTs) and to guide future research.

Methods

A total of nine databases, including Medline, Embase, CENTRAL, Web of science, KCL, CiNii, SinoMed, CNKI, and Wanfang, were searched from inception dates to March 25th, 2022, to identify RCTs of HM for ALS. All outcome measures were extracted and categorized according to core areas and domains.

Results

Forty-four outcome measures were identified from thirty-four eligible trials (3221 patients). These trials measured activity limitation (N = 21), symptom improvement rate (N = 20), score of traditional medicine syndrome (N = 9), pharmacodynamic biomarker (N = 9), quality of life (N = 8), loss of strength (N = 7), and mortality (N = 1). Among the forty-four measures, twelve were self-defined tools without validation. These self-defined measures were widely used in the domains of traditional medicine syndrome score and symptom improvement rate, which were reported in 76% of eligible trials. Concerning the primary outcome measures in included studies, the symptom improvement rates were the most commonly used tools in almost half of the eligible trials (N = 16), and their corresponding definitions were obscure. The following widely employed primary outcome measures were the ALS Functional Rating Scale-Revised and the Modified Norris Scale in six and five studies, respectively. Additionally, adverse events were investigated in fifteen trials, and the level of aminotransferase was most concerned (N = 11).

Discussion

This study revealed that great heterogeneity exists in the assessment of ALS in HM research settings. Most self-defined instruments have been insufficiently validated and were widely used. This study suggests that further work is needed to validate and standardized outcome measures for the assessment of ALS in order to promote HM clinical trials.

P-074

Selecting and collecting outcomes for clinical trials: An international qualitative study exploring stakeholder perspectives

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Introduction

Selecting and collecting data to support appropriate primary and secondary outcomes is a critical step in designing trials that can change clinical practice.

In this study, we aimed to investigate who contributes to the process of selecting and collecting trial outcomes, and how those people are involved. This work serves two main purposes: 1) it provides the trials community with evidence to demonstrate how outcomes are currently selected and collected, and 2) it allows people involved in trial design and conduct to pick apart these processes to consider how efficiencies and improvements can be made.

Methods

One-to-one semi-structured interviews, supported by a topic guide to ensure coverage of key themes. The Framework approach was used for thematic analysis of data, themes were linked through constant comparison of data both within and across stakeholder groups.

Twenty-nine international trialists from various stakeholder groups. Participants worked primarily on designing and/or delivering Phase III pragmatic effectiveness trials, with experience spanning various funders, trial settings, clinical specialties, intervention types, and participant populations.

Results

We identified three descriptive themes focusing on primary and secondary outcome selection and collection, and publication of outcome data. Within these themes, participants raised issues around the following:

1) Outcome selection: clarity of the research question; confidence in selecting trial outcomes and how confidence decreases with increased experience; interplay between different stakeholders; how patients and the public are involved in outcome selection; perceived impact of poor outcome selection including poor recruitment and/or retention; and use of core outcome sets.

2) Outcome collection: disconnect between decisions made by outcome selectors and the practical work done by outcome collectors; potential impact of outcome measures on trial participants; potential impact on trial staff workload; and use of routinely collected data.

3) Publication of outcome data: difficulties in finding time to write and revise manuscripts for publication due to time and funding constraints.

Participants overwhelmingly focussed on the process of outcome selection in our interviews, a topic they talk about unprompted. When prompted participants do discuss outcome collection, but poor communication between selectors and collectors at the trial design stage, means that outcome selection is rarely linked with the data collection workload it generates.

Discussion

Stakeholders involved in the design and conduct of trials fail to connect decisions around outcome selection with data collection workload. Publication of outcome data and effective dissemination of trial results are hindered due to the project-based culture of academic research.

P-075

A systematic review of the accuracy of heart failure ascertainment using routinely collected healthcare data

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Introduction

Heart failure (HF) is an important cause of morbidity and mortality requiring large randomised controlled trials to assess potential therapies. Ascertainment of HF hospitalisations in cardiovascular trials usually involves costly and laborious processes for identifying HF events, gathering evidence for reported events and clinical adjudication. These processes could be streamlined by using routinely collected healthcare data (RCD). However, the accuracy of RCD based methods for HF outcome ascertainment requires assessment. We systematically reviewed studies assessing the utility of RCD to ascertain HF outcomes to assess the feasibility of using such methods in clinical trials.

Methods

Studies that assessed the utility of RCD for HF outcome ascertainment against defined "gold standard" (GS) ascertainment criteria and reported at least one test statistic were identified by searching Medline and Embase from inception to May 2021. Data on study characteristics, details of RCD and GS data sources and definitions, and test statistics were reviewed. The accuracy of RCD for HF outcome ascertainment was meta-analysed using mixed-effects models for studies ascertaining acute and prevalent HF. These models were used to construct forest plots and summary receiver operating characteristics (SROC) plots with hierarchical SROC curves and estimate summary sensitivities and specificities for studies ascertaining acute and prevalent HF and other subgroups of interest.

Results

58 studies (involving 48,643 GS adjudicated HF events) were included in this review. Meta-analysis of 17 acute HF studies showed that RCD algorithms have high specificity (96.2%, 95% confidence interval [CI]: 91.5-98.3), but lacked sensitivity (63.5%, 95% CI: 51.3-74.1) with similar results for 21 prevalent HF studies. There was considerable heterogeneity between studies (I^2>98% for both acute and prevalent HF) which is not explained by differences in RCD coding algorithms, the GS or the country of origin. Strategies used to improve case identification included use of broader coding definitions, combining multiple data sources and using machine learning algorithms of free text data, but these methods were not always successful and at times reduced specificity in individual studies.

Discussion

RCD can correctly identify HF outcomes but misses a substantial proportion of events . This may have an impact on the statistical power of a study to assess treatment effects, but should not introduce bias.

P-076

Developing a Charter to increase the transparency and efficiency of a Blinded Endpoint Review Committee process

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Introduction
A blinded endpoint review committee (BERC) comprises a panel of experts who are blinded to treatment allocation with the role of centrally reviewing and classifying endpoints in a transparent and objective manner. The BERC process is intended to enhance the consistency and integrity of the trial's endpoints and/or outcome measures .
A charter defining the membership, terms of reference, roles, responsibilities, decision making process and relationships of members of the BERC was developed. The aim of the Charter was to document the review process, conventions and outcome definitions to be used. The BERC charter was developed and used in the Baby-OSCAR trial to classify neurodevelopmental outcomes at 2 years of age using routine clinical data where parent-reported data were missing.

Methods/Approach
Three experts were identified including a Chairperson who took overall responsibility for the BERC process. Two were experts in the field of neonatology and child development. The third was selected for arbitration purposes.
The Charter included definitions for classifying neurodevelopmental outcomes at 2 years of age and set out the criteria for which participant data would be reviewed. It included forms for recording BERC decisions and electronic versions of the data capture forms developed and agreed in line with the Charter.
Routine clinical data from two-year developmental assessments were assessed independently by each reviewer from which outcomes were classified. If consensus could not be reached, the third independent reviewer could be approached to classify the final outcome.

Results
This independent process set out by the Charter increased the data available for classifying 2-year neurodevelopmental outcomes in the Baby-OSCAR trial by 12%.The Charter set out a transparent process for deriving outcomes where the information was not available from direct sources. A total of 57, two year discharges have been reviewed to date. Both reviewers agreed on the primary outcome in 85% of cases with 15% requiring further discussion until a decision on outcome was reached. A third independent expert has not yet been required.

Discussion
BERC's are advocated in trials to independently verify key endpoints. The Baby-OSCAR Charter set out a transparent and efficient process allowing fair consensus to be reached when classifying pre-defined outcomes. A Charter such as this one could be adapted and used in trials to set out the scope for the BERC, the review process and conventions in order to harmonise and standardise endpoint assessments thereby reducing missing data and improve reliable data capture.

P-077

An electronic platform for capturing and promoting safe and transparent surgical innovation from early phase studies to randomised evaluation

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Introduction
In contrast to the rigorous development of pharmaceutical products, methods for introducing novel surgical procedures/devices lacks sufficient regulation and standardisation. Incremental evaluation and shared learning are problematic. Surgeon innovators typically advance novel procedures/devices based on individual reflections on peri and post-operative experiences and outcomes. Some surgeons publish findings, but publications take time, report heterogeneous outcomes, frequently focus on successes, and lack long-term data. New procedures/devices can be widely adopted without robust comparison with existing treatments. This study will develop and evaluate the usability and utility of an electronic platform for documenting, analysing, and sharing incremental learning of the early phase introduction and modification of surgical procedures/devices in real-time, to establish when procedures are sufficiently evolved and stabilised for randomised evaluation.

Methods/Approach
Multi-centre study in NHS hospital trusts delivering innovative invasive procedures/devices. Participants will be surgeon innovators and patients scheduled for/who have undergone an innovative procedure/device. The work comprises three phases.

Phase 1 – e-platform development:
a. Drafting of multi-source pre/intra/post-operative data fields, including in-theatre digital imaging to capture: (i) patient selection criteria, (ii) surgeon characteristics, (iii) procedural plans, (iv) intended benefits, (v) expected and unexpected disadvantages/complications, (vi) modifications to patient selection criteria, procedural techniques/components, and peri-operative care/co-interventions, (vii) device functionality/problems, (viii) surgeons' experiences, (ix) procedural outcomes.
b. Iterative refinement of draft data fields via surgeon interviews.
c. Digitalisation of draft data fields within an electronic cloud-hosted platform accessible from within NHS hospital trusts.

Phase 2 - Usability and utility evaluation in NHS hospital trusts:
a. Using a realist evaluation approach, undertake observations and interviews with healthcare professionals to explore views, experiences, contextual factors facilitating and constraining use, and mechanisms by which and in what contexts the e-platform enhances shared learning of surgical innovation.
b. Evaluation of key usability metrics to evaluate e-platform effectiveness, efficiency, and user satisfaction (e.g., task completion rates/times, data completeness/quality, user/error rates, self/observer-reported experiences).
c. Feedback meetings with surgeons to relay incremental learning and refine methods for optimally presenting e-platform data for effective shared learning.

Phase 3 - Evaluation of wider e-platform uptake in NHS hospital trusts and/or innovative procedures/devices (e.g., user uptake, data volume/completeness, integration with NHS IT systems).

Timing of Potential Results
Findings from phase 1 will be presented.

Potential Relevance and Impact
This e-platform will promote efficient evolution and stabilisation of invasive procedures/devices and improve the process by which they are widely adopted, evaluated in later phase trials, and introduced into clinical practice.

P-078

Developing a Core Outcome Set for Dementia with Lewy Bodies

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Background

Methodological heterogeneity in the outcome measurements adopted in clinical trials for dementia with Lewy bodies (DLB) impedes effective evidence synthesis, rigorous meta-analysis, and clinical translation. DLB is the second most common cause of dementia and manifests with an array of clinical symptoms.

Objective

We aimed to develop a Core Outcome Set (COS), an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical DLB trials internationally.

Method

We adopted a multi-faceted approach to COS development, adopting the principles of the Core Outcome Measures in Effectiveness Trials (COMET) initiative. We conducted systematic reviews of outcomes used in intervention trials, qualitative studies, and health economic studies in DLB. A resulting shortlist of outcome measures formed the basis of an e-Delphi consensus process, piloted among members of the study group, before it was administered in two rounds of an international stakeholder group of clinicians, scientists, policy and third sector leads. Lay stakeholders, including people with DLB and their caregivers, also contributed to the e-Delphi process. Consensus on inclusion was determined by at least 70% of respondents grading an outcome measure as "critical for inclusion" and less than 15% grading as "not important". After appraisal of each outcome using Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines, a consensus meeting was conducted, in which all participants were invited to agree on final outcomes and rate each outcome on impact, relevance and clinical feasibility.

Results

Through validated mechanisms we constructed a COS including measurements of motor, cognitive, neuropsychiatric, autonomic, health economic, health provision, and quality of life. A diverse group of international and intersectional stakeholders have lent approval to its use.

Conclusion

We propose a COS for DLB which will be a benchmark which all DLB trials should meet. This standardised approach will could optimise research resources, facilitate multicentre collaboration, and minimize methodological bias.

P-079

Improving research in critical care: A Randomised feasibility trial of administering Desmopressin prior to procedures or Radiological InterVEntions in thrombocytopenic critically ill patients (DRIVE)

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Introduction
Patients with low platelet counts comprise approximately a third of those in critical care and the vast majority undergo invasive procedures that increase their bleeding risk. Optimal management is unclear. Recent meta-analysis found that Desmopressin reduces bleeding risk and red cell transfusion in patients undergoing cardiac surgery. However, significant uncertainty remains on the drug's benefits and risks for other patient groups. The aim of DRIVE was to assess the feasibility of administering Desmopressin or placebo to thrombocytopenic critically ill patients undergoing invasive procedures for prophylaxis against bleeding (ISRCTN12845429).

Methods
The DRIVE trial was designed as a stand-alone, fully protocolised parallel placebo-controlled double blind randomised trial. Patients were recruited if they had platelet count below a specified threshold and were undergoing an invasive procedure which the treating physician considered to have a bleeding risk. The primary outcome was the proportion of eligible patients who are randomised in the trial and received the IMP. Secondary feasibility outcomes included protocol adherence. Secondary efficacy outcomes included laboratory measurement of platelet function, bleeding, and adverse events. The sample size of 40 patients was based on a pragmatic recruitment schedule over 15 months, targeted population size and expected proportion recruited (30%).

Results
A substantial number of screenings were required to identify eligible participants (214/384) between 01 January 2016 and 04 July 2019. Among those eligible, the majority were not randomised because procedures took place outside the working hours of research teams (78%). Of those eligible 18.8% (95% CI (13.8-24.7) were randomised and received the allocated IMP. There were no issues starting IMP infusion, but loss of compliant participants started when infusions were not completed or were not completed within the protocolised timeframe before the start of procedures which could be delayed and subject to unexpected emergencies. As a result, levels of overall adherence were low 59.5% (66.7% vs 52.4% for placebo and Desmopressin, respectively). Consent procedures for those lacking capacity were needed for most. Most randomised participants underwent elective procedures as recruitment immediately on admission was challenging. Safety outcomes indicate that Desmopressin maybe a safe alternative to platelet transfusion. However, efficacy outcomes show no apparent signal.

Discussion
DRIVE exemplifies the necessity of formalised feasibility assessments, and such studies are undereported. Although the study demonstrates feasibility for the primary target and provides estimates for non-adherence to inform the design of a trial, it also reveals important uncertainties in the need for therapy in this group.

P-080

Three-outcome designs for pilot trials with progression criteria

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Introduction
Pilot trials are often conducted in advance of a planned clinical trial to assess their feasibility and help decide if, and how, it should proceed. These decisions may be guided by so-called progression criteria, which pre-specify minimal thresholds for parameters such as recruitment or adherence rates. Progression criteria can take a simple stop/go form, or may incorporate two thresholds in a "traffic light" system: if the estimate falls below the lesser of these, the main trial should not proceed (red); if it falls above the larger threshold, it should proceed immediately (green); and if it falls between the two thresholds, the trial may only proceed after some improvements are made or after other data are considered (amber). Despite their increasing prevalence and their pre-specification being required by NIHR, there has been limited research into the statistical properties of these three-outcome progression criteria.

Methods
Recognising that progression criteria can be viewed within the statistical framework of hypothesis testing, we review three-outcome clinical trial designs originally proposed in the Phase II trial setting and show how they can provide a formal basis for the choice of three-outcome progression criteria and the pilot trial sample size. We then examine the statistical properties of three-outcome progression criteria, to understand the extent to which they can a) reduce the required pilot trial sample size; b) allow for other data to guide the progression decision; and c) allow for adjustments to be made to either the main trial design or the intervention.

Results
Our analysis shows that using three-outcome progression criteria does not lead to a lower pilot trial sample size and can only facilitate adjustments to the main trial design or intervention if the nature and effect of those adjustments are known prior to the pilot trial. We find that three-outcome progression criteria can allow us to use other data when making progression decisions, but that this requires an increased pilot sample size in comparison to the two-outcome alternative.

Discussion
Our results suggest that the applicability of three-outcome progression criteria may be somewhat limited. When they are deemed necessary, the formal statistical framework we have outlined provides a way to determine and justify optimal threshold values.

P-081

Challenges and opportunities for conducting prehospital trauma trials: a behavioural investigation

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Background
Trials in prehospital trauma are not common, which is likely linked to the existence of a number of significant logistical and methodological challenges to consider when designing and delivering trials in this setting. Of the existing studies that have explored these challenges, most focussed on experiences within individual trials rather than across the prehospital trauma trial landscape to identify over-arching factors. In addition, very little research has explored the views of Helicopter Emergency Medical Service (HEMS) teams experiences of prehospital trauma trials. Therefore, the overall aim of this study was to generate evidence on the key challenges and opportunities as perceived by stakeholders on the conduct of prehospital trauma trials, both broadly and specifically for those involving HEMS teams.

Methods
Semi-structured interviews were conducted with two groups of stakeholders: 1. research personnel who had experience of prehospital trials either through direct involvement in conduct or through strategic oversight of national initiatives (n = 7), and 2. clinical staff (n = 16) involved in recruitment to a prehospital trauma feasibility study. Interviews were guided through the use of a semi-structured topic guide, which for the clinical staff was informed by the Theoretical Domains Framework (TDF). Thematic analyses was used to assess the salient barriers and enablers of conducting prehospital trauma trials.

Findings
Across both groups of participants, challenges reported included the lack of research experience amongst prehospital staff, team dynamics within a rotating shift schedule, and the involvement of external organisations with differential infrastructures (e.g. Air Ambulances and HEMS teams) in addition to the scarcity of eligible cases that could affect trial design, set-up, and conduct. Other barriers reported related to the mixed levels of clinical equipoise amongst HEMS staff and institutional pressures to conduct innovative research, which could affect staff motivation. Clinical staff involved in the prehospital trauma feasibility study indicated challenges in relation to the emotional impact of conducting trauma research and how might affect decisions to randomise, and the technical and non-technical skills required to recruit and deliver an intervention in a prehospital context.

Conclusion
This study has highlighted that prehospital trauma trials face many context specific but also generic challenges to their successful delivery. These challenges were identified across multiple levels, within systems, organisations, and individuals. Future prehospital trauma trials could consider the findings to develop targeted solutions to the challenges identified in order to enhance the design, set-up and conduct of trials in this setting.

P-082

A web-app for Sample Size calculation and evaluation of PROGRESSion criteria in pilot and feasibility studies (SS-PROGRESS)

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Introduction
The aim is to develop an easy-to-use and freely available web-app for researchers to help in the design, monitoring, and interpretation of pilot and feasibility studies (PAFS), based on Lewis et al. (Pilot Feasibility Stud 2021; 7:40). The methodology follows recommended CONSORT guidelines for PAFS by focusing on feasibility objectives and assessment, traffic-light progression criteria for decision-making on whether to proceed (with or without amendment) or not to a main trial, and sample size derivation based on feasibility outcomes.

Methods/Approach
This methodology centres on sample size derivation for PAFS based on hypothesis tests of multiple feasibility outcomes against progression criteria. It focuses on binary outcomes aligned to such outcomes across three hierarchical levels: population (e.g., recruitment uptake), randomised/participant (e.g., treatment delivery per protocol), and treatment (e.g., treatment fidelity/compliance/adherence). A sample size inflation approach is used across all levels to ensure the sample size is adequate and at least the nominal required power across all progression criteria evaluations is achieved. Hypothesis testing is justifiably not recommended for evaluating clinical effectiveness/efficacy in PAFS, but is different when testing feasibility outcomes, by providing a framework for acceptance/rejection of progression criteria (in conjunction with other feasibility objectives) and sufficient power to detect meaningful signals for progression. The principle is to test against being in the RED (unacceptable/STOP) zone (H0) when the feasibility outcome is hypothesised to fall into the GREEN (acceptable/GO) zone (H1), with the AMBER zone designating an area where the result is considered neither wholly unacceptable nor acceptable for progression to the main trial (on current standing). The web-app is written using Shiny (an R package to build interactive web applications).

Results Structure and Timelines
We will demonstrate the use of the Shiny web-app, which is expected to be finalised by September 2022, in the application of this methodology, illustrated via various example PAFS scenarios.

Potential Relevance and Impact
This work provides guidelines and clear direction on PAFS sample sizes, evaluation, and progression signaling for relevant feasibility objectives. Our methodology facilitates improved design, monitoring, and evaluation of future PAFS, leading to studies that properly inform various stakeholders regarding progression to main trials. The SS-PROGRESS web-app will provide easy-to-use and freely available software allowing statisticians and trialists to quickly and efficiently implement the methodology, and obtain their sample sizes. It will also enable them to evaluate their results by extracting graphics that can be inserted into monitoring and end-of-study reports.

P-083

A Feasibility Study to Evaluate the Effect Bleeds Have on Patients with Atrial Fibrillation (EQUAL-AF)

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Introduction

Atrial Fibrillation (AF) is the most common, and possibly under diagnosed, cardiac arrhythmia worldwide. Patients can develop further AF-related complications, for example, significant risks of stroke and systemic thromboembolism and increased mortality. Bleeding while taking prescribed anticoagulant therapy could have a significant impact on patient quality of life. The EQUAL-AF study investigated the feasibility of engaging with patients with atrial fibrillation (AF) through primary and secondary care settings, who had experienced recent minor or major bleeds (as defined by the International Society on Thrombosis and Haemostasis (ISTH)) and were receiving active oral anticoagulation therapies (OATs) for the management of AF.

This study also examined the feasibility of collecting information about patients' quality of life (QoL) following a bleed event.

Methods

Clinical study health care professionals in primary and secondary care settings identified eligible patients and invited them to participate. Researchers at Swansea University then followed-up those interested and distributed a survey, which included three validated questionnaires/patient-reported outcome measures (PROMs) - AFEQT, EQ5D-3L, and PACT-Q, to gather health-related QoL data (HRQoL). Patients completed the questionnaires ≤4 weeks following a bleed and again 3 months later. A sub-set of study participants (≈ 10) were invited to complete a semi-structured interview about their bleed experiences and effect on QoL. All survey data were held centrally in a custom database.

Results Structure and Timelines

Following last participant follow-up at the 3-month stage, a descriptive analysis of QoL data was performed. Participants who experience multiple bleeds were included. Anticoagulant information was also compared with bleed classification (minor/major). A thematic analysis was conducted on transcribed interviews using qualitative data analysis software. The survey collected open-ended feedback regarding each of the PROMs used and how appropriately the PROMs captured bleed specific QoL issues for anticoagulated AF patients. This information was used for descriptive analysis only.

Potential Relevance and Impact

This feasibility study tests the success of recruiting sufficient suitable patients and gathering HRQoL data from the AF population, aiming to investigate the impact on QoL in a potential larger-scale future study. Clearer insight into the effect bleeds have on anticoagulated patients with AF could provide clinicians with a better understanding of patient perspectives regarding the management of their AF when prescribing OAT.

The suitability of the PROMs used in this study was assessed for collecting QoL data for patients reporting on bleeds.

P-084

ExPECT: A Feasibility Study Evaluating Complication Rates Following Extraperitoneal End Colostomy Formation

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Introduction
100,000 people in the UK have stomas and stoma appliances cost the NHS almost £230 million per year1. A parastomal hernia (PH) is a common complication of stoma formation and known to have an impact on patient quality of life (QoL). Several meta-analyses demonstrate a reduction in PH formation with mesh prophylaxis but have several limitations. The largest RCT available to date does not demonstrate any benefit from prophylactic mesh placement and there are concerns regarding mesh-related complications (infection, erosion, chronic pain). Case studies suggest equivalent rates of hernia prevention to that of mesh prophylaxis with use of an extraperitoneal (EP) approach during stoma formation. The ExPECT study investigates complication rates between EP colostomy formation (Intervention) or the standard transperitoneal (TP) technique (Treatment as Usual (TAU).

Methods
This feasibility study is a multi-centre, randomised controlled trial (RCT), co-ordinated across 3 health boards in South Wales. Approximately 60 participants will be recruited over 12 months. Participants will be randomised by arm (Intervention vs TAU). Participants will remain blinded to their treatment arm until study close. Follow-up data will be collected at 6 weeks, 6 months and up to 12 months, if viable. Health-related QoL (HRQoL) data (Colostomy Impact Score and EQ5D) will also be collected. For more details please search Clinicaltrials.gov ID: NCT05163873.

Results Structure and Timelines
As this is a feasibility study, statistical analyses will be primarily descriptive. This will include summary statistics: completion rate, missing data, estimates of effect, variance and 95% confidence interval (CI) for the difference between the arms. The data will be presented using tables and graphs. Reports on the rate of early development of PH and the prevalence within each study arm will be produced for all time points. QoL data collected from the HRQoL questionnaires will be summarised descriptively.

Progress to Date
Following the COVID-19 outbreak, study activity and site activation was interrupted or delayed across all health boards due to site staff having increased workload levels with COVID-related priorities and having no capacity to run the ExPECT study in conjunction with this. However, the ExPECT study is now open to recruitment at the lead site in Swansea from December 2021. Research staff have already recruited 10 participants, and eight have been randomised and have completed their surgical procedure. No SAE's have been reported to date. The remaining two sites will be activated and begin recruiting to the study in the upcoming months.

P-085

A review of sample sizes in pilot cluster randomised trials from 2010-2020

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Introduction
Over the past 10 years there has been an increase in the number of registered and published pilot cluster-randomised controlled trials (cRCTs). However, there is minimal guidance regarding the appropriate sample sizes for pilot cRCTs, despite the fact these studies are often used to estimate parameters for main trials and all trials should justify their choice of sample size.
We conducted an audit of pilot cRCTs from 2010-2020 to document sample size for these trials, their justification, and explore trends across types of trial.

Methods
We performed a search of PubMed and Web of Science between 2010-2020. The search terms “pilot” or “feasibility” were used, alongside terms to identify cRCTs.
From included studies we collated information including planned and actual sample size (participants and clusters), number of study arms, whether the sample size was justified, and whether an ICC was estimated. We also collected data regarding cluster type, therapeutic area and type of funding.

Results
The search produced 3168 records of which 178 studies met the inclusion criteria.
Almost all studies (90%) had two arms. Most studies were publicly funded (76%). Just over half (56%) utilised clusters in a healthcare setting, including primary care (12%), secondary care (17%), and social care (16%) groups, and healthcare professionals (11%).
We found a median of 4 planned clusters per-arm (IQR 3-6; range 2-150) and median planned participants of 75 per-arm (IQR 40-200; range 20-3000). The largest median sample size was found in studies with clusters in an educational setting (175 participants per-arm, IQR 75-305). Studies randomising health professionals had the smallest (44 participants per-arm, IQR 30-96). Both had a median of 4 clusters per-arm suggesting larger studies tend to recruit larger rather than more clusters.
Many studies did not justify their choice of sample size. Where reported, the most common justification was to estimate parameters for a main trial to ensure adequate power. However, many studies did not report an ICC estimate.

Discussion
Four clusters per-arm is the most commonly utilised sample size for pilot cRCTs. There is little consistency in the justification for the chosen sample size. While most pilot cRCTs are intended to provide estimates of key parameters for a main trial, many did not estimate the ICC, which is an important parameter in cRCT design, particularly sample size calculation. Future work will explore whether and when 4 clusters per-arm is an appropriate sample size.

P-086

Adapted EMDR intervention for people with intellectual disability and PTSD - Trauma-AID

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There is extensive evidence that people with intellectual disabilities (PwID) are more likely to suffer severe and prolonged types of abuse leading to post-traumatic stress disorder (PTSD). The Trauma-AID study is a randomised controlled trial (RCT) of an intervention for PTSD adapted for PwID. The intervention is an adapted version of eye movement desensitization and reprocessing (EMDR). Our aim is to determine the clinical and cost-effectiveness of EMDR for symptoms of PTSD in PwID, compared with treatment as usual (TAU).
The study comprises of the main RCT preceded by a preliminary study to validate an adapted International Trauma Question for ICD-11 (separate abstract); a feasibility study to ensure acceptability of the intervention; a pilot phase to measure the initial recruitment and delivery.
The primary clinical outcome is the Impact of Events Scale – Intellectual Disabilities (IES-ID) score at the 8-month. Secondary outcomes include clinical measures of depression, anxiety, mental health and quality of life for both the participant and carer collected at baseline and at 4, 8 and 14 month follow-ups, with a nested qualitative study to assess fidelity, adherence and factors that influence outcome.
We trained an initial tranche of 26 therapists across 4 sites before extending to include a further 3 sites and 19 more therapists. The main study requires 144 participants with their carers to help evaluate treatment impact.
We have completed the feasibility with the following outcomes:

- Manualisation of adapted EMDR for use in the trial;
- Training of research assistants,
- Completion of EMDR training by 46 therapists, with sign-off
- administration of the complete PES+EMDR protocol to 28 patients, with review of its acceptability to patients and carers

The feasibility study was expanded due to COVID restrictions to evaluate the use of hybrid (face-to-face and remote) procedures for consent, treatment and assessment

- Hybrid PES-EMDR intervention, including both logistical and clinical information
- Train existing therapists on remote delivery of EMDR
- Train research assistants in face-to-face and remote data collection, and assess the feasibility of remote evaluation
- Develop tools to evaluate costs of remote v face to face

The study has been significantly delayed due to the impact of the pandemic on Learning Disability services. We are now open for recruitment in 4 our 7 sites and have invited a further three new sites to join, allowing us to train additional therapists to deliver the study under a revised schedule.

P-087

Feasibility of automated real-time monitoring of surgical patients' experience with shared decision making

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Introduction
High quality patient-centred shared decision making (SDM) is central to modern healthcare, however, optimal ways to improve patients' experience remain unknown. Technological advances allow real-time reporting of experiences with SDM that may facilitate the development and evaluation of interventions in trials. This study examined the feasibility of automated, real-time measurement of surgical patients' experience with SDM using electronic patient-reported outcome measures (ePROMs).

Methods/Approach
A prospective study included adult patients booked for planned surgery (general, breast, orthopaedic, urological, vascular and neurosurgery) in two hospitals. Diagnostic endoscopy was excluded. A software system was developed to automatically identify patients booked for surgery, to administer two validated PROMs (CollaboRATE, SDM-Q-9), and to provide a report within 24 hours. Mixed methods usability testing assessed system effectiveness (error rates), system efficiency (time per task), and user satisfaction. Response rates were assessed with descriptive statistics and uni- and multivariable logistic regression explored the association between response and demographic data.

Results Structure and Timelines
The software system was implemented in two hospitals in April and December 2021, respectively. Systems usability testing demonstrated high effectiveness (9 testing sessions, 169/171 (99%) task completion success; 2 non-critical errors), efficiency was good (median ePROM completion time 120 seconds n=2,254) and qualitative interviews highlighted good accessibility and low burden. Data collection will continue until April 2022 and up-to-date recruitment rates and response statistics will be reported. To-date, 7,381 patients were sent surveys, of which 3,543 (48%) completed both ePROMs. Univariable regression revealed an association between response and female sex, middle age (40-69), low deprivation (lowest IMD quintile), and treatment by general surgeons compared to other specialties, but these were all attenuated in the multivariable model.

Potential Relevance and Impact
Automated, real-time monitoring of SDM is feasible across multiple surgical specialties. This may facilitate efficient evaluation of interventions to improve SDM in trials.

P-088

Exploring Heterogeneity in Responses to Intensive Treatment in Patients with Rheumatoid Arthritis (RA) Using Group Based Trajectory Models (GBTMs)

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Background
Traditionally rheumatoid arthritis (RA) trials classify patients as responders and non-responders based on achieving remission from disease activity. This simplistic dichotomisation ignores the graduated range of treatment responses. Group Based Trajectory Models (GBTMs) provide an alternative approach that considers this. They can identify patient subgroups with similar outcome trajectories, helping clinicians match patients to appropriate treatment strategies. Our aim was to use GBTMs to explore baseline factors associated with different levels of response to intensive treatment in patients with RA previously enrolled to a clinical trial.

Methods
We used data from the TITRATE trial, which enrolled 335 RA patients: 168 randomised patients received intensive management (regular assessments with treatment escalation and psychosocial support), 163 of whom completed the study. TITRATE tested the hypothesis that intensive management gives more 12-month remissions measured using disease activity scores on 28-joint counts (DAS-28) compared to standard care in moderately active RA. We applied GBTMs to monthly DAS28 scores over one year to group patients receiving intensive management into treatment trajectories and evaluated differences in baseline variables between these groups.

Results
GBTMs identified three distinct trajectories: good responders (n=40), moderate responders (n=76) and poor responders (n=47). DAS-28 sub-components (including tender and swollen joint counts) were consistent with those of the full composite score. Baseline body mass index (BMI), disability, fatigue, and depression levels were significantly different between trajectory groups. Obesity (BMI>30) was lowest (10%) in good responders, compared to 38% in moderate, and 43% in poor responders (P=0.002). Depression (Patient Health Questionnaire-9 > 15) was also lower occurring in 8% of good responders, 14% of moderate responders, and 38% of poor responders (P<0.001). The key difference in treatments was the use of high-cost biologic drugs: only 5% good responders received biologics compared with 30% of moderate responders and 51% of poor responders (P<0.001). Most good responders had endpoint remissions with low disability, pain and fatigue scores; few poor responders achieved any favourable outcomes.

Discussion
GBTMs identified three trajectories of disease progression in patients with moderately active RA, with obesity, disability, fatigue, and depression all associating with treatment responses. This approach has the potential to provide solutions to precision medicine and allow patient-oriented treatment strategies based on varying characteristics. Further studies in other patient groups are needed to validate our findings.

P-089

Efficiency enhancement in testing treatment efficacy across subgroups using treatment crossover designs

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Background
When a promising predictive marker is available for a new treatment under development, it should be used to optimize the patient population for the treatment. Almost all the methods proposed for clinical trial design and data analysis with predictive markers thus far suppose single-arm or parallel-group designs. However, treatment crossover designs are another promising choice under some conditions on disease and treatment (such as stable diseases and treatments with short-term responses and minimal carry-over effects), because it could largely enhance the efficiency of the predictive marker analysis thorough within-patient treatment comparison, as shown in the context of testing main treatment effects in the absence of predictive markers.

Methods
We derive a statistical test on treatment efficacy across marker-defined subgroups in the context of 2×2 crossover design, and evaluate its improved efficiency, compared with a similar test derived under a parallel-group design with two treatment arms, by simulation experiments supposing various treatment effect profiles across subgroups.

Timing of Potential Results
The numerical evaluation is currently ongoing and its results would be available before the conference. As a preliminary assessment, we have shown smaller variance of our crossover predictive marker analysis in testing marker predictiveness or treatment-by-marker interactions.

Potential Relevance & Impact
Enhanced efficiency by our crossover analysis in testing treatment effects across subgroups would indicate the crossover design as an attractive choice of clinical trial design when a promising predictive marker is available and assessment of treatment efficacy across marker-defined subgroups are warranted in a clinical trial with relatively small sample size.

P-090

What is the impact on participant recruitment of a pen incentive and a brief participant information leaflet? A factorial randomised study within a trial

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Introduction
Many strategies are used by trialists to improve recruitment, but few have been rigorously tested. We aimed to evaluate two such interventions; 1) a study branded pen and 2) brief participant information leaflet, included within study invitation packs for the Multiple Symptoms Study 3 (MSS3) trial.

Methods
A 2x2 factorial 'study within a trial' (SWAT) was embedded into MSS3 – a randomised trial to evaluate a community-based clinic for patients with persistent, medically unexplained, physical symptoms. Potential MSS3 participants received postal invitation packs sent via GP practices, with the addition of a MSS3 branded pen and/or brief participant information leaflet (PIL) or neither of these. The primary outcome was randomisation rate, with secondary outcomes including return rate, time to return, reasons for non-randomised returns and cost-effectiveness.

Results
One hundred and eight GP practices posted 6946 invitations, from which 318 participants (4.6%) were randomised to the host trial. Between those sent a brief PIL (n=3467) and not sent a brief PIL (n=3479) there was no significant difference in randomisation rates (166 (4.8%) vs 152 (4.4%); OR 1.10, 95% CI 0.88-1.38). However, response rates were significantly higher in those sent the brief PIL (573 (16.5%) vs 513 (14.7%); OR 1.14, 95% CI 1.01-1.30). Between those sent the pen (n=3464) and not sent the pen (n=3482) there was no evidence of increased randomisation (145 (4.2%) vs 173 (5.0%); OR 0.84, 95% CI 0.67-1.05) and the difference in response rates was not statistically significant (563 (16.3%) vs 523 (15.0%); OR 1.10, 95% CI 0.96-1.25). For both SWAT interventions, time to response was comparable between groups. The main reason for non-randomisation across arms was ineligibility, followed by loss of contact or participants declining to proceed. The cost per additional randomised participant was £119.50 for the brief PIL and was not calculated for the pen, given the lower proportion randomised.

Discussion
There was no significant evidence of effectiveness of the brief PIL intervention or the pen intervention on recruitment to the host study. There was evidence of increased response rates to the initial invitation in the brief PIL group, compared to those not receiving a brief PIL in their invitation pack. Meta-analyses of studies using the same SWAT interventions should be conducted in order to provide definitive results.

P-091

Using re-randomisation designs to increase the efficiency and applicability of retention studies within trials: an overview

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Introduction
Poor retention in randomised trials can lead to serious consequences to their validity. Studies within Trials (SWATs) are used to identify the most effective interventions to increase retention. Many interventions could be applied at any follow-up time point, but SWATs commonly assess interventions at a single time point, which can reduce efficiency.

Methods
The re-randomisation design allows participants to be re-enrolled and re-randomised whenever a new retention episode occurs (i.e. a new follow-up time point where the intervention could be applied). The main advantages are: a) it allows the estimation of an average effect across time points, thus increasing generalisability; b) it can be more efficient than a parallel arm trial due to increased sample size; c) it allows subgroup analyses to estimate effectiveness at different time points. We present a case study where the re-randomisation design is used in a SWAT.

Results
In our case study, the host trial is a dental trial with two available follow-up points. The Sticker SWAT tests whether adding the trial logo's sticker to the questionnaire's envelope will result in a higher response rate compared with not adding the sticker. The primary outcome is the response rate to postal questionnaires. The re-randomisation design could double the available sample size compared to a parallel arm trial, which results in the ability to detect an effect size around 28% smaller.

Discussion
The re-randomisation design represents a novel approach to the evaluation of SWATS; the design can increase efficiency and generalisability of SWATs for trials with multiple follow-up time points.

P-092

A Study Within A Trial (SWAT) of waitlist comparator versus usual care only comparator designs implemented in an open-label parallel groups cluster randomised trial

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Introduction

The success or failure of a randomised trial rides largely on the ability to successfully recruit and retain participants. Interim checkpoints in trials that focus on recruitment and retention are now commonplace. A lack of interventions for particular populations may create concerns around equipoise and ethics when trials seek to allocate interventions at random. For these reasons, waitlist comparator designs (where those allocated to the comparator arm are offered the intervention at the end of the trial) are sometimes proposed. SWAT protocol 151 (https://tinyurl.com/3t9kywky) was developed to be embedded in trials where there was interest in using a waitlist comparator design. Here we describe its implementation in a recently conducted study.

Methods/Approach

We implemented this SWAT in a two-arm open-label cluster randomised feasibility trial of an emotional literacy programme for children with intellectual disabilities in special educational needs and disabilities (SEND) schools. For both the SWAT and randomisation to intervention or comparator, school was the unit of randomisation. A sampling frame of potentially eligible schools was compiled in advance and these were randomised 1:1 to receive an information sheet describing a design with a usual care only comparator or a waitlist control comparator. In the former, schools allocated to usual care only did not receive access to the programme at the end of the study, whereas in the latter they did. Schools were not made aware of the different design options being studied. We aimed to compare differences between allocations in terms of recruitment, randomisation, usual care during the trial follow-up period, and retention.

Results

We approached 39 schools, with 20 approached using an information sheet describing a usual care only comparator and 19 approached using an information sheet describing a waitlist control comparator. Overall, 8/20 (40.0%, 95% CI: 19.1% to 63.9%) schools were enrolled using the usual care only comparator design and 3/19 (15.8%, 95% CI: 3.4% to 39.6%) were enrolled using the waitlist control comparator design. Subsequent randomisation meant that only one school allocated to the waitlist control comparator was randomised to the comparator arm, precluding useful estimation of usual care and retention.

Discussion

We successfully implemented SWAT 151 in our study and found numerically greater support for a usual care only comparator design compared to a waitlist control comparator design. Design-focussed SWATs lend themselves to exploration in feasibility studies, as they can provide important empirical evidence to support design choices in large-scale effectiveness studies.

P-094

The challenge of setting up and running a series of SWATs in trials involving children and young people

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SWATs are used increasingly to evaluate trial processes, particularly recruitment and retention, although few have been undertaken in trials involving children and young people.
In the TRECA study we undertook a planned series of six SWATs to assess the effects of digital, multimedia information used within trial recruitment. In this presentation we will outline the main challenges we encountered, including:
- governance concerns (especially trial approvals and data sharing);
- funding issues for host trials (particularly CRN funding);
- ethics concerns on SWAT methods;
- host trial hiccups and the consequences for SWATs;
- data completion challenges;
- internet accessibility and quality.
We will discuss the impact of anticipated and unanticipated challenges on the TRECA SWATs, and suggest ways to overcome them in future work.

P-095

A SWAT to determine whether video and online multimedia resources improve recruitment of children to clinical trials

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Introduction
Randomised controlled trials (RCT) are the gold standard method for testing the effectiveness of interventions but many struggle to recruit. Poor recruitment can impact the power and external validity of an RCT, and potentially its viability. Potential participants often receive written information to help them decide if they wish to participate; however, written information sheets have been criticised for their length and complexity. This is a particular concern for people with low levels of literacy and for children. Multimedia interventions, incorporating text, audio and animations, may be a better way of providing information to potential participants. Multimedia animations are potentially easier to understand and can reach out to participants from a wider range of backgrounds, making it easier to involve under-represented populations. We aim to evaluate the effectiveness of a multimedia website and video animation, in addition to written information, to improve trial recruitment in a Study within a Trial (SWAT), embedded within the OSTRICH (Orthotics for Treatment of Symptomatic Flat Feet in Children) host RCT.

Methods
OSTRICH aims to recruit 478 participants aged 6-14 years with symptomatic flat feet. The SWAT will be a cluster RCT, with recruiting site as the unit of randomisation. The sample size will be constrained by the number of recruiting sites and the number of potential participants approached to take part in the OSTRICH host trial. Sites will be randomised 1:1 to provide potential participants with written information alone or written information plus multimedia website and video animation using minimisation based on geographical region and number of patients seen with symptomatic flat feet. TRECA, TRials Engagement in Children and Adolescents, registered the SWAT (SWAT 97), but for inclusivity reasons we do not include a multimedia intervention only condition. During development, images that would eventually form the basis for the animation/script were presented to a group of parents. What followed was extensive patient public involvement work including adapting the images to be diverse and ethnically representative.

Results Structure and Timelines
The primary outcome is recruitment rate to the host trial, defined as the proportion of potential participants in each group randomised into the OSTRICH trial. Cost-effectiveness of the MMI is a secondary outcome. The OSTRICH study commenced recruitment in Spring 2022. We are about to start recruitment to this SWAT.

Potential Relevance and Impact
This study will contribute to the body of evidence of the effectiveness of interventions to improve recruitment.

P-096

Do courtesy telephone calls or postcards increase the retention rates of participants in RCT's?

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Introduction
High follow-up rates are crucial for successful delivery of RCTs. Trial teams experience challenges with maintaining follow-up rates, which can introduce bias which affects the validity and generalisability of findings. To maintain high follow-up rates, telephone calls are used by trial teams to enable a positive relationship between research teams and participants. However, this is a time intensive method and there is limited evidence to support this intervention. A written card sent to participants may be an alternative method of building relationships and is a less time intensive method. The objective of this SWAT was to evaluate if a telephone call to newly recruited participants, in an ongoing NIHR HTA funded RCT (ARTISAN), resulted in higher questionnaire return compared with a written card equivalent.

Methods
Participants who were recruited into the ARTISAN trial and consented to being contacted by telephone and post were eligible for the SWAT. 406 participants were randomised in a 1:1 ratio by minimisation with a random factor to receive introductory information by either a courtesy telephone call or via a written postcard. There were no additional inclusion or exclusion criteria. The primary outcome was the questionnaire response rate at 6 months. Secondary outcomes included questionnaire response rate at all time points, the timeliness and completeness of responses, and the cost of interventions. The primary analysis will be a chi-squared test to assess statistical association. Secondary analyses will include a logistic regression adjusting for age, gender and host trial treatment allocation will be performed to investigate the effects of these variables. A per protocol analysis will also be performed.

Potential Results and Timelines
Results will be available late September. We will present the difference in proportion of response rates at the primary and secondary time points, the time to response to the questionnaires (date of first posting to date of questionnaire received by study team and number of reminders needed), completeness of responses (number of missing items) and cost of intervention per participant.

Potential Impact
The findings will enable us to determine if telephone or written interventions improve retention rates of eligible participants during a RCT. These results will inform trial teams to enable more targeted interventions for future RCTs. Analysing additional variables in the future, with different trial populations, may further enable more focused intervention techniques, saving both time and resources.

P-097

PURPOSE Study: The influence of patient support group delivered research awareness strategies on research recruitment and retention

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Introduction
PURPOSE is a study within the TIPAL Phase 3 clinical trial investigating the effects of anti-acid medication on the progression of idiopathic pulmonary fibrosis. The PURPOSE study was developed through collaboration among the University of East Anglia (UEA), Norwich Clinical Trials Unit (NCTU) and Action for Pulmonary Fibrosis (APF). The three partners were keen to develop effective ways of communicating with the pulmonary fibrosis (PF) community about the TIPAL trial and overcome some of the barriers to participation. The group identified the potential for people with lived experience of PF to play a pivotal role in changing the research recruitment landscape by championing research within support groups.

Methods
The PURPOSE study involves guiding and supporting people with lived experience of PF to be Research Champions (RCs). RCs aim to increase awareness, knowledge and excitement about research, in particular clinical trials including TIPAL. At the end of the study, the intervention will be assessed quantitatively and qualitatively; including exploring any differences in the number of patients recruited into TIPAL between those with and without RCs, support group members' questionnaire feedback and focus groups. RCs were recruited for PURPOSE from within a network of PF support groups. Twenty-five support groups agreed to take part, from approximately 70 groups supported by APF nationally. The study is designed in two phases: participating support groups were randomised according to region to either have an active Research Champion in Phase 1 (at study set-up) or Phase 2 (after 12 months). Sixteen support groups in Scotland, Wales, North-West England, East of England, London and South-East England were randomised to Phase 1. Nine support groups in Northern Ireland, Yorkshire & Humberside, West Midlands, East Midlands and South-West England were randomised to Phase 2.

Timing of Results
Phase 1 groups nominated a Research Champion from June 2021 and Phase 2 support groups will be nominating a Research Champion in June 2022. It is anticipated evaluation of the Phase 1 data including questionnaire responses, focus groups, feedback from Research Champions and development of Phase 2 initiatives will occur in Summer 2022.

Potential Relevance & Impact
Although the aim of the project is primarily focussed on TIPAL recruitment and retention, PURPOSE may provide a model for the wider research community and if the intervention is successful, could indicate the benefit of Research Champions within other trials.

P-098

A theory-informed study within a trial (SWAT): improving questionnaire response rates with SMS pre-notifications and reminders using a Sequential Multiple Assignment Randomised Trial (SMART) design

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Introduction

There is a need to design and test interventions to improve trial retention. Embedding studies within a trial (SWATs) is a robust approach for evaluating retention interventions. SWATs using novel experimental designs can be used to optimise trial conduct processes. We designed a SWAT using a highly efficient experimental design to evaluate the impact of theory-informed short message service (SMS) pre-notifications and SMS reminders on retention rates.

Methods

We embedded a SWAT using a sequential multiple assignment randomised trial (SMART) design in two host pilot trials: WeSureCan (n=88, three follow-up time points) and ROSETA (n=80, two follow-up time points), and anticipate including an additional host trial: ROSETA optimisation trial (n=512). SMS pre-notifications and SMS reminders were developed to target behaviour change techniques (BCTs) addressing beliefs about consequences of not returning a questionnaire. The SWAT will determine the effect of SMS pre-notifications and reminders on retention rates.

All participants recruited to the host trials available for online follow-up are randomised to SMS pre-notification or no pre-notification at the start of follow-up using block randomisation stratified by the host trial allocation. Participants who have not completed follow-up questionnaires within six days are further randomised to receive a standard SMS reminder or non-standard SMS reminder using simple randomisation without stratification. At each subsequent follow-up participants retain their allocation to pre-/no pre-notification and are re-randomised to standard/non-standard reminder.

The primary endpoint is response rate at one month post follow-up. Secondary endpoints include return rates in each pre-/no pre-notification and reminder type subgroups, time to questionnaire return, proportions of item-level missing data, proportions of complete questionnaires and intervention cost.

Results Structure and Timelines

Analyses will be conducted and reported for each host trial and repeated to combine data from the trials. Results are expected in early 2024 for the two pilot trials with remaining analyses anticipated in 2026. Logistic regression models will be used to analyse the differences in response rates for each of the main effects (pre-notification vs. no pre-notification and standard vs. BCT reminder) and for combinations of the two interventions.

Potential Relevance and Impact

Our SWAT utilises multiple randomisations with an innovative SMART design. It will enhance our understanding of the effectiveness of SMS pre-notification and BCT-based reminder messages in the context of clinical trials using online data capture for patient-reported questionnaires. It provides an example of how to maximise information gained via innovative design and implementation across multiple host trials.

P-099

How does the use of a video animation to introduce a complex intervention affect participant engagement and uptake within trials?

Miss Sadia Ahmed[1], Professor Andrew Clegg[2,3], Professor Suzanne H Richards[4], Professor Amanda J Farrin[1]
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Introduction
SWATs are self-contained research studies, which often investigate refinements to trial processes involving recruitment and retention. However, this novel SWAT was designed to evaluate a trial process relating to intervention implementation. The SWAT's host trial (PROSPER) evaluates the effects of a personalised care planning intervention for older adults with frailty. The PROSPER feasibility study observed poor intervention uptake and unclear explanations of the intervention from the delivery team in the first session. A video animation was co-developed with PPI, researchers and professional animators, as a potential solution to this problem. The aim of this SWAT was to investigate whether the use of a video animation to introduce the intervention improves participants' uptake of and engagement with the intervention.

Methods
A mixed methods SWAT consisting of a nested randomised controlled trial (RCT) and a qualitative interview study was embedded within the intervention arm of the PROSPER host trial. Intervention deliverers were randomly assigned to either the video animation or no video animation. The comparator was a verbal explanation accompanied with the information sheet alone, without the use of a video animation. Quantitative data about participant uptake and engagement with the intervention is collected through trial case report forms and will be analysed using descriptive statistics. Qualitative interviews are conducted with participants and intervention deliverers to explore their views and perspectives on the video. Interview data will be analysed using thematic analysis.

Results Structure and Timelines
Data collection is ongoing. To date, 318 participants have been randomised to the host trial intervention arm and included in this SWAT. Qualitative interviews have been conducted with 15 participants and 3 intervention deliverers. To assess engagement and uptake, the number of participants proceeding with the intervention after the initial visit in the control and intervention arms will be compared as well as the number of goals set by the participants. Themes representing the views of participants and intervention deliverers will be developed, supported by quotations from the qualitative interviews.

Potential Relevance and Impact
This SWAT is one of the first to test a refinement to intervention implementation, through the use of a video animation. It is important to robustly test whether or not this refinement improves participant uptake and engagement, as these are vital elements of intervention implementation which are necessary prerequisites for intervention effectiveness. This SWAT has been undertaken as part of a PhD funded by MRC-NIHR-TMRP.

P-100

A SWAT to explore research awareness and readiness in long term care facilities for dementia research in Ireland

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Context
Over 80% of residents in long term care (LTC) facilities live with dementia, thus there is a critical need to undertake dementia-related research in these settings. However, conducting clinical trials in LTC poses significant challenges, particularly considering the impact of the COVID-19 pandemic on the sector. Challenges include ethical issues, high staff turnover, research governance, outcome measure choice, and general awareness and prioritization of research in LTC settings by staff, residents, and families. Thus, to foster study uptake, recruitment and conduct in LTC, it is important to understand the level of research awareness and readiness within the sector.

Objective
To explore research awareness and readiness in LTC facilities in Ireland that support residents with dementia.

Method
Using an embedded SWAT in an ongoing feasibility-pilot cluster randomised trial in Ireland, we are exploring motivators, facilitators, and barriers to research participation for LTC facilities, their staff, and residents, as well as perceived research priorities for research among key LTC stakeholders. The host trial, 'SENSE-Cog Residential Care' is evaluating a novel multifaceted hearing and vision rehabilitation intervention to improve quality of life and other outcomes in LTC residents with dementia in Ireland. SWAT participants include LTC staff, key gatekeepers (e.g. management, owners) and family members of residents with dementia. The sampling framework for facilities is the list of accredited LTC facilities across Ireland offering dementia services, aiming to include 200 facilities in total. Data collection is through online surveys and semi-structured interviews. The survey is based on a review of relevant literature and the formulation of statements along the dimensions of altruism/common good, personal interest, dementia and dementia awareness, study design and information, personal risk, and logistics. Each item is rated on a five-point Likert scale regarding the impact on respondents' decision to participate in a study (e.g. 'taking part in a study would interfere with my work schedule'; 'the study information is easy to understand'). The interview component of the study builds on survey trends and probes those further with a sub-sample of respondents.

Analysis
Quantitative survey results will be analysed using descriptive statistics and distribution analysis. Guided Content Analysis will be used to categorize and interpret free-text data and interview transcripts.

Conclusion
The results from this study will help inform future research in LTC settings, particularly a future definitive trial, as well as lay the foundations for a network of research-ready care homes in Ireland.

P-101

Does Participant Information Sheet design affect recruitment for an interventional trial in an Emergency Department setting? A Study Within A Trial (SWAT)

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Introduction
Trial recruitment is a hot topic in trial methodology and exploring barriers and enablers to recruitment is a common discussion point. Participant information sheets (PIS) can be long and complex, potentially impacting the patient's decision to enter a trial, either due to a lack of understanding or willingness to read this alongside non-study information provided at the same time.

This SWAT seeks to explore if improving the design of a PIS influences recruitment rate or its value in patient decision making. It has been conducted within a host trial taking place in an emergency setting, where time is a premium, and decisions on trial participation are needed much more quickly than in non-emergency settings.

Methods/Approach
We have conducted a randomised SWAT, comparing the standard format PIS with one that has been adapted to be visually appealing with improved readability. Patients considered eligible for the host trial were provided with a randomly allocated PIS and consent rates will be compared. Those consenting to take part in the host trial were then asked to complete a questionnaire designed to explore the value of the PIS in their decision making to take part in the trial and results of this will be compared across the two information sheets. There was no formal sample size calculation, as this is dictated by the recruitment to the host trial.

Results Structure and Timelines
Comparisons will be presented as odds ratios to illustrate any association between the assigned PIL and the consent rate, or the impact on decision making. A distinction will be made between those declining to consent following provision of study information, versus those who were not recruited due to eligibility. Adherence to the randomisation will also be reviewed and the effectiveness of the SWAT evaluated.

Potential Relevance and Impact
The results, if significant, will provide tried and tested improvements to the PIS that can be shared with the research community. Even where the PIS has no impact on recruitment, it may be positively favoured for decision making, therefore this information would be valuable to share too. The results can be shared for a meta-analysis or repeated to determine if this relatively low-cost intervention could be a cost-effective means to improve consent rates in a trial and reduce overall recruitment duration.

P-102

Do recruitment SWAT interventions have an impact on participant retention in randomised controlled trials: A systematic review?

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Introduction
Recruiting and retaining sufficient participants is crucial to the validity and reliability of randomised controlled trials (RCTs). Given this, and to prevent research waste, evidence-based methods for recruitment and retention to RCTs are extremely valuable to trialists. Cochrane Reviews of strategies to improve recruitment and retention have identified limited interventions with high or moderate evidence of their potential to improve recruitment or retention. Little consideration however appears to have been given as to whether recruitment interventions can also have an impact in increasing participant retention.
This review will establish whether any embedded recruitment strategies have also assessed the impacts on retention. Where this has been conducted, the review will assess whether interventions are effective and if so whether they are cost effective.

Methods
The existing Cochrane Reviews of strategies to improve recruitment and retention in RCTs will be used to identify randomised studies within a trial (SWATs) of recruitment interventions which also assess the proportion of participants retained at any time point. The search strategies will be re-run in MEDLINE (from date of last search) and relevant repositories searched to obtain any further studies published. Two reviewers will assess titles and abstracts for inclusion, followed by full text review of potentially relevant articles. Disagreements will be resolved by a third reviewer. Double data extraction will be completed for all relevant studies and Cochrane Risk of Bias and GRADE assessments will be completed.
The primary outcome will be proportion of participants retained at the study primary outcome time point (or first time point if primary outcome is undefined). Secondary outcomes will include cost effectiveness and retention at subsequent time points.

Timing of Potential Results
This review has commenced with data extraction currently in progress. Ten studies have been identified for inclusion from the Cochrane reviews, with subsequent searches yielding 56 articles for full text review. The results of this review will be available in Q1 of 2022.

Relevance and Impact
Identifying if any recruitment strategies have also been assessed for retention effectiveness and if so whether any are effective, may help to minimise future research costs and waste. Where potentially effective strategies have been identified, subject to further SWAT evidence, this will allow for targeted SWATs to be completed to fill the evidence gap.

P-103

The use of adaptive analysis for late phase randomised controlled trials in intensive care with mortality outcomes

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Introduction

Randomised controlled trials (RCTs) in intensive care face special challenges. Studying effects in heterogeneous populations with mortality as the primary endpoint of interest results in trials needing large sample sizes (1,2). Adaptive trials that undertake interim monitoring may identify futility or efficacy with smaller sample sizes which would be especially valuable for trials in Intensive Care. We undertook a systematic review to ascertain how frequently adaptive designs are being used for large-scale intensive care trials, and when used, what adaptive elements they include and what statistical methods are employed in ongoing monitoring.

Methods/Approach

We searched for RCTs published between January 2017 and December 2021, using electronic databases (MEDLINE, Embase, Web of Science and Scopus).

RCTs included clinical treatment interventions that were evaluated on patients managed in ICUs which used mortality as the primary outcome. The review excluded cluster trials, pilot/feasibility studies, and trials examining behavioural & psychological treatments. Screening and data extraction was carried out in COVIDENCE independently by two authors using a standardised piloted template. Disagreements were resolved by consensus.

Results Structure and Timelines

Our search strategy identified 12,569 records. After removing duplicates, 7,197 records were imported to COVIDENCE for screening. The review will be completed by end of September and results of this review will report the following information:

- Trial and population characteristics, type of intervention and disease, type of outcome
- The array of adaptive designs used, including the types of adaptive elements, number and type of interim monitoring with statistical methods used
- Proportion of trials stopped early with reasons, the planned and actual sample size, proportion and type of trials with adaptive designs by pandemic status (before and during the pandemic).

Potential Relevance and Impact

During the COV19 pandemic, the adaptive design framework provided flexibility to critical care treatment trials in order to obtain timely results. Adaptive trials that undertake ongoing monitoring offer an opportunity to identify futility or efficacy with smaller sample size and thus improve the efficiency of clinical trials in intensive care. We need to understand how much and how well they are being used. ,

Additional Information

The review was registered by PROSPERO with registration number CRD42021280984.

P-104

Standardisation of IPD language domain scores for meta-analysis; the REhabilitation and recovery of peopLE with Aphasia after StrokE (RELEASE) study.

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Background
Important clinical-relevant insights can be lost when using standardised mean differences to synthesise common outcome data from different outcome measurement instruments.
Aims: We aimed to synthesise continuous outcome IPD from disparate distributions across multi-lingual measures of stroke-related language impairment on a clinical meaningful scale, to maximise meta-analyses, improve rigour and clinical relevance.

Methods
The international RELEASE study explored alternative approaches including normalising, internal normalising, direct linear, the Early Breast Cancer Trialists' Collaborative (EBCTC) Group's algorithm, and an adapted version of the EBCTC group's algorithm to combine disparate language rehabilitation outcome data by domain; overall language ability (OA); auditory comprehension (AC); naming; reading comprehension; writing; functional communication (FC).
For each domain we identified the "anchor measure;" the instrument used by most datasets. A linear transformation from the remaining "minority measures" to the anchor measure was applied to each quartile, minima and maxima; quartiles in the minority instrument were mapped to corresponding anchor measure quartiles. Checks were performed to assess ranges, values and directions of changes for consistency. Language and version variations were treated separately.

Results
A range of outcome measurement instruments were used to capture each domain of assessment; OA=21; AC=35; naming=33; SP-O=19; reading=21; writing=18; FC=16. Normalising, internal normalising, direct linear transformation approaches were considered but rejected due to feasibility, clinical-interpretability and loss of clinical meaning. Our adapted EBCTC algorithm was feasible, preserved clinically meaningful data, and increased available data for meta-analyses: OA 733 to 2,699 IPD; AC 505 to 2,750 IPD; naming 831 to 2,886 IPD; reading 460 to 770 IPD; writing 454 to 724 IPD; and FC 402 to 1,591 IPD.

Discussion/Conclusion
Our adapted algorithm provided a feasible, valid approach to support meta-analysis of IPD with shared outcome data across multiple outcome measurement instruments. This supported inclusive IPD meta-analysis while maintaining clinical relevance, transparency and interpretation.

P-106

Current practice in the measurement and interpretation of intervention adherence in randomised controlled trials: a systematic review

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Introduction
Randomised controlled trials (RCT) remain the optimal study design for evaluating and inferring a causal relationship between competing health and social care interventions. Ideally all randomised participants should fully receive their allocated intervention; however, this rarely occurs in practice. Low intervention adherence can increase the risk of Type II error and therefore impact the interpretation of trial results and subsequently implementation decisions. We aimed to describe current practice in the definition, measurement, and reporting of intervention adherence in non-pharmacological RCTs, and how this data is incorporated into a trial's interpretation and conclusions.

Methods
We conducted a systematic review of all phase III RCTs published between January 2018 and June 2020 in the National Institute for Health Research Journals Library for the Health Technology Assessment, Programme Grants for Applied Research, and Public Health Research funding streams. Two reviewers independently screened reports and one author extracted trial characteristics and findings, with a second reviewer independently checking for accuracy and completeness. A narrative summary was undertaken to synthesise findings.

Results
Of 237 reports published, 76 met the eligibility criteria and were included. Most RCTs (n = 68, 89.5%) reported adherence, though use of terminology varied widely; nearly three quarters of these (n = 49, 72.1%) conducted a sensitivity analysis. Adherence measures also varied greatly between intervention type, with behavioural change (n = 10, 43.5%), psychological therapy (n = 5, 83.3%) and physiotherapy/rehabilitation (n = 8, 66.7%) interventions predominately basing their measurements on recording the number of sessions attended. Whereas medical device and surgical interventions (n = 17, 73.9%) primarily record the number of participants receiving the allocated intervention. Only two reports (4.1%) provided a rationale for applying an intervention threshold. The terminology and measurement clearly matters as a third (n = 33, 67.3%) of studies reported a difference in findings between primary and sensitivity analyses which will have important implications for clinical practice.

Discussion
Although the majority of clinical studies report elements of adherence there is a lack of consistency in the use of key terminology, and no systematic approach to its measurement, analyses, interpretation, or reporting. Given the importance of adherence within clinical trials, there is an urgent need to develop a standardised approach or framework to increase transparency and improve interpretation of study results.

P-107

Percentage change as a primary outcome in randomised controlled trials of obesity/overweight: a systematic review of design and analysis approaches

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Introduction
In obesity randomised clinical trials (RCTs), using percentage change (PC) as the primary outcome results in difficulties interpreting treatment effects; a person with a 20kg reduction in baseline weight of 100kg (-20% PC) and another with a 20kg increase in baseline weight of 80kg (+25% PC) have a mean change of 0kg, but also a mean PC of +2.5%. Furthermore, estimating treatment effects by comparing PC between arms is less efficient than, for example, analysis of covariance (ANCOVA) on post-treatment weight, where adjustment is made for measures at pre-treatment visits. Despite these limitations, PC in weight appears to be a common primary outcome used in obesity RCTs due to its simplicity in disseminating treatment effects. Therefore, a review and further exploration on the extent and impact of using PC as a primary outcome in obesity RCTs is required.

Methods/Approach
We will conduct a systematic review using PubMed to assess all completed phase III RCTs in obesity/overweight published in major medical journals (BMJ, JAMA, Lancet, NEJM, or PLoS Medicine) between 2017 and 2021. Our aim is to assess: i) how many RCTs used PC as their primary outcome; ii) if it was used to calculate the sample size, what method was used; and iii) what method was used for analysing the primary outcome.

Results Structure and Timelines
For all eligible trials we will report the primary outcomes used and the proportion of studies using PC as their primary outcome. Methods for sample size calculation and final analysis approach will also be reported, and case studies will be used to describe in detail some of the concerns that have been raised in past research.

Potential Relevance and Impact
Our review will show how widespread is the use of PC as a primary outcome in phase III obesity/overweight RCTs and what approaches in the design and analysis of these trials have been used. Following our review, we will use simulation studies to investigate the impact of the methods used on sample size calculations compared to other approaches to assess whether efficiencies in the design stage (via a reduction in sample size) or analysis (via bias reduction) can be made. This body of work may be used to shape trial design and analysis guidance for obesity trials where PC is considered a quantity of clinical interest.

P-108

Methods used to measure implementation of complex interventions within trials and the strategies employed to optimise their implementation: a systematic methods overview

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Introduction
It is important for trialists to understand how best to measure and optimise implementation of complex interventions in trials to ensure efficient trial conduct, maximise understanding of trial results and reduce research waste. However, there are no reviews of the methods used to measure implementation of complex interventions, or strategies employed to optimise implementation of complex interventions within trials. This systematic methods overview synthesised the methods to measure implementation and strategies to optimise implementation of complex interventions within trials reported over a 5 year period (2015-2020).

Methods
Medline, EMBASE, CINAHL and PsycINFO were searched using an iteratively developed search strategy for studies reporting methods used to measure implementation or strategies to optimise implementation of complex interventions within trials. A narrative approach was taken to report the findings. The reported methods to measure, and strategies to optimise, implementation of complex interventions were categorised using themes from the treatment fidelity framework from the National Institute of Health's Behaviour Change Consortium: design, training, delivery, receipt, enactment.

Results
Ninety-seven studies were included for analysis. Of these, around two thirds (n=69) applied a framework to inform the implementation, most commonly the Medical Research Council guidance for process evaluations. Most studies (n=95) reported the methods to measure implementation, whereas only 29 reported strategies to optimise implementation of a complex intervention. Considerable heterogeneity was observed in the methods and strategies reported. Fidelity was measured in 59 studies (60%), mostly using a checklist (n=17). Eight studies utilised audio or video recording to measure fidelity. Other reported aspects of implementation included: dose, reach, receipt, attendance, engagement, adherence, context and maintenance. No one study measured all aspects of implementation with some studies only measuring fidelity. Analysis revealed significant overlap in terminology: terms such as fidelity, intervention delivery and quality of delivery were used interchangeably to refer to similar concepts. More studies reported strategies of optimisation relating to intervention delivery (23/97) than design (11/97) or training of intervention providers (11/97), with fewest studies focusing on receipt (3/97) and enactment (3/97). Ongoing support and monitoring were the most reported strategies to optimise intervention delivery.

Discussion
This systematic overview highlights considerable heterogeneity in methods for measuring implementation; and the lack of reporting of strategies to optimise implementation of complex interventions in trials. Trialists should aim to be comprehensive in the reporting of methods for measuring and strategies for optimising implementation. A framework is needed to aid reporting in this area.

P-109

User engagement in randomised controlled trials for digital mental health interventions: a systematic review and meta-analysis

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Introduction
Digital mental health interventions (DMHI) including apps and websites help individuals overcome barriers to mental health support. However, the way individuals interact with the DMHI, defined as engagement, is autonomous and heterogeneous and it's not clear how this affects efficacy. This heterogeneity means the true efficacy of the DMHI may be underestimated. This study aims to assess current practice of reporting engagement and how engagement is considered in analysis of RCTs for DMHI across a range of common mental disorders (CMD).

Methods
A systematic review of primary results for RCTs of DMHI published between 2016 and 2021, identified through a search of Embase, MEDLINE, PsycINFO, and CENTRAL. Studies were included if 1) the evaluation considered an app or website where participants were autonomous in access and engagement and 2) the DMHI targeted a CMD as defined by Cochrane, without comorbidity. Data extracted included trial design features, participant characteristics, intervention components, engagement metrics, and how engagement was considered in the analysis. Data will be summarised descriptively and the impact of adjusting for engagement will be quantified by pooling the percentage change between treatment estimates with and without adjustment.

Timing of Potential Results
The search identified 6,015 papers, of which 187 papers were eligible and included. Data extraction is underway, 116 papers extracted so far, and full results will be ready prior to the conference. Current data suggests most trials used a parallel (91%) superiority (98%) 2-arm (78%) design and assessed interventions delivered through a website (78%) which focused on changing behaviours (89%) through the delivery of structured education (79%) or therapy (78%). Engagement metrics reported include number of sessions, total logins, time spent, and communications either to peers or health professionals. However, few papers reported a recommended or optimal level of engagement for participants (23%). In papers that had a pre-specified engagement definition very few performed an analysis to assess the impact on efficacy (22%). For those that did, a per-protocol approach (83%) was mostly used, excluding those in the DMHI arm not meeting the engagement criteria, which may lead to biased estimates.

Potential Relevance & Impact
The full results will identify current practice in reporting of primary results in RCTs of DMHI. This will highlight the importance of reporting and analysing engagement metrics in DMHI trial designs. Recommendations will be drawn from the review results to develop an approach to incorporate engagement into efficacy analysis.

P-110

Using artificial intelligence in the analyses of surgical videos as a method to monitor adherence and quality assure interventions delivered in trials: A systematic review

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Introduction
Embedding quality assurance (QA) measures within surgical randomised controlled trials (RCTs) can help standardize surgical procedures and monitor protocol adherence. An important aspect of QA is monitoring how interventions are delivered with surgical videos. However, review of these videos requires knowledgeable surgeons and takes considerable time. Whilst a large amount of work has been undertaken to understand the role of artificial intelligence (AI) in healthcare more generally, the application of these techniques to the analysis of surgical videos is currently unclear. This systematic review aims to summarise existing knowledge of the use of AI in the automated analysis of intra-operative videos, to ascertain how these techniques might be applied to QA assessments in RCTs.

Methods
Systematic searches of OVID Medline and EMBASE will identify all potentially relevant studies. All primary studies where AI has been applied to the analysis of videos (recorded by conventional digital cameras, laparoscopic or robotic-assisted) of surgical procedures will be included. Searches will be developed in collaboration with an expert subject librarian, using free text and Medical Subject Headings related to 'artificial intelligence', 'surgery' and 'video'. Data extraction will detail study design and characteristics, governance, video data sets, AI models, measures of accuracy, validation and reported limitations.

Results Structure and Timelines
A narrative synthesis will be performed, in accordance with the synthesis without meta-analysis (SWiM) guidelines, with descriptive analyses where appropriate. The findings will be reported according to the specific AI objective(s) which may include, but not limited to; surgical phase recognition, instrument recognition, skill analysis, and assisted video annotation etc.

Potential Relevance and Impact
Whilst recording surgical procedures has become more common, manual review of these data is arduous. Automating the extraction and/or analysis of information from surgical videos has the potential to greatly benefit QA processes within RCTs in surgery. To the authors knowledge, there has been no systematic review examining the use of AI to facilitate automated analysis of surgical videos. Findings will identify evidence gaps and inform future research by highlighting methods and successes as well as drawing on lessons learnt and any reported limitations.

P-111

Design and conduct of randomised clinical trials evaluating surgical innovations in ophthalmology: a systematic review

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Introduction
Ophthalmology is a high volume surgical specialty.
Randomized clinical trials (RCTs) assessing efficacy and safety of novel surgical techniques are necessary to evaluate and compare surgical options but have unique methodological challenges, such as considerations about the surgical learning curve, quality assurance of surgeries performed, surgeon's expertise, and preferences. The IDEAL Collaboration proposes recommendations for evaluation of surgical innovations according to the different phases of development. Our study sought to investigate the design, conduct and reporting of RCTs of novel surgical techniques.

Methods
A systematic review was conducted. The protocol of the study was prospectively registered in PROSPERO (CRD42021253297). RCTs evaluating novel surgical techniques for cataract, vitreoretinal, glaucoma and corneal diseases were included. Medline, SCOPUS, EMBASE, Cochrane Library and Clinicaltrials.gov were searched. The search period was January 1, 2016, to June 16, 2021.

Results
Fifty-three ophthalmic surgery RCTs were identified in the fields of glaucoma (n=12), vitreoretinal surgery (n=5) cataract (n=20) and cornea (n=16). Of these, in the context of the IDEAL staging, 43 RCTs were 'Phase 2B' and 10 'Phase 3'. A description defining the surgeon's experience or level of expertise was reported in 30 RCTs (57%); and was presented in both, control and intervention groups, in eleven (21%). Specification of number of cases performed in the particular surgical innovation being assessed prior to the trial was reported in 10 RCTs (19%); and an evaluation of quality of the surgical intervention in seven (13%). Prospective trial registration was recorded in 12 RCTs (23%), retrospective registration in 13 (25%) and there was no registration record in the remaining 28 (53%) studies.

Conclusion
In this systematic review of RCTs assessing novel ophthalmic surgical procedures, description of important aspects of the study design such as surgical learning curve, surgeon's previous experience, quality assurance, and trial registration details were often missing.

P-113

Integrating clinical trials into routine clinical care: A survey to explore the trial communities' views and experiences

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Introduction

In 2015, the 'PRioRiTy PSP' (Prioritising Recruitment in Randomised Trials (PRioRiTy) Priority Setting Partnership (PSP)) used the James Lind Alliance consensus method to identify and prioritise the top 10 unanswered questions about trial recruitment research. The top priority question asked how we can better integrate randomised trials into routine care and make best use of clinical care pathways. We explored the views and experiences of trialists, methodologists, clinicians, and patient and public representatives with an interest in trial design and conduct about integrating clinical trials into routine clinical care. These results are presented on behalf of the Recruitment theme of the TMRP's Trial Conduct Working Group.

Methods/Approach

This project used an electronic survey , distributed to those involved in the design and conduct of RCTs using existing UK and Irish trial networks. Respondents were asked to share three barriers and three facilitators to integrating trials into routine healthcare, drawing on their knowledge and experience, giving context to their answers by specifying details such as RCT speciality and healthcare settings relevant to their responses. Although not compulsory, research governance approvals were sought and granted to allow the responses to be used for future research. Survey responses were analysed thematically by two researchers.

Results

Sixty-eight individuals, predominantly from academic institutions (n=44), provided up to three free-text barriers and up to three solutions/facilitators to integrating trials into routine care. The barriers and facilitators were frequently related. Barriers identified included lack of time, with research being perceived to be an additional burden for an under-pressure workforce, staff attitudes, with a lack of 'buy-in' from staff identified, and inflexibility across the trial or service – such as perceived difficulties with governance procedures. Solutions included minimising the research burden (identified as being important for both patients and clinicians), fostering a research culture and normalising research in standard care – such an through the integration of research at multidisciplinary team meetings.

Discussion

The trial community's knowledge and experiences highlight how the perceived rigidity of the healthcare system underpins many of the challenges of integrating trials into routine care. Findings indicated that there is an opportunity to improve perceptions of inflexibility within the system by addressing attitudes, and eventually, cultures around RCTs. Future research and initiatives to better integrate trials into routine care will do well to pay attention to attitudinal concerns of staff, rather than focus exclusively on logistical and organisational solutions.

P-114

Should early phase trial designs incorporate blinding and placebo?

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Introduction
To minimise bias, ICH guideline E6 states that the double blind trial is the optimal design (1). However, this does not necessarily apply to early stage trials with non-efficacy outcomes, particularly first-in-human studies (2). We assess current practices and guidelines, and advocate for open-label designs, through two trials which we recently designed.

Methods
We searched clinicaltrials.gov in May 2022 for "phase 1", "first in human", and "placebo" to assess the prevalence of placebo-controlled designs in first-in-human trials. In our first case study, the outcome is pharmacokinetics following an oral tablet treatment in a resource-limited setting. Our second example trial will assess a topical treatment for a dermatological condition, conducted in healthy volunteers. The primary outcome is safety.

Results
Historically, the majority of first-in-human trials were blinded and placebo-controlled (3), with typically 8-10 participants (two placebo), yet this design is "anecdotal" (4). Regulatory authorities do not require placebo-controlled designs (5). We found that 622/1595 (39%) first-in-human studies included placebo (399/1123, 36% since 2017).
For our first trial, we proposed an open-label approach since the pharmacokinetics outcome is objective. However, there was concern about unintended study effects related to dietary changes during the hospital stay leading to gastrointestinal problems. Two mitigation strategies were proposed: inclusion of a control group who would follow all trial procedures except active treatment and pharmacokinetics sampling; and an independent endpoint review committee to assess adverse events, which is a secondary objective.
In our second trial, we expect no systemic absorption among the healthy volunteers with intact skin, therefore separate control participants are unwarranted, or could be replaced by pre-dose application of the treatment vehicle with a suitable wash-out period, to assess systemic adverse events. For local adverse events, we recommend intra-participant controls, e.g. randomising one arm to active treatment and the other to placebo, due to individual variability in dermatological sensitivity.

Discussion
Over a third of first-in-human studies continue to incorporate placebo control. Yet in early phase trials with small sample sizes, adverse event causality assessments should be based on temporality and expert opinion, not whether placebo participants experienced similar symptoms. Inclusion of placebo implies blinding, adding complexity and cost. Intensive pharmacokinetics sampling lacks justification in placebo participants who do not contribute evaluable data. Open-label trials allow for real-time adverse event assessment, benefiting individual clinical management and study adaptation if indicated. As clinical trialists, we should be bold in advocating for novel early phase trial designs.

P-115

Motivations behind randomisation method selection and the criteria that should be used to evaluate methods

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Introduction
There exist many methods to randomly allocate participants to groups when conducting a randomised controlled trial, but a wide variation in the application of the methodology. Previous research looks at which randomisation methods are being used but not the motivations behind why these decisions are made. This research aims to explore researchers' current motivations behind randomisation method selection, and additionally to identify a clear set of criteria against which the method should be evaluated.

Methods
We will conduct 4 focus groups each with 6-8 participants including clinical trial methodologists from 3 key areas: statisticians, database programmers and other trialists involved in randomisation method selection. Focus groups will contain a mix of participants from each role and will be conducted via Microsoft Teams and transcribed. A framework analysis will be used to identify important themes around motivations for choosing a randomisation method and how researchers check methods are performing as expected.

Timing of Potential Results
Focus groups are expected to take place during May and June 2022. Transcribing and framework analysis will be conducted between July and September meaning some preliminary results will be available by October. We will describe the motivations for selecting a randomisation method, and the most important features of a method to evaluate its performance. These will be presented both from the perspective of the statistician, and other key roles in the unit such as programmers and other trialists.

Potential Relevance & Impact
With such a wide variation in the application of randomisation methods, it is important to understand the motivations behind the decisions that are made. Firstly, this will allow us to better understand the existing decision-making process, to better understand the cause of the variation in practice, and to identify where improvements can be made. Secondly, understanding the features that researchers consider most important will allow us to develop recommendations on the circumstances in which methods perform best and that are tailored to the features researchers consider most important. This will enhance future randomisation method selection and thereby improve the efficiency of randomised trials.

P-116

Creating a Youth Advisory Group for a tuberculosis meningitis trial in low- and middle-income country

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Introduction

Pediatric clinical trials are operationally and ethically challenging especially in Low- and middle-income countries such as Vietnam where a general lack of clinical trial awareness is an obstacle to trial participation and may be particularly relevant in under-represented populations.

OUCRU Vietnam is currently participating in SURE – a randomized trial of 6 months intensified anti-tuberculosis and 2 months anti-inflammatory treatment for HIV-infected and HIV-uninfected African and Asian children with tuberculous meningitis (TBM). We set up a youth advisory group (YAG) in OUCRU with the aim to collect participants' feedback and improve design and set up of ongoing and future pediatric trials in Vietnam.

Method

8 to 12 participants from the SURE trial are recruited into the YAG using purposeful sampling, selecting on age (10 to 15 years old), living location (within reasonable distance of study site), and capacity to independently give feedback (GCS score of 15). Each YAG member is given a questionnaire containing multiple choice questions specifically designed to capture their feedback and feelings about the trial materials, procedures, and their participation. Participants will also be asked to join a meeting to further share their personal experience while hearing from others.

Result

As of June 2022, 6 participants, 4 girls and 2 boys, participated in the YAG. Based on the answers to our questionnaire, the main motivation for participating in the SURE trial were in order (1) helping other children with TBM (4/6), (2) parents or carers encouragement (2/6) and (3) good medical care (2/6). Regarding the trial procedures, all children reported that the doctor explained the study in a clear manner. 3/6 participants felt the consent process was simple and 5/6 chose a document to read as the best support for assent as compared to a comic or video. None of the participants complained about the number of follow up visits but 1/6 reported that the trial has too many blood tests and lumbar punctures. All participants had mixed feeling regards to study drugs intake (taste and quantity).

Conclusion

The results are still preliminary and data collection is ongoing, but the available feedback proves to be very insightful to understand children's perceptions, emotions and expectations about the trial. This data will help OUCRU researchers to further reflect on the challenges of pediatric trials conducted in Vietnam with young and sick participants and should lead to adapting protocols and accommodating study procedures to maximize recruitment and protocol adherence.

P-117

Following the roadmap to a better randomisation method: simulation study to choose an appropriate Big Stick Design

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Introduction
For a recent open-label RCT, we considered alternatives to standard randomisation methods of simple randomisation, minimisation with random element and stratified block randomisation. In the third case, we realised that varying the block size would not prevent selection bias: this method being vulnerable to counting previous allocations and guessing. We decided to randomise using the Big Stick rule, with all allocations being fair coin flips unless an unacceptable imbalance is possible. We then needed to select the maximum tolerable imbalance (MTI) parameter to define performance.

Method
Following a recently-published "Roadmap for randomization" by the Randomization Working Group of the DIA-IDSWG, we evaluated 12 possible MTI parameters for our randomisation design using a simulation study. Designs had either constant or piecewise increasing MTI functions. For comparison, we also evaluated randomisation using blocks of size 6. Unpredictability in terms of correct prediction rate and mean absolute imbalance within sequence were chosen as measures of interest. The two measures were combined as a weighted sum to compute an overall score, which was compared between the 12 designs. We considered three weighting schemes for relative importance of imbalance and randomness. We also evaluated the Type I error of a log-rank test under a true null hypothesis where selection bias resulted from observed imbalances. Ten thousand replicates were performed for all scenarios. Finally, we explored post-hoc the relative weighting of balance and randomness to find the point at which permuted block randomisation would be considered equally preferable to the big stick with the same imbalance limits.

Results
When randomness and imbalance control were weighed equally, preferable schemes had imbalance limits of 5, 6, or increasing to 6. If imbalance was more important, limits increasing to 6 or between 3 and 6 were preferred. If randomness was more important, imbalance limits of 6, 8 and 10 were preferred. Block randomisation of size 6 was only preferred equally to big stick with same maximum imbalance when the balance weighting was more than 8 times that for randomness. Block randomisation and the worst big stick design under selection bias were associated with Type I errors of 22% and 8% respectively. All other designs had Type I errors between 5% and 6.5%.

Conclusions
For the trial of interest, we were able to consider alternative randomisation methods to select a suitable randomisation design and understand the impact on selection bias and imbalance control.

Reference: Berger et al (2021) https://doi.org/10.1186/s12874-021-01303-z

P-118

Stratified merged randomisation as an alternative to minimisation: a simulation study

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Introduction
In small clinical trials it is often considered necessary to use randomisation procedures such as minimisation to prevent large imbalances occurring by chance between trial arms among pre-selected baseline factors. Stratified merged "Van der Pas" randomisation is a relatively new method of randomisation that aims to achieve a tight balance between treatment arms in small trials while still being difficult to predict. This method is a variation on stratified block randomisation, where instead of block randomisation within strata, a merged allocation list is generated within strata based on two separate basis allocations. The aim of this study was to evaluate the balance and predictability of stratified merged randomisation as a potential alternative to using minimisation in clinical trials.

Methods/Approach
In the context of two and three arm trial designs, a simulation method was used to assess the level of between-arm balance after using stratified merged randomisation, simple randomisation, and minimisation procedures with random elements of various sizes. The simulation design was informed by the three arm DEFINE early phase clinical trial, which used a minimisation procedure with 20% random element and four minimisation strata. We studied the performance of the randomisation methods after varying the per group sample sizes from 10 to 500 and random elements from 0% up to 50%, while keeping the number of strata constant. A total of 200 replicate trials were generated per scenario. Balance was assessed through calculation of, among other metrics, the mean maximum percentage imbalance for each simulated trial. Predictability was assessed using the correct guess probability based on numbers recruited to each arm.

Results
In two and three arm trials, stratified merged randomisation provides similar levels of between-arm balance to using minimisation with random elements of around 30-40%, but it provides superior unpredictability. The smaller the sample size, the more important the choice of method and/or random element used for minimisation. Using minimisation with 10-20% random element provides much greater balance for small trials with samples sizes in the range of 20 to 70 per arm.

Discussion
Stratified merged randomisation is particularly suitable for small unblinded trials where maintaining unpredictability of the randomisation procedure is important. However, if the trial is blinded or if balance is a priority then much better balance can be achieved in small trials by using minimisation with 10-20% random element.

P-119

An updated review of randomised controlled trials using the post-randomised consent design methodology

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Introduction
A post-randomised consent design in randomised controlled trials, for example Zelen's design, is often proposed to increase recruitment and decrease resentment bias. This methodology removes pre-consent conversations with patients around clinical uncertainty, randomisation and all treatment options. The use of this methodology is debated, particularly on ethical principles and criticism due to high crossover rates with associated loss of statistical power. Despite this, it continues to be utilised and additionally some pragmatic designs such as Trial Within a Cohort and cohort multiple Randomised Controlled Trial also employ a similar post-randomised consent, making this relevant to these designs.
The objective was to update the previous literature review conducted on this topic, to investigate the justifications given for using a post-randomised consent design and to assess the quality of the identified trials.

Methods
A protocol was written and made available on the open access platform Open Science Framework (https://osf.io/4gvku/) prior to commencing the searches. The search strategy was conducted in MEDLINE, EMBASE, CENTRAL, CINAHL, clinicaltrials.gov, WHO-ICTRP, PsychINFO, Google Scholar, Science Citation Index (Web of Science by Institute for Scientific Information) and OpenGrey. Eligible studies were randomised controlled trials using post-randomised consent design methodology published since 25th April 2005 – 15th June 2021. Animal studies and study protocols were excluded. Articles were limited to those written in English.

Results Structure and Timelines (what form would the results takes)
Seventy-five studies, from 17 different countries have been identified and the data extracted. By the time of the conference we will present findings by narrative description and any descriptive statistics on consent type utilised, justification provided, average crossover rates, analysis type, sample size calculation, recruitment rate, any patient preference information and the therapeutic area. We will look at the quality of the studies included and investigate whether the justifications provided remain similar to those found in the previous review or not.

Potential Relevance and Impact
This paper will help provide knowledge on the use of post-randomised consent design in relation to the justifications and perceived benefits given for utilising this methodology. This would be relevant for those considering a post-randomised consent design, or in understanding or for reviewing research that has used this methodology. Patient preference will be considered and so will be relevant to future participants of trials which may consider, or use this design. Searches have found literature from different countries so this will be of relevant not just to the UK.

P-120

Developing Principles for the Design and Implementation of n-of-1 Trials (The 'DIAMOND' study)

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Introduction
n-of-1 trials are multi-period crossover trials designed to evaluate health technologies within individual patients. The DIAMOND study (Development of a generalisable methodology for n-of-1 trials delivery for very low volume treatments) aimed to develop a set of principles for the design of n-of-1 trials in order to facilitate their implementation, particularly in rare disease research.

Methods
The development of key principles for designing n-of-1 trials was informed by two research stages. The first was a review of the characteristics of randomised n-of-1 trials published between January 2011 and May 2021. The second was a workshop which sought to gain the perspectives of a variety of stakeholders (clinicians, researchers, and patient representatives) on principles for the design and implementation of n-of-1 trials. The workshop was supplemented with discussions with study collaborators to review and finesse the principles.

Results
The review identified 52 randomised n-of-1 studies, 8 of which (15.4%) were conducted in rare diseases. There were no apparent differences in trial design according to whether they were conducted in a rare or non-rare disease. Workshop discussions centred on the types of questions that n-of-1 trials can be used to answer, the treatments they can be used to assess, and potential outcomes of n-of-1 trials.
A set of practical principles were developed based on the results of the review and insights from the workshop. They provide guidance on when an n-of-1 trial might be a viable or appropriate study design and discuss key decisions involved in the design of n-of-1 trials, including determining an appropriate number of treatment periods and cycles, the choice of comparator, recommended approaches to randomisation and blinding, the use of washout periods, and approaches to analysis.

Discussion
The principles will support clinical researchers to understand key considerations when designing n-of-1 trials. It is hoped they will facilitate the wider implementation of the study design.
A report will be published detailing the principles as well as complementary statistical programs and journal articles. Two courses (one for statisticians and one for non-statisticians) will be run in Autumn 2022.

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Investigating the impact of oncology phase II trial design parameters on their ability to successfully screen new treatments

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Introduction
Phase III oncology trials have significantly high attrition rates, where many treatments fail to show efficacy over standard treatments. Design of phase II trials contribute to these inefficiencies and there is much debate regarding optimal phase II design. We investigate the effect of the relationship between phase II and III trial endpoints, randomisation, using one-stage or two stages and the operating characteristics of phase II trials in oncology, on the efficiency of the phase II and III process.

Methods
Evaluation of design parameters was based on undertaking multiple phase II and III trials until a successful phase III trial is observed, assuming many treatments are available for testing. Phase II and III trials were conducted assuming the true effect of each treatment was drawn from a standard normal distribution. Phase III trials were assumed to be randomised, with a continuous primary endpoint, 80% power and 5% significance level. Specific design scenarios were considered. The effect of the correlation between the phase II and III trial endpoints was explored analytically, by ranging the variance of the true treatment effect, while randomisation, number of stages and operating characteristics of phase II trials were explored using simulations. The number of phase II and III patients required to lead to the first successful phase III trial was used to measure efficiency of design parameters.

Results
For the scenarios considered, the number of patients required to lead to the first successful phase III trial decreased from 3200 to 1000 patients, on average, as the correlation between endpoints increased from 0 to 1. Randomised single-stage phase II trials required 730 patients to lead to the first successful phase III, while Jung's randomised two-stage design required 554. A'hern's exact single-arm single-stage design required 463 phase II and III patients while Simon's single-arm two-stage design required 438. The type I error, α, significantly affected the efficiency of phase II trials. Less stringent α= 0.1,0.15 and 0.2 yielded 417 phase II and III patients on average, while stringent α= 0.01 or 0.05 required 555 phase II and III patients to lead to the first successful phase III trial.

Discussion
Understanding the impact of differing design parameters on the efficiency of phase II trials better equips us with the tools needed to improve their design. Based on the scenarios considered we identified Simon's single-arm two-stage design with a less stringent type I error yielded the greatest efficiency.

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How do we generalize, or 'transport', the findings of randomized clinical trials?

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The strength of randomized controlled trials (RCTs) in providing robust cause-effect conclusions (internal validity) is generally accepted, but their generalizability (external validity) is less clear-cut. There are two restrictions to such generalizability. First, as Cartwright (2011) argues, the experimental constraints within the trial may restrict generalization to contexts lacking these constraints. Here we can note Basu's (2014) distinction between demonstrating circumstantial causality (within the trial) and demonstrating universal causality (beyond the trial). Second, in the absence of random sampling, uncommon in RCTs, we cannot appeal to the principles of sampling theory to establish external validity.

We will discuss other, rather less formal, ways to generalize – or, to use Justice et al's (1991) terminology, transport – findings beyond the context of an RCT. First, mechanistic understanding of interventions may suggest that estimates of some treatment effects may be transportable to other contexts; e.g., interventions working on microbiological or haemodynamic principles are likely more transferable than those working on psychological or educational principles. Second, the greater the magnitude of a treatment effect, the more plausibly it may be considered to survive transfer to certain other contexts. Third, clinical judgment may allow reasonable assumptions concerning other samples or context to which findings can be transported, through evaluating clinical and other characteristics of trial participants vis-à-vis those of another clinical setting. Hence, a clinician may conclude that although his or her patients are on average older or clinically more severe than those in a particular trial, the information from the trial can be appropriately tailored or adjusted to this new context. Caution is needed, however, for whilst conclusions might be transportable across contexts that are superficially dissimilar, apparently similar contexts may conceal important differences that severely limit such transfer. The decision here requires an understanding, from clinical knowledge and experience, of which differences are likely to modify a treatment effect.

Finally, replication may help, in two ways. On the basis of inductive logic, it may make a causal inference more credible as the frequency with which it is demonstrated increases. Additionally, replication of a trial, in new settings, will provide greater coverage of the target population of interest, and may also indicate the consistency, and thus the greater likely transportability, of an estimated treatment effect.

Generalizability of RCT findings does not, therefore, hinge wholly on statistics. Mechanistic, contextual and clinical knowledge are important; however, this requires RCTs to be reported in appropriate detail.

P-123

Utilising QueryTree Software for Data Reporting – for non-technical staff!

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Introduction
QueryTree is an open-source reporting tool software that is used worldwide to connect to any Microsoft SQL server, PostgreSQL or MYSQL database. The benefits of this software include, its user-friendly interface to assist with building query reports and advanced report building from a SQL database.
QueryTree allows both technical and non-technical research colleagues to build complex reports from all tables within a research SQL database. A virtual table can be created within SQL based on the results set of a SQL statement which can then be selected, filtered, grouped, aggregated, and visualised within the QueryTree software.
During the COVID-19 pandemic many studies rapidly accelerated their use of electronic database tools, requiring ways to extract data from new online research software platforms. QueryTree is a simple solution for non-technical staff to extract data reports from SQL databases.

Methods/Approach
Keele Clinical Trials Unit (CTU) have been investigating how best to utilise digital tools for non-technical staff accessing and building data reports from our SQL Databases.
Two methods of how to build reports, dependent on your requirements, will be presented:
Simple query report – using QueryTree to build a simple query report which will include ways to select, filter and add any calculations.
Advanced query report – using QueryTree to build an advanced query report which involves integrating multiple tables of data, with a user-friendly interface and will require no experience in coding.
During June 2022, a QueryTree training event held at Keele CTU will further explore whether QueryTree is a successful digital tool for enabling non-technical staff to build research data reports.

Results Structure and Timelines
The QueryTree training event, will be presented and reviewed on how QueryTree can assist with: maximising the efficiencies of CTU resources and expertise; involving non-technical staff in data management responsibilities; and sharing data extraction activities across a CTU.

Potential Relevance and Impact
Online data collection of research has increased across CTUs during recent times. Many CTUs rely on technical staff for all data management activities, from extracting data, to producing data reports.
Presenting the Keele CTU lessons learnt so far, from our use of QueryTree with non-technical staff, will disseminate how CTUs can further maximise their resources, by involving non-technical staff in data management activities, that can enhance engagement with data being collected and create efficiencies in the use of resources.

P-124

Accessible software to accelerate non-commercial trials for rapid patient impact (ASSITANT)

Mr Nigel Kirby[1], Ms Yvonne Moriarty[1], Prof Kate Button[1], Dr Paul Channon[2], Prof Monica Busse[1]
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Introduction
Non-communicable diseases (NCDs) lead to premature deaths in approximately 15 million individuals globally. Accessible digital approaches to developing and evaluating NCD complex interventions are critical to the United Nations sustainable development target, of reducing premature mortality through prevention and treatment of NCDs by one third by 2030.
Our team have created a web based system where potential research participants can register and view study information rather than having to visit a clinic which was used in the LEAP-MS study.
We will develop this system further so it is more widely available to researchers and health care staff in other organisations. We will work with these professionals to understand what they require from the system.

Methods/Approach
We are employing a user-centred design process. Initially, we will work together with health care professionals and researchers to define the context and specify the users' requirements via focus groups. This will be followed by the further development of the system and then the evaluation, which will focus on user acceptability including Think Aloud interviews whilst users interact with the system . The software system will consist of two parts, the clinical data system, REDCAP, a current off the shelf system which requires limited programming knowledge and a bespoke web application which will facilitate research participant activity.

Timing of Potential Results
The updated system will be ready for demonstration at the conference. The results of the think aloud interviews will also be ready for the conference.

Potential Relevance & Impact
Our vision is to see our software utilised in the conduct of high-quality evaluations relevant to addressing the challenge of NCDs globally. By the end of the 6-month project (September 2022), we will deliver the software along with clinician researcher training protocols. Over 2-5 years, we will implement the software in trials in the UK, USA and targeted lower & middle income counties. We will capture its impact quantitatively (number of license agreements) and qualitatively (user views of the impact of the system). Our proposed system will rapidly accelerate delivery of remote trials to improve access to evidenced based NCD management approaches to large numbers of individuals living with NCDs. The system will allow access to participants who researchers wouldn't traditionally be able to recruit into trials. Broader populations will allow researchers to answer more generalisable based questions and thus providing rapid indicators of the outcomes to inform policy making.

P-125

Clinical trial empowerment through effective delivery and efficient data management of large and complex COVID-19 trials through automation and interconnectivity of modern-day E-Systems

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Introduction
Clinical trials are the most robust mechanism to evaluate the efficacy and safety of a new vaccine, treatment, medical device, and other health system interventions. However, the conventional clinical trial system still poses challenges inhibiting research efficiency. The traditional clinical processes and methods relating to participant recruitment, data collection, safety follow-up of the participant, and data analysis can inflate costs, increase participant and site team burden, and increase the research timelines. In contrast, leveraging technology and modernised clinical trials helps in data management efficiency, improves participant safety and real-time engagement, and directly affects the quality of research while reducing the cost and time.

Methods
Setting up a modernised clinical trials infrastructure to support a robust response to the COVID-19 pandemic was done by: (1) Direct data entry using the electronic data capture system REDCap. (2) real-time data processing and data cleaning through the development of data cleaning tools. (3) reducing manual efforts by connecting databases and other health systems. (4) implementing e-diary and surveys to increase participant engagement, improve safety, and enable real-time access to participant data.

Results
Automation and interconnectivity of modern-day E-Systems, improved the overall quality of trials by reducing the manual effort, improving the screening process, increasing participant engagement, and improving participant safety. Furthermore, modernised clinical trials infrastructure allowed for high volume data to be collected, processed, and cleaned over a short period, resulting in a robust and effective response to the pandemic.

Conclusion
Modernised clinical trials infrastructure helped in a robust response to the COVID-19 pandemic resulting in the development and licensing of a vaccine in a record-breaking time.

P-126

Hybrid models of data collection: During COVID and beyond - what we have learnt so far

Mrs Jo Smith[1,2], Dr Elaine Nicholls[1,2], Mrs Zoe Johnson[1,2], Mrs Claire Bratt[1,2], Mr Taylor Capey[1,2], Miss Stefannie Garvin[1,2], Mr Steve Harper[1,2], Mrs Sarah Lawton[1,2], Dr Martyn Lewis[1,2], Mr Karl Rogers[1,2], Miss Sarah Stokes[1,2], Dr Martin Thomas[1,2], Mr Simon Wathall[1,2]
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Introduction
The National Institute for Health and Care Research (NIHR) INCLUDE framework highlight that research findings from clinical studies should reflect the population to whom the study applies. To achieve this, reducing barriers for people to access research studies is important. One example of removing barriers to participation, is providing data collection tools in multiple formats for patients. Keele Clinical Trials Unit (CTU) now has growing experience of collecting patient data online (a development that was accelerated by the COVID pandemic) in a range of study settings and populations. The aim of this presentation is therefore to share our learning from using multiple methods of data collection in our research studies. We will support our findings using data from our active research studies.

Methods/Approach
The views and opinions of a multidisciplinary CTU (patients, software developers, trial managers, statisticians, administrators) were obtained, on the experiences of using a hybrid model of data collection (a combination of online and paper-based data collection tools) for our research studies. Keele CTU Data Interface Working Group reflected on the findings, to determine the advantages and disadvantages of conducting a hybrid approach to data collection. Consideration was given to key areas such as questionnaire development, data quality and efficiencies.
For Keele CTU studies using the hybrid approach to data collection, descriptive statistics will be used to describe response rates to self-reported data collection tools across multiple studies, alongside the characteristics of the participants who responded using each data collection type. Our findings on patient preference for data collection type i.e. when given a choice of method (online or paper), which do the majority prefer, will also be reported.

Results Structure and Timelines
As our included studies are actively recruiting or in follow-up, results will be taken from the most up-to-date data available prior to the conference, therefore providing the most comprehensive picture of our findings. Reflective statements gained from our experiences will be displayed alongside quantitative findings from the studies that have been using a hybrid method of data collection.

Potential Relevance and Impact
The findings from this presentation will resonate with many CTUs undertaking a hybrid approach to data collection and will promote sharing of good practice between CTUs. As we continue to explore the best ways in which to collect data, it is hoped that our developments will have a positive impact for patients, as our methods aim to be as inclusive as possible.

P-127

Right data, right time: presenting a new tool for extracting data management requirements from clinical trial protocols

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Introduction
A clinical trial protocol is a document describing how a trial will be conducted, including details of all data to be collected. However, protocols are often long with dense paragraphs of text describing processes and rationale. It is crucial to identify all data collection and data checking requirements accurately to implement these protocols. Failing to do so can endanger the integrity of the trial (due to failure to collect all necessary eligibility or endpoint data) or put participants at undue risk (if essential safety checks are missed). To the best of our knowledge, there are no freely available tools for collation of data management requirements from trial protocols. We present a new tool, the Protocol Data Collection Assessment Template (PDCA), for systematically listing all data management requirements from the protocol and linking these to system and process solutions.

Methods
The tool consists of a template spreadsheet and accompanying instructions. The user first reviews the protocol and copies any sentences/paragraphs that describe a potential data collection or checking requirement into the spreadsheet. A series of meetings then take place to discuss how these requirements will be met, ensuring contribution from all stakeholders including clinical, statistical and database teams, with decisions documented in the spreadsheet. The spreadsheet is then completed with details of how these requirements are being met, such as CRF questions, database checks and data management procedures.

Results and Discussion
The PDCA has now been used successfully in our unit for several new protocols and protocol updates across various disease types and settings. It has led to identification of inconsistencies in the protocol that had been overlooked in previous reviews but that could then be changed before finalisation. It has also flagged up missing or incorrect questions on study CRFs and missing database checks.
The process still has its challenges. It's often a time-consuming exercise and it can be difficult to keep the PDCA updated in line with new drafts of protocols and updated CRFs, database checks and data management process documents. Several updates have already been made to the template after feedback from users, including the option to separate requirements from a protocol into phases for staggered release in a database system, and a new version of the template that is specifically for use in protocol updates rather than first releases.

P-128

Ethnic diversity in orthopaedic research: a clinical audit.

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Background
Question: What is the proportion of research participants in Orthopaedic studies from ethnic minorities compared to white participants, and how does this compare to the ethnic makeup of the orthopaedic population at two trauma centres in East London?

Methods
A prospective three month audit (From November 2021 to February 2022) of all patients screened for participation in clinical research in the orthopaedic departments of Whipps Cross Hospital and Royal London Hospital. Baseline data for orthopaedic service attendees during this period was collected from patient records through the local business intelligence unit. Patients were categorised by ethnicity (white, non-white) and study status (screened out, included, declined). Proportions of recruitment by ethnic group were compared to baseline service use data and borough data.
Additional information was collected regarding the studies that they were being considered for, which will be used for sensitivity analysis (pending).

Results
The results of audit data show no significant difference in study status between white and non-white groups. Of note, when comparing the ethnic makeup of the general population, the orthopaedic population and the study population there are proportional differences that indicate that non-white patients are using these services and participating in research less - reasons for this will be discussed and include wider catchment area of specialist services hosted by RLH and culturally driven service access habits which are as yet unexplored. Limitations of this audit include a large number of missing data in trauma cases and other cases that cannot be accounted for - which may lead to bias.

Conclusion
We have appraised the proportion of ethnic minority patients participating in orthopaedic research and we have established a structure to monitor its status in future studies. The missing data issue raises questions around the validity of ethnicity data collected from patient records and highlights the unresolved relationship between ethnic identity and health research intentions. These may be addressed further through a qualitative audit of the experiences of those who do not disclose their ethnic identity, are screened out of research, or decline to participate.

NB: analysis is still being finalised and this section may be updated.

P-129

The INCLUDE Socioeconomic Disadvantage Framework – a tool to help researchers design and conduct more inclusive clinical trials

Dr Heidi Gardner[1], Mrs Katie Biggs[2], INCLUDE Socioeconomic Disadvantage Public Contributor Group[3], Dr Frances Sherratt[3]
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Introduction
Patients with experience of socioeconomic disadvantage are underrepresented and underserved by clinical trials. Failing to include these patients as participants in research means that trial results may not be generalisable to a broad population. We describe the development process of the INCLUDE Socioeconomic Disadvantage Framework. The Framework aims to improve acceptability, accessibility, and/or applicability of clinical trials for patients experiencing socioeconomic disadvantage, and forms part of the NIHR's INCLUDE initiative to improve the inclusion of underserved groups in clinical research.

Methods
The Framework was developed over several phases between April 2021 and May 2022: (1) Outlining what is needed; (2) Initial draft; (3) Stakeholder feedback; (4) Modifying draft; (5) Stakeholder feedback; (6) Finalise framework. A team of six public contributors informed the development of the framework through stages 1-6. Wider stakeholders included: methodologists, funders, patient and public contributor experts, health professionals, trialists, diversity experts, and linguists. All meetings were held online.

Results
Our work comprises guidance on the scope of the Framework, understandings of socioeconomic disadvantage, and background on the Framework development, four key questions, and four associated worksheets. The four key questions include: (1) Who should my trial results apply to? (2) Are people from different socio-economic backgrounds likely to respond to the intervention in different ways? (3) Will my trial intervention and/or comparator make it harder for people from different socio-economic backgrounds to engage with the trial? (4) Will the way I have planned and designed my trial make it harder for people from different socio-economic backgrounds to consider taking part?

Our findings emphasise the dynamic nature of socioeconomic disadvantage, as well as the various implications for daily-life that could influence inclusion and engagement in trials. To guide trial teams through use of the Framework we encourage them to consider socio-economic indicator examples grouped under the '3Ps' headers: pockets, places, and prospects. We encourage addressing the Framework key questions and worksheets with an all-team approach, including people with lived experience of socioeconomic disadvantage.

Discussion
The Framework has been finalised and will soon be launched. It should be used by trial teams to identify potential barriers to research faced by patients experiencing socioeconomic disadvantage, supporting the design and conduct of trials that better represent such patients. Future research will draw current and developing NIHR Frameworks together to examine the barriers and opportunities to make research more inclusive, especially for those who may be part of intersectional underserved groups.

P-130

Understanding why ethnic minority groups are underrepresented in trials through a rapid Qualitative Evidence Synthesis (QES) and mapping evidence to find solutions

Dr Heidi Gardner[1], Dr Katie Gillies[1], Prof Shaun Treweek[1], Ms Anna Kearney[2], Dr Ratna Sohanpal[3], Mr Taylor Coffey[1], Dr Linda Biesty[4]

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Introduction

Trial populations often lack ethnic diversity. If trial participants do not reflect the patients the trial is designed to serve, results may not apply to them. We should understand why trials currently lack diversity to ensure trials are accessible and acceptable to people from ethnic minority backgrounds. The qualitative evidence synthesis (QES) we will present explores the trial participation experience of people from ethnic minority groups.

Methods

Search strategy

We searched the Online Resource for Research in Clinical triAls (ORRCA) database up to 2018 for qualitative recruitment research focusing on ethnic minority participants. This was supplemented with a comparable search of relevant databases up to May 2021.

Study selection and sampling

One reviewer screened titles and abstracts for eligibility, a second screened 20% of these for screening accuracy. A third reviewer screened excluded abstracts for process validation.
Characteristics including gender, location and ethnicities of participants, trial setting, clinical area, and intervention type were extracted from eligible full texts. We purposively sampled data-rich (assessed on a 5-point scale) studies for a complementary range of participant characteristics, perspectives, and experiences.

Data extraction

One reviewer extracted data (participant quotes and author interpretation) and a second checked data for accuracy.

Data analysis and synthesis

We will consider three levels of influence – system, individual, and interpersonal – that may contribute to disparities in trial experiences of ethnic minority individuals (Hamel et al. 2016) to guide our best-fit framework approach to analysis and synthesis.
Two reviewers will use the GRADE-CERQual approach to assess confidence in the findings of this review.

Evidence mapping

We will map findings against recruitment interventions in relevant systematic reviews, the QUB SWAT repository, and SWATs funded by the NIHR and HRB-TMRN.

Results and Timelines

A total of 547 titles and abstracts have been screened, 42 of which were eligible. These were purposefully sampled to give a final sample of 27 included studies. Quality appraisal is complete and data extraction is ongoing. Findings from the evidence synthesis will be synthesized and mapped against existing interventions (July/August 2022) and highlighted during this presentation.

Potential Relevance and Impact

This QES will ensure trialists understand potential barriers and facilitators to recruitment of ethnic minority groups across trial settings and contexts. Our mapping will enable trialists to make informed judgements on the applicability and acceptability of existing interventions for recruiting ethnic minority individuals and encourage evaluation of interventions likely to be effective.

P-131

Patient reported outcome assessment must be inclusive and equitable

Prof Melanie Calvert[1,2,3,4,5,6,7,8], Dr Samantha Cruz Rivera[1,2,3], Dr Ameeta Retzer[1,4], Dr Sarah E Hughes, Dr Lisa Campbell[9], Ms Barbara Molony-Oates[10], Dr Olalekan Lee Aiyegbusi[1,2,4,5], Dr Angela M Stover[11], Mr Roger Wilson[12,13,14], Dr Christel McMullan[1,2,6,15], Ms Nicola Anderson[1,16], Dr Grace Turner[1,6], Dr Elin Haf Davies[17], Mr Rav Verdi[14], Prof Galina Velikova[18], Dr Paul Kamudoni[19], Dr Syed Muslim[1,2,8], Dr Adrian Gheorghe[20], Dr Daniel O'Connor[9], Dr Xiaoxuan Liu[1,2,16,21], Prof Albert W Wu[22], Prof Alastair Denniston[1,2,3,7,16,21,23]

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Background
Patient-reported outcomes (PROs) are collected in clinical trials to provide valuable evidence on the risks and benefits of treatment and in routine clinical practice to support patient-centred care. To increase the positive impact of PRO data and to avoid the unintended consequence of increasing health disparities, we need to consider the needs of under-served groups and identify approaches to ensure greater equality, diversity and inclusion (EDI).
Aim: To propose actions to promote representation of under-served groups in the collection of PRO data.

Methods
A rapid literature review to identify and summarise key publications and consultation with international stakeholders (n=20) and patient partners (n=2) to 1) identify barriers to EDI and 2) formulate key actions to promote representation of under-served groups in the collection of PRO data.

Results
Several challenges to EDI were identified. These included a lack of valid and reliable PRO measures that have been co-developed with, or are relevant to, the target population. PRO measures developed with limited patient input risk omission of key concepts of importance to under-served groups. This is particularly true if these groups are excluded from concept elicitation due to communication barriers arising from learning disabilities, low literacy, or digital exclusion. Failure by trialists and clinicians to use translated and culturally validated PROs threatens to increase racial and ethnic disparities through exclusion of minority ethnic groups from PRO reporting. Lack of culturally appropriate and linguistically validated measures limits the use of PROs within low- and middle-income countries.
To promote the representation and participation of under-served population in PROs several actions were proposed: 1) widen participation by ensuring individuals involved in PRO co-development are representative of the target population; 2) be mindful of the clinical characteristics of the disease when designing or

selecting a PRO to minimise barriers to completion; 3) acknowledge cultural values through the use of translations; 4) providing accommodations to ensure individuals are able to complete a PRO regardless of ability to read, write and problem solve; 5) consider ways to promote digital inclusion; and 6) engage regulators in EDI discussions early in the drug development life cycle.

Conclusion

PRO data needs to reflect the diversity of modern society. Implementation of specific actions to address EDI, both in trials and routine care, can promote representation of under-served groups, reduce health disparities, and result in the collection of meaningful PRO data for the benefit of all.

P-132

Methodological and ethical considerations for designing Studies Within a Trial (SWATs) of recruitment interventions for trials involving adults lacking capacity to consent

Dr Victoria Shepherd[1], Prof Fiona Wood[1], Dr Katie Gillies[2], Dr Abby O'Connell[3], Dr Adam Martin[4], Prof Kerenza Hood[1]

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Introduction

Interventions aimed at improving recruitment and retention of participants in trials have burgeoned in the past decades, with a corresponding growth in randomised Studies Within Trials (SWATs) to evaluate their (cost-)effectiveness. However, these have primarily focused on populations making their own decisions about whether to participate. Trials involving adults lacking capacity to consent encounter additional challenges, however there is a lack of recruitment interventions and SWATs to improve the evidence-base for conducting trials involving this under-served group.

After developing a recruitment intervention (a decision aid) for family members making a decision about trial participation as a consultee or legal representative in the UK, we have designed a SWAT to evaluate its (cost-)effectiveness in a number of host trials (CONSULT). We encountered a number of methodological and ethical considerations when designing the SWAT, primarily because, unlike in SWATs to date, the recruitment intervention is aimed at a 'proxy' decision-maker who is not a participant in the host trial and does not receive the trial intervention. Using the CONSULT SWAT as a case example, we will discuss the methodological and ethical issues that need to be considered for SWATs in trials with adults lacking capacity to consent and propose solutions to address them.

Discussion

Proxy consent is itself ethically complex, and so when conducting a SWAT which aims to affect proxy consent decisions there may be additional ethical issues to be considered. SWATs involving consultees/legal representatives also encounter practical challenges around consent and multi-level data collection where, in addition to collecting the SWAT participant's data, assessing the impact of the intervention on recruitment and retention in the host trial involves linking the intervention receiver (SWAT participant) with the deliverer (researcher) and the host trial participant (person lacking capacity). Methodological issues concern decision-making about the appropriate randomisation level, ensuring the integrity of the host trial, how best to evaluate resource use, and uncertainty about differential recruitment and heterogeneity between host trial populations that may impact on the ability to meta-analyse.

Conclusion

Developing a SWAT to evaluate the (cost-)effectiveness of a recruitment intervention for adults lacking capacity to consent in non-emergency trials raised a number of methodological and ethical considerations. Our hope is that describing these issues, together with our proposed solutions, can inform the development of future SWATs in trials with these populations. Improving the conduct of trials involving adults lacking capacity will contribute to the much-needed evidence-base for this under-served group.

P-133

Identifying the scale and impact of excluding potential participants from clinical research based on their ability to communicate in English

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Introduction
Language has been recognised as a barrier to recruitment in several different research settings, and although there are no strategies to objectively measure language proficiency, it is frequently used to exclude potential participants from studies. With many studies struggling to meet their recruitment target on time, we asked the question of how much excluding those who cannot communicate in English can impact on recruitment potential and hoped to better understand why these participants are excluded. There is little research to explore language as a barrier to recruitment in Emergency Medicine trials, so we focussed our study on this area of research, where trials are presented with unique challenges.

Methods
Using a mixed method approach, we sought screening data on completed studies on the NIHR Trauma and Emergency Care portfolio that had taken place in the East Midlands, alongside a short survey of research professionals working in NHS Trusts, Clinical Trials Units and Research Ethics Committees in the East Midlands to gather opinions on the use of this exclusion criterion. We used descriptive statistics and thematic analysis to review the survey responses and gather perspectives on exclusion of those who could not communicate in English, comparing responses for those involved in Trauma and Emergency Care research, and those not.

Results
Detailed screening data on reasons for exclusions were not routinely reported and researchers we contacted generally did not collect this, so we had limited data to be able to fulfil our primary objective. Responses to the survey indicated that research professionals were aware of the exclusion of participants and the drivers behind this were generally financial in origin. Respondents acknowledged the issues this raised, including ethical and moral implications and the impact on external validity and generalisability of the results.

Discussion
There is not enough information available to quantify the problem as originally hoped, which makes the development of initiatives more difficult when wanting to explore cost-effective options. A lack of awareness of initiatives to support inclusion of non-English speakers demonstrates that we have some way to go to make any real improvements, and work in this area is needed. Funders will need to work with teams to address the financial burden of translators and interpreters, but translation at the consent stage is not enough, and cross-cultural adaptation is needed

P-134

Equality, Diversity, and Inclusion in Oncology Trials: An audit of ICR-CTSU managed trials.

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Introduction
Clinical trials are crucial for testing the clinical utility of novel cancer therapies. Therefore, the aim should be for trial participants to reflect the population affected by the cancer under investigation. Informed by NIHR's INCLUDE guidance, we reviewed trials conducted by ICR-CTSU to identify whether data was collected to assess equality, diversity, and inclusion of trial participants. The aim was to ascertain if any under-served groups were being inadvertently systematically excluded.

Methods
Clinical trials managed by ICR-CTSU which gained ethics approval between 2011-2021 were included. The first approved version of a trial's protocol, patient information sheet, and patient completed questionnaire were reviewed, together with the first version of case report forms (CRFs). These documents were reviewed for a broad range of items that would identify underserved groups, including ethnicity, gender, and socio-economic factors. The audit's scope did not cover trial processes in participating hospitals.

Results
30 trials met the criteria for review; 19/30 were CTIMPs (15 Investigator Initiated Trials (IITs), 4 funded non-commercially) and 11/30 were non-CTIMPs (1 IIT, 10 non-commercially funded). All protocols' eligibility criteria allowed all ethnicities and English comprehension levels; 26/31 (84%) CRFs collected ethnicity. 27/30 (90%) protocols specified a minimum age and all CRFs and questionnaires recorded date of birth. 14/30 (47%) protocols and 48/61 (79%) patient information materials used a gendered term, although none stated if they referred to gender identity or biological sex. Where applicable, 15/17 CRFs recorded sex, one recent trial specified "sex at birth". Medical history and patient health were well recorded in CRFs and questionnaires but socio-economic factors were not. Patient information materials were generally accessible, with a mean of 20 words per sentence and 2 sentences per paragraph.

Discussion
This audit illustrates that ICR-CTSU trials are reasonably inclusive within the bounds of cancer clinical trials. The nature of cancer and its treatments necessarily restricts eligibility to patients with certain types and stages of cancer, especially in regards to biological sex. Areas for improvement include trial accessibility and clarification around the use of gendered words. The challenge of fully assessing adequate inclusion of underserved populations remains as socio-economic factors are justifiably not routinely collected, as they fall beyond the data generally required for protocol-specified trial endpoint assessments. Overall, this review has highlighted the need to continue to consider underserved populations during trial development at ICR-CTSU.

P-135

Improving the inclusion of an under-served group in trials: development of the INCLUDE Impaired Capacity to Consent Framework

Dr Victoria Shepherd[1], Ms Katherine Joyce[2], Dr Samantha Flynn[3], Mrs Madeleine Clout[2], Dr Amanda Lewis[2]
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Introduction
Trials involving adults with impaired capacity to consent are challenging, resulting in this under-served group often being excluded from trial participation. Researchers encounter barriers such as a lack of knowledge of the additional legal and ethical requirements, and perceived methodological issues around recruitment and data collection processes. Following recent initiatives to improve the inclusion of under-served groups in trials, there have been calls for guidance on how trials can be designed to ensure that people with impaired capacity have the opportunity to participate in, and benefit from, research. Building on the National Institute for Health and Care Research (NIHR) INCLUDE project, we developed an INCLUDE framework to help researchers design trials to be more inclusive of this population.

Methods
Led by members of the MRC-NIHR Trials Methodology Research Partnership's Trial Conduct Working Group with expertise in trials involving populations with impaired capacity, the framework was developed in conjunction with both researchers working in relevant specialties and people living with impairing conditions and their carers. The development process comprised three phases: 1) the scope and content of the framework was established and the INCLUDE Ethnicity Framework structure adapted to be relevant to the population of interest; 2) a scoping phase explored the relevance of the framework to different populations through consultation with UK research specialty leads and piloting of the framework in a range of trials; 3) a consultation phase explored the views of people living with impairing conditions and carers about the framework to identify missing content areas, with the framework further refined following their feedback.

Discussion
The INCLUDE Impaired Capacity to Consent Framework is intended to be used during early stages of trial design in order to inform funding applications and can be revisited during further development of the trial. It comprises two parts: four key questions to help researchers identify which groups of people with impairing conditions should be included in their trial, and worksheets to further explore these questions. The worksheets cover intervention design, eligibility criteria, recruitment and consent processes, data collection and analysis methods, and public involvement and dissemination activities. Researchers then summarise the actions that could improve the inclusivity of their trial, and any relevant resources needed, using the links to further information provided. A multi-media implementation toolkit is being developed to support researchers to use the framework, and to engage stakeholders including funders who will be key to ensuring uptake of the framework.

P-136

How inclusive were UK-based randomised controlled trials of COVID-19 vaccines? Results of a systematic review investigating enrolment of Black adults and adult ethnic minorities

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Introduction

Improving inclusivity in medical research, particularly clinical trials, has become a pressing issue over recent years. Initiatives such as the INCLUDE framework, established by the NIHR in 2017, were created to "help trial teams think carefully about which ethnic groups should be included in their trial" in order to make results representative and generalisable, and "what challenges there may be to making this possible". Whilst INCLUDE aims to improve inclusivity in clinical trials, it is also important to investigate recent practices and assess if more action needs to be taken.

Methods/Approach

The COVID-19 pandemic provided numerous challenges to the medical research community, including the rapid implementation of large, high-profile, UK-based vaccine trials. These studies created large, quickly reported sets of homogenous data, and therefore the opportunity to investigate inclusivity and how representative these trials were. A systematic review of published papers reporting randomised COVID-19 vaccine trials in the UK was conducted to investigate whether those randomised into COVID-19 trials were truly representative of the UK population.

Results

From an initial screening of 544 papers, data were extracted from 7 publications, covering 20,437 individuals randomised across 16 regions within the UK. The mean proportion of Black adults randomised was 0.59% (95% CI: 0.13%, 1.05%), representing a statistically significant disparity when compared to 2011 Census data (2.67%, $p < 0.001$). Mean adult ethnic minority presence as randomised was 8.94% (95% CI: 2.07%, 15.80%), significantly lower when compared to census data (16.30%, $p=0.039$). The results are consistent with past NIHR findings where a review of 1,509 participants found only 5.72% came from minority ethnicities. Reviewing inclusion/exclusion criteria found that 4 of 7 trial papers (57%) listed insufficient English language level as grounds for exclusion, whilst two trials (28%) focused exclusively on adults aged 50 and above, creating potential barriers for inclusive recruitment.

Discussion

Four of the trials included in the review referred to prioritising inclusivity within the protocol. This suggests trials that are attempting inclusive practices require additional guidance and support to recruit more representative samples of the UK population. Failing to do so will continue to make trial results less generalisable and may also exacerbate existing disparities in medical research for minority ethnicities. The review also allows for future work to be undertaken, primarily a re-review once all COVID-19 studies are complete and published. Research on other areas of inclusivity, including disability and poverty, should follow accordingly.

P-137

A scoping review to identify how people experiencing socioeconomic disadvantage are included in the development and evaluation of complex interventions for health.

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Introduction
In 2017, the NIHR INCLUDE project identified groups of underserved people that are underrepresented in randomised controlled trials. Underserved groups can vary across the types of studies, diseases/conditions, or interventions under investigation, but there are common barriers across trials, such as lack of trust, communication issues and the burden of the research, that all affect the inclusion of people experiencing socioeconomic disadvantage.
Complex interventions are interventions with a number of interacting parts, often involving communication between clinicians and patients. The additional communication and burden elements of such interventions may lead to further unnecessary exclusion of underserved groups and the individuals most in need of the intervention.
To understand the existing research around inclusion of underserved groups in the research around complex interventions, a mapping review would be helpful, but due to the numbers identified during scoping for a mapping review across several underserved groups, I am undertaking a scoping review focussing on socioeconomic status.

Methods/Approach
A scoping review will be undertaken to identify the research across the phases of complex intervention development where there is a focus on including people from low socioeconomic status groups. Search strategies have been developed using existing related systematic reviews, frameworks and guidance.
I will map the research focused on low socioeconomic status groups across the phases of complex intervention research: Development; Feasibility; Evaluation; and Implementation and detail the methods used in the research.
Further details will be extracted on the definition of socioeconomic status and how it is measured, the types of interventions, conditions and populations being studied, and any further information on how inclusion of people experiencing socioeconomic disadvantage has been achieved.

Timing of potential results
By the time of the conference, I will have the data to report the PRISMA for my final searches and details on where complex intervention research has focussed on socioeconomically disadvantaged groups.
I will be able to report the key themes around the definitions of socioeconomic status and report on how socioeconomic status is measured in research. I will report the methods used to develop and evaluate complex interventions in and for low socioeconomic status groups.
Potential Relevance & Impact:
The review findings may help researches to include people experiencing socioeconomic disadvantage in their research when developing and evaluating complex interventions. I have also identified a number of other reviews that could be done in this area.

P-138

ACCESS: A collaborative study between CTUs and researchers to identify the activities needed to improve representation of under-served groups in trials and understand their implementation

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Introduction
Participants in clinical trials rarely reflect the populations that could benefit from the findings. Barriers to trial involvement for underserved populations are well documented in the literature, but activities to overcome these barriers in the UK and Ireland are not well known. This study aims to identify the activities that are currently being implemented, or could be implemented, in the UK and Ireland to improve the representation of underserved groups in clinical trials.

Method
A scoping review was conducted to identify existing inclusive activities in clinical trials. The search was focused on minority ethnic groups, older people, those that lack capacity to consent and those from low socioeconomic backgrounds. Data were extracted on activities used to improve representation of these underserved groups and a list of activities was created.
Five roundtable discussions, comprising a mix of researchers, clinicians and PPI members representing different underserved groups added to this list of activities to improve recruitment of underserved groups.
Three trials were then chosen, covering different disease areas, care settings and interventions, to be theoretically redesigned to be more inclusive. Utilising the INCLUDE ethnicity framework, and two frameworks in development, the research team highlighted where the trial could be made more inclusive.
Roundtables comprising a mix of PPI, trialists and clinicians will discuss these suggestions alongside the list of activities developed and any additional suggestions to make the trials more inclusive.
Interviews with researchers experienced in trials will be conducted to explore the feasibility of implementing these activities and any potential barriers to their implementation.

Results, Structure and Timelines
Eight papers were included in the scoping review, which covered activities relevant to recruitment sites, recruitment settings, advertising, community engagement, bilingual staff, the consent process, widening the inclusion criteria, incentives, communication between study team and participants, flexibility, and patient documentation.
The roundtables highlighted several additional activities that largely fell under these categories, but additional themes such as tackling researcher biases, training for research staff and more diverse PPI contributors also emerged.
The three trial redesigns, and subsequent implementation interviews, will result in further activities, in addition to a more comprehensive understanding about what activities are feasible for study teams.

Potential Relevance and Impact
We will produce guidance that will help clinical trial units and researchers to design trials that are more accessible to underserved groups, and ultimately increase the representation of underrepresented groups in clinical trials leading to greater applicability of research.

P-139

Community outreach student initiative: targeting marginalised groups to help increase engagement to Covid-19 clinical trials

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Introduction
The North West of England has regularly reported high rates of Covid-19 in the country, with Bolton being one of its largest towns in England. It has a significant ethnically diverse population comprising of Black, Indian, Pakistani, and Bangladeshi communities – communities who have been disproportionately affected by Covid-19. It also has a university situated in the heart of the town.
Recruitment to clinical trials nationally is typically low among ethnic minority and underserved communities. Through an innovative student-led community outreach programme, our aim is to help marginalised groups to be better informed about, and even join, the PRINCIPLE and PANORAMIC trials in the search Covid-19 treatments.

Methods
The University of Bolton partnered with the trials' Inclusion and Diversity Lead to develop a 3-month student-led community outreach initiative. This involved empowering international students, from Nigeria, the Middle East, Europe and South Asia, to actively engage with the local communities in different languages to promote the trials.
Induction training sessions with the relevant information were provided to the volunteering students, who spoke more than ten languages collectively. They developed a suite of culturally sensitive resources about the trials using videos, leaflets and posters in different languages. These were promoted through social media, the University's website, and in places such as busy marketplaces, shopping malls, the North West Bolton Business Expo-2022, and University grounds themselves.
The students wore purposely-designed hoodies to promote the trials and to help identify them as trial ambassadors.

Results
The initial community outreach work with PRINCIPLE received positive feedback from the target audience indicating it was highly popular and informative. These measures, along with other outreach work, have enabled the trial to be representative in its recruitment of the South Asian diaspora, as reported in Lancet (2021).
The success of this initiative gained further approval to support recruitment for other trials, and for a second consecutive year a new cohort of students was recruited under a fresh 3-month initiative.
All costs for developing information leaflets and promotional materials, including the hoodies were provided by the University of Bolton.

Discussion
Recruitment to clinical trials needs to be more inclusive and better representative of our diverse population. Effective and more targeted strategies with dedicated investment are vital. Utilising students in university towns and cities located in areas of high deprivation and densely populated ethnic minority communities, are one way forward in improving recruitment of underserved communities to clinical trials.

P-140

Ethnic minority clinical trial participation: A narrative review of the barriers to recruitment

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Introduction
Adequate participant recruitment is critical for the delivery of clinical trials however a substantial number of trials fail to meet their recruitment targets. Inadequate recruitment can lead to extended study duration, greater resource usage and findings that are not as statistically viable. Racial and ethnic minorities have historically been underrepresented in clinical trials making it challenging to apply research outputs to the wider population. Despite efforts to try and address the barriers to the recruitment of ethnic minority populations, challenges still persist. This review will discuss the barriers to recruitment of ethnic minority patients in the clinical trials and potential strategies to improve participation.

Methods
A narrative review of both primary and secondary literature (including expert reviews) using the following keywords: barriers, trial recruitment, ethnic minority, research participation, clinical research and clinical trials. A multilevel model was used to categorise the barriers into system (healthcare and hospital infrastructures) and interpersonal (persons directly involved). Potential strategies to address the barriers were also discussed.

Timing of Potential Results and Potential Relevance & Impact
Interim analysis of 30 studies showed there are multilevel factors affecting clinical trial recruitment of ethnic minority groups. The main barriers to recruitment are mistrust, a lack of public understanding/education surrounding clinical trials, economic barriers and the opportunity to participate (ethnic minorities not being asked). Of the 30 findings; 14 were derived from primary research, 7 were derived from secondary research (reviews), and 9 articles were expert reviews.
Several studies with black ethnic minority participants make reference to the Tuskegee Syphilis Study conducted from the 1930s to the 1970s. The study initially involved 600 Black men – 399 with syphilis, 201 who did not have the disease. Participants' informed consent was not collected. The study played a huge role in spreading mistrust. The impact on black ethnic attitudes toward the medical establishment are believed to be substantial.
The COVID19 pandemic shone a light on the issues regarding the vaccines and the considerable concerns regarding conspiracies around the virus in my community (Afro Caribbean).
This review will provide a comprehensive summary of the barriers to ethnic minority recruitment with a focus on mistrust. Understanding the barriers will help to create targeted strategies to ensure inclusion and diversity within clinical trials.

P-141

Routine Data in Clinical Trials – the GBS3 Trial data flow model

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Introduction
The GBS3 Trial (ISRCTN49639731) assesses whether universal testing of pregnant women for Group B Streptococcus colonisation reduces early-onset neonatal sepsis, compared to the current UK risk-factor based strategy. Approximately 320,000 pregnant women from 80 maternity units in England, Scotland and Wales are needed for this cluster randomised trial. The testing policy becomes the standard of care for the duration of the trial and written informed consent for participation is not sought, to avoid selection bias. Data is not collected manually, due to the burden on clinical staff and the high costs it would incur. To our knowledge, routinely collected health data (RCHD) has not been used in perinatal clinical trials to the extent it will be in GBS3.

Methods
GBS3 has obtained the relevant approvals to use RCHD without consent. To both define the trial population and obtain the primary and secondary outcomes, we are requesting maternity datasets from NHS Digital (England), and the Scottish and Welsh equivalents, microbiology data from the three national public laboratory sources and neonatal datasets from two national dataset providers and one electronic health record system provider. Mother and baby data can be linked via NHS number (CHI number in Scotland), date of birth and postcode.
Data provider security requirements create a two-step process to limit the release of personal identifiable information. The trial population is defined from maternity datasets through participating hospitals codes where women gave birth within the trial time window. Their babies are then identified by linkage and their identifiers used to request data from the microbiology and neonatal datasets.
All data is directly sent by each data provider to a Trusted Research Environment where is safely stored and remotely processed, linked and analysed by designated analysts.

Timing of Potential Results
The first data downloads and linkage will be undertaken in autumn 2022 and the success of the linkage will be assessed. Results from GBS3 are expected by August 2024.

Potential Relevance and Impact
The GBS3 data flow model is used to overcome some of the limitations of the traditional individual and manual approach, enabling a large study at lower cost. NHS data-opt out, approximately 7% in our population, is a limitation of this method. Our approach, which is becoming increasingly popular in the clinical trial community, has the potential to inform future trials on the strengths and limitations of perinatal RCHD use in clinical trials.

P-142

A data linkage and pseudonymisation tool to facilitate the efficient use of electronic health record data in clinical trials

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Introduction
To maximise patient participation, reduce selection bias, and increase efficiency, researchers are increasingly asking sites to provide Electronic Health Record (EHR) data as part of the trial dataset, including in a de-identified format for eligible patients who are not approached to provide informed consent. However, there is huge variability in NHS staff time and skills in extracting, processing, and providing this data to researchers.
The ability to easily link datasets, matching EHR data with trial-specific data such as patient-reported outcome measures, is crucial to data analysis and presents a technical challenge for trialists.

Methods/Approach
We have developed a secure and efficient data linkage and pseudonymisation tool (DLPT), which is being tested and refined in a large host trial; a three-year stepped-wedge cluster-RCT.
The template DLPT can be adapted to process data from any source which is able to export data to a spreadsheet, e.g. hospitals, GP practices, social care settings, and schools. It is generalizable across disease areas and trial designs.
The DLPT is used by trial site staff to process, link and de-identify data at source, and produces a .csv file for direct upload into a trial database.
In our approach, trial data is held in a single, purpose-built database, and can be analysed and archived as a single package. Thus, the host trial benefits from consistent data management (e.g. quality checks, access/export permissions). Patient data no longer needs to be sent by email or shared via online storage. Record matching is automated for increased accuracy and efficiency. Compared to previous processes, this represents a significant reduction in burden on CTU and NHS staff.

Results Structure and Timelines
The project is due to be completed by the 30th of June 2022. After this date, the template DLPT, manuals and a template data flow diagram will be made available to other researchers to enable wider implementation of this methodology via the Norwich CTU website.

Potential Relevance and Impact
Developing methodology to permit the automated linkage of multiple complex datasets, including EHR and patient-reported outcome measures, has potential cost and time benefits to care providers, researchers and funders. Furthermore, it is anticipated that the process will facilitate easy integration of under-utilised datasets into trials, overcoming barriers to research questions that have previously been difficult to answer, and leading to better value for money in future trials.

Funding
NIHR CTU funding call 2020: “Supporting efficient / innovative delivery of NIHR research”

P-143

Assessing the accuracy of routine data sources for identifying operation type in cardiac surgery patients

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Introduction
The Outcome Monitoring After Cardiac Surgery (OMACS) study is an observational study of patients undergoing cardiac surgery at Bristol Heart Institute (BHI). Routine data sources are utilised where possible to minimise manual data collection, including identification of operation type. In the OMACS study we access two routine databases:
i) Patient Administration and Tracing System (PATS) - validated data collected by clinicians for reporting to the national cardiac surgery audit.
ii) Patient History Database (PHD) - OPCS procedures codes collected by trained coders for financial reconciliations and feeding into Hospital Episode Statistics (HES).
The aim of this study is to assess the accuracy of these databases for identifying operation type in cardiac surgery patients.

Methods
OPCS codes from PHD and operation type from PATS were collated for all OMACS patients who underwent cardiac surgery in 2020.
The total number of patients identified as undergoing Coronary Artery Bypass Graft (CABG), Aortic Valve Replacement/Repair (AVR) or Mitral Valve Replacement/Repair (MVR) in the two databases was compared. Where discrepancies in procedure type are identified, the medical notes will be checked to establish which routine database is accurate.

Results
In total, 536 patients consented to OMACS and had surgery during 2020. Of these, 493(92.0%) had data available in PHD and PATS. Twenty (3.7%) had data in PATS only, 17(3.2%) in PHD only. Six patients (1.1%) were not identified in either database. Of the patients with operation data in both datasets, operation type (CABG, AVR or MVR) was reported consistently for 465/493 patients (94.3%), including patients undergoing multiple procedures. The operation type in PATS and OPCS codes in PHD did not match for 28 patients (5.7%).
Medical records are being checked for discrepancies to confirm the procedure performed.

Potential Relevance and Impact
Correct identification of operation type is key in surgical trials. This work shows that whilst operation type was recorded consistently across 94.3% of patients, use of routine data to identify operation type may not always be reliable. This study looked at the most common cardiac procedures, assessing broad categories of operation type. More detailed data such as incision mode or number of grafts may be less reliable.
We suggest risk assessing the use of routine data during the planning stage of a study and involving clinical staff/ teams who are responsible for reporting clinical data in these discussions. We advise using multiple sources to enable a validation procedure, such as described here.

P-144

The use of routinely collected health data as primary outcome in a decentralised RCT: the HEAL-COVID experience

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Introduction
HEAL-COVID is an adaptive randomised controlled trial aiming to identify treatments that may be beneficial for people discharged from hospital after recovering from COVID-19. To reduce the burden on sites that were already overwhelmed during the pandemic, we collected the primary outcome (mortality or hospital readmission) using routinely collected health data (RCHD) from across the four UK nations. Requesting, receiving and analysing data from the four sources was not without its challenges.

Methods
Applications were submitted to NHS Digital, NHS Scotland and SAIL and a separate arrangement was made with Northern Ireland where no equivalent data provider exists. Once agreements were in place, participant randomisation numbers, health record numbers, DOBs, randomisation and end of participation dates are securely uploaded to web systems or sent securely to data providers via email.
The requests are then used to extract RCHD for participants and then transferred to Liverpool Clinical Trials Centre where it is linked with the minimal data provided by participating sites. The process is repeated monthly and data are used for monitoring and reports to oversight committees.

Results
Obtaining approvals for data access from each provider was an iterative process and timelines extended beyond those anticipated. Each nation had their own requirements for uploading identifiers to request data. This led to unanticipated increases in workload. However, this was reduced for subsequent requests due to ongoing support from data providers. Prompt communication was essential in working towards solutions. For analysis, RCHD from all nations was combined, leading to more challenges, such as handling variations in data formatting and using different fields to define the relevant outcomes.

Discussion
The aim of using RCHD to reduce site and participant burden was achieved, as site staff did not have to complete case report forms or address potential queries. However, there was a substantial increase in workload for the statistical team who prepare the data requests and analyses. Use of RCHD as a primary outcome in a trial of a medicinal product is possible, however careful consideration needs to go into the planning for the lone use of this data for monitoring safety, especially for drugs that have a less well known safety profile.
Expertise regarding data linkage within the trial management group is essential when using RCHD. Close collaboration between RCHD providers and research teams requesting data, as well as ability to deploy additional resources is needed to deliver a manageable process over time.

P-145

Assessing the suitability of death records from routine sources: a study within a trial

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Reassurance on the utility of healthcare datasets is needed before they can replace trial-specific data collection. This can be assessed in trials that have collected data in both ways. NHS Digital collates national data for patients in England. The 'Civil Registration – Deaths' is a person-level dataset representing death registrations. SWAT125 was designed to support trialists in comparing the completeness, agreement, and timeliness of death data between the two sources. We apply this SWAT to trial-collected and healthcare systems datasets for 2 clinical trials.

This is a SWAT comparison of routinely-collected and trial-collected death data in participants enrolled in the STAMPEDE trial (ISRCTN78818544). STAMPEDE is a large, international, multicentre, randomised controlled trial in prostate cancer. We use trial and routinely-collected healthcare data from the second added comparison ("M1|RT comparison") in this multi-arm multi-stage platform trial, where 2061 eligible patients were enrolled. The primary outcome for the SWAT is the completeness and agreement of the data from the two sources. Completeness is assessed by summarising the number of deaths, current survivors and, where necessary, patients with indeterminate status. Agreement of death reporting is calculated using kappa statistics. Where a death is reported in both sources, data values in each source will be compared in respect to the date of death and the cause of death; we will then consider the potential impact of discrepancies on the trial's analysis. Maturity of follow-up is assessed by calculating median follow-up in the two data sources, using the reverse Kaplan-Meier method.

Work is currently ongoing. Results from the STAMPEDE analysis will be available for the ICTMC conference in October 2022. Work on a second large trial in prostate cancer may also be available.

The processes and efforts in accessing healthcare datasets to enhance clinical trials are reported to be improving with funders encouraging use. However, suitability of such data has not been carefully evaluated. This project contributes to the accumulating evidence base to determine where collection of data through routine sources is sufficient. If national death data is shown to have sufficient utility, then death data collection in these trials can be replaced by routine healthcare systems data.

P-146

VIRTUAL CLINICAL OUTCOME ASCERTAINMENT IN A PROSTATE CANCER TREATMENT TRIAL

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Introduction
The ProtecT randomised trial (Prostate cancer testing and treatment trial) compares active monitoring, radiotherapy and surgery for localised disease. The primary outcome is prostate cancer mortality and second secondary clinical outcomes of disease progression and metastasis. The primary outcome at 10 years was comparable between groups so follow-up was extended to a median of 15 years (November 2020). The COVID-19 pandemic stopped site visits so we developed several virtual methods and assessed their relative effectiveness.

Methods
Previously, research nurses at 9 hospitals completed annual paper Case Report Forms (CRFs). In the 15-year follow-up, NHS routine data were to be used to target site visits by a central research nurse using a REDCap eCRF. In March 2020 a shorter 2-page eCRF of essential outcome data was created and site PIs agreed to help collect data in July 2020.

Results
Approvals were gained by December 2020 for a protocol amendment, updated study end date and GDPR terms in site agreements which delayed the research nurse renewing their NHS Research Passport to access sites. Staff at four sites completed eCRFs supported by the trial data manager and research nurse through training, emails and virtual calls. At three sites the research nurse gained remote access to hospital electronic health records (EHR) by April 2021 after extensive governance approvals, IT training and EHR software on multiple laptops. At two sites, site staff interrogated their EHRs during virtual calls (planned around clinical commitments) while trial staff completed the eCRFs. An average of 15 reviews were completed during a 2-hour call.
Secondary clinical outcomes were obtained for 97.5% of participants (1435/1474). All methods gave comparable completion rates: 95.8% for site staff (575/600 participants) although data cleaning took longer and eCRFs were less complete; 98.8% for remote EHR access (594/601); and 97.3% for virtual calls (215/221) which reduced data cleaning as some queries were resolved immediately although calls were sometimes outside office hours. Other benefits included travel and accommodation savings, lowered carbon footprint, and that site staff could obtain information outside their hospital EHR.

Discussion
Three remote clinical outcome capture methods were successful after site visits ceased due to the COVID-19 pandemic although they had different benefits and challenges. However, enabling remote data capture delayed analysis by 6 months.

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P-147

Evaluation of tracking methods in web-based interventions

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Introduction
Trial participants' use of a web-based intervention can be recorded and monitored, providing an immediate indication of the degree to which each participant used their assigned intervention. Accurate information on usage is crucial to determine how usage impacts on participants' outcomes. Trial participants can navigate on an intervention website performing different interactions such as viewing modules or videos, completing tasks, downloading documents or accessing subpages. Usage data are most objectively tracked by web analytics tracking methods. A recent systematic review showed that there is an increasing trend in the use of web-based interventions in trials, but although the majority of trials reported collecting details on usage, more than half did not state the tracking method used.

Methods
Results from a systematic review, a mixed methods study (TRACK study) and a focus group study are combined to present an overview of the most popular tracking methods used in trials. A data simulation project investigated availability and reliability from these methods.

Results
Results from the systematic review and qualitative studies suggest that the most popular tracking methods in trials are Google Analytics, Open Web Analytics, Matomo, Amplitude and server logs; these methods can be implemented and configured, raw data extracted and data stored for unlimited time but technical knowledge is required. Trialists from the TRACK study noted multiple advantages of these methods such as being free to use, level of details, automated tracking, friendly dashboard, easy access to reports, unlimited data storage, ability to track participants without influencing them and availability of additional features. Disadvantages included the need for technical knowledge for configuration and use, difficulties with extracting and understanding the data, data linkage and, for server logs especially, unstructured and hard to handle data. All tracking methods are compliant with General Data Protection and Regulations except for Google Analytics. Methods are free to use and paid versions are available for some. The data simulation project demonstrates that tracking methods can generally be configured to uniquely identify users, except for Open Web Analytics, and the usage metrics obtained using these methods are reliable and accurate.

Discussion
Tracking methods can be successfully used for free in the context of web-based intervention trials to provide reliable and accurate usage data, but technical knowledge is required for their configuration and use. The results from this evaluation will benefit trialists by providing insight about which tracking method would be most suitable for their trial purposes.

P-148

A paperless approach to clinical trial systems: from specification to validation, and beyond

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Introduction
Over the past decade, it has been widely accepted that a paperless approach to certain aspects of clinical trials can increase quality, efficiency and, in many cases, reduce risk. Handling large amounts of clinical trial data on paper can become very expensive, difficult to maintain, and has been linked to a higher rate of data errors and omissions.
Tangible improvements can be made to studies when they are designed with modern technology in mind. For example, participant diversity and inclusion can be increased or the time and money spent on the collection, management, and validation of clinical trial data reduced.
Computer system validation (CSV) is the documentation and proof that a process, service, or product yields an expected result. It is an important part of the development and testing of computer systems within clinical trials and applies not only to specialist eSystem vendors, but also to Clinical Trials Units (CTUs).
Can a paperless approach to CSV further improve both quality and efficiency, while also satisfying the regulatory requirement to be always 'inspection ready'?

Methods/Approach
When designing clinical trial management and data capture systems there can be an immense resource overhead. A user requirement specification is created from a protocol, which is then developed into a computer system. However, before any computer system can be implemented for use in a clinical trial, an appropriate level of CSV is required. CSV ensures all systems meet the approved specification, adhere to the CTU's standard operating procedures and good clinical practice (GCP), ultimately producing reliable data.
We provide a case study of a randomised control trial (non-regulated) where bespoke clinical trial management software is integrated with a third-party electronic data capture solution, REDCap Cloud. We discuss the application and implementation of the procedures put in place to minimise paper sign-off on specification, testing and validation documents. We consider the ability of version control software, cloud computing environments and automated build/deployment pipelines to aid in meeting regulatory GCP guidelines.

Discussion
By replacing historically paper-centric tasks in our CSV processes we have seen a visible improvement in the efficiency of system development. We have strengthened the traceability of task execution and have a higher degree of confidence in the approval steps required across a system's development. The remaining challenge we face is to ensure regulatory inspectors have a means of accessing electronic records at inspection, either via designated user accounts or tailored reports.

P-149

Electronic recruitment and consent in a multi-centre randomised clinical trial in an orthopaedic trauma setting

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Introduction
The Covid pandemic led to the introduction or faster adoption of new ways of working. Recruiting patients to a clinical study without face-to-face contact could reduce unnecessary travel, save clinic and patient time, and lower infection risk. Within a trauma or emergency setting, when limited time is available for the identification of eligible patients and the consent process, an in-clinic setting for recruitment is often favoured. To date few trials, where prospective patient consent needs to be obtained in a more acute situation, have attempted to recruit without the patient and researcher sharing a location.

Aims
To enhance recruitment with an entirely remote recruitment function.

Setting
The FAME trial, investigating different treatment options for people with a broken ankle, opened in December 2019. Throughout the Covid pandemic, patients with an unstable ankle fracture continued to attend Emergency Departments, where new patient pathways often reduced researcher contact to a minimum.

Methods
In response to requests from sites, a bespoke “virtual consent” function allowed research staff to remotely screen patients and consent them and allowed the participant to enter baseline data in a home setting whilst being guided by research staff. The virtual consent function was linked seamlessly to REDCap, FAME’s clinical database and the randomisation system, RRAMP. Neither patient nor researcher was required to be present in the hospital. Both required a phone and internet browser access, ideally different devices. The central research team at the University of Oxford provided a simple flowchart and site training through remote meetings.

Results
Since the virtual consent function was introduced to the FAME trial, 454 participants have been randomised, 29 (6%) using virtual consent, across 9 of the 23 recruiting sites.

Discussion
Feedback from sites indicates that the virtual consent function is popular. Self-isolating researchers can continue to work; patients can be randomised at home following virtual fracture clinics. While research resources were and continue to be under pressure, patients have been randomised who would otherwise have been missed. We recommend that the option of an entirely remote recruitment function is considered as standard for other trials.

P-150

An interview study within a clinical trial that used healthcare technologies for children with asthma – insights and implications

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Background
Healthcare technologies are becoming more commonplace, however clinical and patient perspectives regarding the use of technology in the management of childhood asthma have received little attention. Within a clinical trial of asthma management in children, we conducted a qualitative study designed to examine the experiences and perspectives of healthcare staff and families on (i) the use of smart inhalers to monitor medication adherence and (ii) the use of algorithm generated treatment recommendations.
Methods: We interviewed trial staff (n = 15) and families (n = 6) who were involved in the trial to gauge perspectives around the use of smart inhalers to monitor adherence and the algorithm to guide clinical decision making.

Findings
Staff and families indicated that there were technical issues associated with the smart inhalers. While staff suggested that the smart inhalers were good for monitoring adherence and enabling communication regarding medication use, parents and children indicated that smart inhaler use increased motivation to adhere to medication and provided the patient (child) with a sense of responsibility for the management of their asthma.
Staff were open-minded about the use of the algorithm to guide treatment recommendations, but some were not familiar with its' use in clinical care. There were some concerns expressed regarding treatment step-down decisions generated by the algorithm, and some staff highlighted the importance of using clinical judgement. Families perceived the algorithm to be a useful technology, but indicated that they felt comforted by the clinicians' own judgements.

Conclusion
The use of technology and individual level data within appointments was considered useful to both staff and families: closer monitoring and the educational impacts were especially highlighted. Utilising an algorithm was broadly acceptable, with caveats around clinicians using the recommendations as a guide only and wariness around extreme changes in treatment considering contextual factors not taken into account.

P-151

Designing a Single Online Screening and eConsenting System to Maximise Recruitment for Three Concurrent Randomised Controlled Trials of Complex Interventions for Improving Student Mental Health

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The aim of the NURTURE-U study is to develop and evaluate an acceptable, effective, cohesive system of whole-university and stepped care student wellbeing and mental health support. This study comprises three concurrent randomised controlled trials (RCTs) which will evaluate different approaches of support. Participants will be allocated to a trial based on their screening assessment. Screening, consenting and data collection is to be conducted online in the form of surveys. A key requirement of the solution is participants' user experience of the enrolment process (screening and consenting). The participants' journey, from screening to baseline completion, should be perceived as a single survey whilst accommodating segregation of trial data. A system or integrated systems to facilitate this had to be developed.

The defined process allows individuals to enter the screening survey, consent and complete screening before being, automatically, evaluated for trial eligibility. There are four possible outcomes from the study screening. If an individual consents to participate in a trial, they then continue to complete the baseline survey for their allocated trial.

REDCap Academic (RCA) was selected as the solution system, due to its versatility as an EDC system with survey capabilities and extensive API. Desired features include RCA's ability to prepopulate (pipe) data from one survey to another, allowing participants to be seamlessly transferred into an alternative project within RCA whilst completing a survey.

Four RCA validated projects were created: one screening and one for each of the three trials. Once participants complete enrolment for a trial, they are automatically transferred to the trial's baseline survey without any break in survey flow. This transfer includes piped data, such as screening ID, linking the screening record to the trial record.

User Acceptance Testing by the study team and students will conclude in August 2022, providing feedback on student engagement of the system design and user experience, prior to deployment in Autumn 2022.

A single, unified, online screening and consenting system to determine eligibility against multiple trials is an efficient trial enrolment solution. By negating the need for potential participants to complete multiple screening surveys for different concurrent trials, it is anticipated that the system will aid recruitment, as well as reducing burden on both potential participants and trial teams.

P-152

The Rubik's Cube™ of Information Systems in Clinical Trials: The importance of the IS function in the successful development and delivery of clinical trials

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Information Systems (IS) in Clinical Trials Units (CTUs) includes activities undertaken by IT and Data Management (DM) teams. Despite the importance of these activities, IT and DM teams are often not involved in important decisions about trial methodology. In 2019, the UKCRC CTU Network IS Operations Group (ISOG) sent out a survey to all 53 UKCRC-registered CTUs, asking what services were provided by CTU IS teams. One of the questions was "At what stage in the grant application process is the IT/IS function commonly asked to provide input?". Less than half (12; 46%) of the 26 CTUs answering this question replied "Very early stages".

Furthermore, Higher Education Institutions (HEIs)/CTU host IT departments are frequently unaware of the regulatory and compliance requirements burden in clinical trials. Trying to demonstrate the need for inclusion and investment needed for IS can be difficult. For example, metrics HEIs tend to focus on, such as grant income, citations of research papers/outputs and the Research Excellence Framework (REF), do not directly translate to metrics that can be provided by CTU IS teams.

In 2021, the UKCRC ISOG set up a working group to look at the perceptions of IS in clinical trials, exploring ways to support IS teams and help communicate the value IS teams provide.

It was quickly apparent to the working group that attempting to present the full range of IS activities in a sequential way would not adequately describe the complexity and interconnectivity of the various factors. The process was likened to 'solving a Rubik's Cube' with different elements each needing to be moved into the correct place and every element effecting the pieces around it. Common IS activities were identified during several brainstorming sessions and then grouped into six broad categories: Regulation, Trial Design, Collaboration, Data, Software Development and Infrastructure.

These categories were agreed by the ISOG group and the initial outputs of a "Rubik's Cube of IS in Clinical Trials" poster and corresponding slides were provided to UKCRC-registered CTUs for onward dissemination.

Additional opportunities and resources are being explored to support CTU IS teams with the aim of improved understanding of the IS teams' roles in the design and delivery of clinical trials. In the longer-term, this should increase the quality, and efficiency, of clinical trials.

P-153

Reuse, Reduce, Recycle – A case study in digitising the complex world of clinical trials at UCL

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Introduction
UCL's vision is to maximise the efficiency of digital platforms by centralising management and "doing things once". Thereby increasing efficiency, reducing risk and ensuring best practice.
Across the diverse portfolio of clinical trials, UCL will; reuse digital systems and processes across multiple units, reduce the use of legacy, duplicate or bespoke systems and recycle existing platforms at UCL. Initially covering electronic data capture (eDC), training and electronic trial master file (eTMF) management.
The challenges are; ensuring a single set of platforms can work cross UCL, agreeing support structures, inconsistent funding models and finding the right skills to support the initiative.

Approach
ISD created an Agile clinical trials product team with access to funding providing centralised IT resources to clinical trials.
The team created; appropriate governance structures to mitigate organisational and regulatory risks, an Agile product definition ensuring UCL trials needs are met by the software systems and operational support, ensuring systems can be used and managed effectively.
The product team analysed new and existing platforms available at UCL and the priorities across the units. Using Agile methodologies, priorities were converted into quarterly objectives and sprints to deliver value quickly.

Results
Reuse: Since mid-2021, the product team has created two central IT services for the eDC and eTMF systems. Onboarding, training, licensing, supplier management and support are now delivered from a single team to three trials units.
Reduce: Allow the deprecation of existing clinical data management systems and enable a move to Software as a Service platforms, approximately cost neutral through license savings elsewhere.
Recycle: Remedy Force (A service desk tool) is used to manage user onboarding and delegation logs and Moodle (An online learning platform) delivers system training.

Discussion
The units are keen to utilise these central resources, benefitting from the efficiencies in governance, operations and funding, but we recognised that any form of centralisation can cause anxiety within teams running their own services.
Communication and understanding the work of trials units has been key to overcoming any barriers. While the product team sits in ISD it is led by a manager with extensive experience of clinical trials. Consequently, there has been a notable increase in collaboration, as sharing platforms necessitates communication across departmental silos.
Following the implementation of eDC and eTMF, UCL is investing in a quality management platform, assessing DocuSign (eSignature tool) for eConsent and JIRA (Issue and project tracking) for database release and change management.

P-154

Automated Check-in Data Collection (AC DC): the use of check-in screens for research in general practice

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Introduction
Choosing the optimal way to collect research data is a predicament faced by many researchers. The automated check-in screen is a cost-effective solution which frees up receptionist time for other more complex tasks in general practice. We investigated the possibility of re-purposing the function of the automated check-in screen, for use as an efficient research data collection tool and a way of providing patients with the ability to take control of their choices.

Method
A cross-sectional study was undertaken in nine general practices within NIHR Clinical Research Network (CRN) West Midlands (WM). All registered patients aged 18 years and over, self-completing an automated check-in screen prior to their general practice consultation, during a three-week recruitment period, were eligible to participate. Once a patient had confirmed their attendance for a booked appointment using the touch screen, two research questions appeared for completion.
Any check-in queries made to practice administration staff by patients as a result of the study, were anonymously logged in a study diary, to assess the impact of check-in completion on general practice operationalisation and workload.

Results
Almost 90% (n=9,274) of patients self-completing an automated check in screen participated in the Automated Check-in Data Collection (AC DC) study (61.0% female, mean age 55.1 years (18-98 years, SD=18.5)). 96.2% (n=8,922) of participants answered a 'clinical' research question, reporting the degree of bodily pain experienced during the past 4 weeks (32.9% experienced no pain, 28.1% very mild or mild pain, 39.0% moderate, severe or very severe pain). 89.3% (n=8,285) of participants answered a 'non-clinical' research question, on willingness to be contacted about future research studies. 46.9% (n=3,889) of participants responded, "Yes, I'd be happy for you to contact me about research of relevance to me". The general practice operational disruption caused as a result of the AC DC Study was considered, negligible.

Discussion
Using automated check-in facilities to integrate research into routine general practice, is an efficient and effective way to collect brief research data from patients. The method could also be used for pre-screening potential participants, for later invitation to a research study. With the COVID-19 pandemic initiating an extensive digital transformation in society, now is an ideal time to build on these opportunities and investigate alternative, innovative ways to collect research data.

P-155

Implementing a social media recruitment strategy: lessons learnt in the Eczema Monitoring Online randomised controlled trial

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Introduction
Participant recruitment is critical for the success of randomised controlled trials (RCTs), but remains challenging. Given the growing number of internet users worldwide, social media is becoming increasingly popular for recruitment. The global coronavirus (COVID-19) pandemic has accelerated the use of social media as a modality of recruitment for RCTs, when traditional recruitment methods were reduced. We describe our effective social media recruitment strategy for the Eczema Monitoring Online (EMO) RCT, which evaluates the effect of regular patient-reported symptom monitoring on eczema severity.

Methods
Over a four-month period, participants were recruited into the EMO trial (ISRCTN45167024) via free advertising on Twitter, Facebook, Instagram and Reddit (unpaid methods), followed by paid Facebook advertisements (paid method). Some participants also joined the trial by word of mouth and internet searching. Unpaid methods were used intermittently for 63 days, while the paid method for 16 days. Potential participants who clicked on the study advertisement link were directed to the study website, where they could sign up to participate. Consenting, randomisation and data collection occurred exclusively online, using the Research Electorinic Data Capture (REDCap), a secure database management web platform. The number of expressions of interest, enrolment yield, recruitment cost, baseline characteristics and retention related to the social media methods were assessed.

Results
This multi-platform based recruitment strategy resulted in 400 expressions of interests, leading to 296 participants. Unpaid methods accounted for 136 (45.9%) participants, incurring no direct financial cost. Paid Facebook advertisements reached 129,757 individuals, resulting in 123 (41.6%) participants for a total cost of £259.93 (£2.11 per participant) and other methods resulted in 37 (12.5%) enrolments. Paid adverts predominantly attracted younger participants below the age of 20, whereas unpaid methods mainly drew in participants between 20-29 years of age. The social media platforms recruited an ethnically diverse participant population. Weekends and evenings generated increased traffic for the adverts, which enhanced recruitment. Completion rate of follow-up was nearly identical for participants recruited from the unpaid methods (81.8%), compared with the paid method (81.9%).

Discussion
Unpaid social media posts were the most effective in recruiting participants, however it was time consuming for the researcher. Paid Facebook adverts rapidly recruited a high number of participants for a low cost and provided flexibility to target specific audiences. Our findings indicate that social media is an efficient and cost-effective tool that can support recruitment to clinical trials.

P-156

Utilising high-dimensional data in randomised clinical trials

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Introduction
Randomised controlled trials are the gold standard for assessing the effectiveness of an experimental treatment. However, the probability of success of clinical trials remains relatively low. With recent advances in the high-technology sector, there is a rapidly growing amount of human molecular biomarkers that could be used to inform drug mechanisms and lead to increased success of clinical trials.

Methods
We conducted a review of recently published randomised clinical trials that utilise high-dimensional genetic data. The review included articles that were published between 2019 and 2021, through the PubMed database. We summarised the clinical area, the type of high-dimensional data, the number of covariates used, number of treatment arms, and the purpose of collecting high-dimensional data.
We also will provide an overview of available methods for utilising high-dimensional data in clinical trials, such as univariable and multivariable approaches, penalised approaches, machine learning, clustering methods, principal component analysis and adaptive signature design. We will discuss the use of these methods in clinical trials.

Results
Out of 174 screened articles, 101 (58%) were randomised clinical trials that collected high-dimensional data and were therefore included in the review. The most common clinical areas were oncology (29.7%), followed by chronic diseases (27.7%), nutrition and ageing (17.8%) and cardiovascular diseases (6.9%). Most of the trials analysed gene expression data (69.3%) followed by DNA data (20.8%). A few articles analysed proteomics, metabolomics, and multiple types of (omics) data. The most common method of analysis (44.6%) was univariable analysis (one covariate at a time). Articles that describe multivariable analysis used relatively straightforward standard statistical methods. Most of the clinical trials were two-arm trials. The purpose of collecting genetic data varied from being primary and secondary outcomes to exploratory analysis to investigating biological pathways.

Discussion
Utilising high-dimensional data in clinical trials can improve efficiency and increase patient benefit. New methodological approaches are required for more efficient analysis of the increasing amount of high-dimensional data collected in randomised clinical trials. We highlight the limitations and barriers for the use of high-dimensional data in trials, suggest potential avenues for improvement and discuss future perspectives.

P-157

The impact of Covid-19 on recruiting men to the Game of Stones weight management trial: feasibility and full trial differences.

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Introduction
Men living in disadvantaged areas are more likely to experience poor health outcomes and obesity related co-morbidities, and are less likely to engage in weight loss interventions than either women or men living in advantaged areas. Game of Stones is a 3-arm parallel group RCT recruiting in England, Northern Ireland and Scotland, comparing text messages with and without endowment incentives with a 12-month waiting list control group, to address weight management in men. Recruitment strategies and processes planned to mirror those of the successful feasibility study conducted in two centres in Scotland in 2017 [1]. However, Covid-related protocol changes were required, providing a unique opportunity to contrast recruitment processes and participant demographics between the feasibility study and the full trial.

Methods
Recruitment of men aged 18+years with a BMI ≥30 was planned via two strategies: community (posters, leaflets, information stands) and GP opt-in referral letters. For exploratory subgroup analysis purposes, the aim was to recruit similar numbers via community and GP strategies and 50% from more disadvantaged areas (Index of Multiple Deprivation 1-2). However, pandemic-related adaptations to the successful feasibility study recruitment processes were required including: covid screening and safety measures, website sign-up, poster QR codes to replace leaflet distribution, and social media advertising to compensate for reduced footfall at community recruitment venues during periods of Covid-19 restrictions.
Participant demographics, co-morbidities, and recruitment targets, were compared descriptively with the feasibility study.

Results
Recruitment for the full trial across the three UK countries was completed in May 2022. Approval for GP recruitment referral letters was not granted in Northern Ireland due to pandemic pressures. Comparing full trial (n=585) vs feasibility study (n=105): recruitment period: 10.5m vs 3.5m; mean recruitment rate: 19 vs 15 participants per site per month; community recruitment: 63% vs 57%; GP recruitment 37% vs 43%; proportion living in disadvantaged areas: 36% vs 60%.
Co-morbidities, age, and education differences between the full trial and feasibility study participants will be presented.

Potential relevance and impact
The changes made to recruitment processes due to the Covid-19 pandemic led to more participants being recruited by community strategies than planned, resulting in fewer men living in disadvantaged areas enrolling on Game of Stones. Given the disproportionately negative outcomes of Covid-19 for people living with obesity, the implications of adapting recruitment processes and the role of primary care in engaging men in research will be discussed.

1. https://doi.org/10.1186/s12874-020-01136-2

P-158

Where have all the patients gone? What the Screened, Eligible, Approached and Randomised framework tells us about why patients are lost to trial recruitment.

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Background
Current CONSORT requirements include reporting numbers of patients screened and recruited to a trial, but not those 'lost' during screening. The SEAR (Screened, Eligible, Approached, Randomised) framework [Wilson et al. 2018] developed through application of the QuinteT Recruitment Intervention, tracks how patients progress on the recruitment pathway. It identifies points and reasons for loss to recruitment, reporting proportions of potential participants who are screened, identified as eligible, invited to participate and join the trial, with reasons for leaving the pathway at each stage. Once points at which patients are lost are identified, targeted actions can be tailored to the individual trial.
This study investigates how the SEAR framework was applied across 5 contrasting trials, reporting insights this delivered to benefit recruitment.

Methods
Five trials, purposively sampled to include an integrated QuinteT Recruitment Intervention (designed to optimise recruitment and informed consent) and a range of surgical/non-surgical interventions/comparators across a range of specialties (nephrology, breast cancer, head and neck surgery) were included in this investigation. Numbers and proportions of patients screened, eligible, approached for a discussion about the trial and randomised were collected for the whole trial and by trial site. Within- and cross-trial differences in these proportions were compared to provide evidence of where on the pathway patients were lost to recruitment and identify compensatory actions.

Results
Substantial loss to recruitment was identified at different points on the recruitment pathway in different studies: exclusion of potentially eligible patients from screening, failure to approach all eligible patients, and loss of a substantial proportion of patients following a discussion about the study. We found diverse and often unexpected trial/site-specific reasons for these losses that, once shared with trial management teams, led to tailored actions to optimise recruitment, for example site-specific workshops to address differential application of eligibility criteria, organisational issues around who approached patients/when and targeted recruiter training in information provision.

Discussion
SEAR data analysis provides an overview of the points at which patients are being lost to recruitment in a trial, but also in particular sites within a trial. SEAR data are most useful when triangulated with qualitative data to identify optimum solutions [Rooshenas et al. 2019]; but even in isolation they rapidly highlight points on the recruitment pathway for targeted interventions to optimise recruitment. Tailored recruitment interventions can be more rapidly identified by integrating SEAR as routine for trial data collection within CONSORT processes.

P-159

Behavioural optimisation to address trial conduct challenges: case study in the UK-REBOA trial

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Background
Clinical trials comprise multiple processes at various stages of the trial lifecycle. These processes often involve complex behaviours such as recruiting vulnerable patient populations and clinicians having to deliver complex trial interventions successfully. Few studies have utilised a behavioural framework to assess challenges and develop strategies to effective trial recruitment and delivery of trial interventions. This study reports the application of an innovative methodological approach to understand core trial processes, namely recruitment and intervention delivery, using a behavioural science approach to develop strategies designed to mitigate trial process problems.

Methods
The UK-REBOA trial aims to evaluate the clinical and cost-effectiveness of Resuscitative Endovascular Balloon Occlusion of the Aorta (a novel intervention) in injured patients with exsanguinating haemorrhage. A behavioural investigation ('diagnosis') was conducted using theory-informed (Theoretical Domains Framework, TDF) semi-structured interviews with site staff from the UK-REBOA trial to examine trial processes which could be improved in relation to trial recruitment and delivery of the intervention. Interviews were analysed using the TDF to identify influences on behaviour, which were then mapped to techniques for behaviour change and developed into potential solutions.

Findings
The behavioural diagnosis of the challenges experienced during trial processes highlighted factors relevant to a range of TDF domains: Skills; Environmental context and resources; Beliefs about capabilities; Beliefs about consequences; Social influences; and Memory, attention, and decision processes. Within the solution development phase, we identified 24 suitable behaviour change techniques that were developed into proposed solutions to target reported process problems with the aim of changing behaviour to improve recruitment and/or intervention delivery. Proposed solutions included targeted changes to trial training content, suggestions to restructure the environment (e.g. reinforced the purpose of the trial with information about the social and environmental consequences) and other strategies to reduce barriers to recruitment and intervention delivery.

Conclusion
In this presentation we will demonstrate the feasibility of applying a behavioural approach to investigate ('diagnose') behavioural trial process problems and subsequently develop and implement targeted solutions ('treatment') in an active trauma trial. We will share how understanding the factors that affected behaviour, attitudes and beliefs in this trauma trial allowed us to implement theoretically informed, evidence-based solutions designed to enhance trial practices.

P-160

The role of trainees and the NIHR Associate PI scheme to support screening and recruitment to a multicentre RCT: an example from the Sunflower Study

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Introduction
Recruitment to RCTs requires a teamworking approach (1),with many studies benefitting from the contributions of surgical trainees as recruiters. On the large-scale multi-site Sunflower study (2), an embedded QuinteT Recruitment Intervention (QRI) (3) helped identify the reciprocal benefits of trainee involvement, and engagement with the NIHR Associate PI (API) scheme (4). The aim of this study is to explore the ongoing involvement of trainees in the Sunflower RCT incorporating the inclusion of Radiology (additionally to Surgical) APIs, and the piloting of a scheme to maintain engagement from trainees once they complete their 6 months on the API scheme.

Methods/Approach
We will present a mixed-methods analysis: qualitative data sources are interviews with trainees and consultants where they reflect on their engagement with the API scheme whilst working on Sunflower. We will also present an analysis of Sunflower recruitment activity from the study database and a descriptive analysis of the number and specialty of trainees engaging with the study and review the outcomes of the post-API scheme pilot.

Results Structure and Timelines
Sunflower opened in February 2019 and 52 centres are currently participating. Over 300 trainees have logged activity on the study database. A total of 102 have applied to the API scheme via the Sunflower study, 31 have attained their certificate of completion and 25 are currently involved in the scheme, of which NN are radiology trainees To date, 8589 patients have been screened and 3783 patients have been recruited. In acute contexts, 33% of patients were approached about the study by Trainees (consultants 16%; research nurses 51%). We will present updated details of activity by discipline, for both acute and elective admissions. Trainees have participated in RCT sub-studies, and with the expansion of the API scheme to include radiology trainees have provided supplementary modes of support to recruitment. In our talk, we will also report on progress to encourage ongoing engagement with the study once trainees have completed the API scheme.

Potential Relevance and Impact
The NIHR API scheme provides a framework for supporting trainees to develop into future research leaders. The results from the large-scale Sunflower study will be useful to RCT CIs and trials units in understanding the opportunities and challenges of engaging with the API scheme and with trainees more generally to support recruitment and other RCT activity as well as providing insights into strategies to continue trainee involvement once they have completed the API scheme.

P-161

Optimising recruitment to a randomised trial of surgery versus no surgery: the Mesothelioma and Radical Surgery 2 (MARS 2) study

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Introduction
Recruitment to randomised controlled trials (RCTs) can be challenging, particularly for trials that evaluate very different treatments. The MARS 2 RCT was anticipated to face recruitment challenges, so a QuinteT Recruitment Intervention (QRI) was embedded to unearth and address difficulties to help achieve recruitment target.

Methods
A multi-faceted, flexible, mixed method approach was used to investigate recruitment obstacles. Interviews (recruiters/patients) and recruitment consultations were audio-recorded, transcribed, and along with recruitment screening logs, were subject to simple counts, content and thematic analyses. Key findings were fed back to the trial management group and strategies to target identified issues were developed and actioned. Data collection, analysis, feedback and strategy implementation continued cyclically throughout the recruitment period.

Results
There was support for MARS 2 and recognition of the importance of the study and the value it would bring to advancing the evidence-base for mesothelioma, but recruitment challenges were evident. Aside from organisational and logistical difficulties with study implementation commonly recognised by interviewees, it was apparent that many recruitment challenges stemmed from issues related to equipoise. Although informants were clear on equipoise across the clinical community, individual levels of equipoise amongst those referring and recruiting to the study varied. Personal levels of equipoise were not necessarily static and could vary depending on the presenting patient. This created tension between clinical equipoise and the clinician's opinion of which option was in the patient's best interest. These issues around equipoise seemed to impact recruitment in various ways from referring the patient for study consideration, to determining eligibility, and to explaining the study and treatment options. Having identified the key issues, QRI-informed actions were devised and implemented to raise awareness, offer support and share good practice in a bid to safeguard informed consent and optimise recruitment until the target had been reached.

Discussion
Future RCTs like MARS 2, dealing with a condition with a poor prognosis that offers very different treatment options, are likely to face similar recruitment challenges. However, how these emotional and intellectual challenges manifest themselves will be trial specific. This emphasises the importance of understanding the individual and complex recruitment pathway and its own set of issues that are particular to that trial, as a basis for developing and delivering bespoke tailored strategies to address them.

P-162

Self-referral pathway in a dermatology randomised controlled trial: are self-referred patients representative of the patient population?

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Introduction
Recruiting to target in randomised controlled trials (RCTs) is often challenging, therefore, implementing a combination of effective recruitment strategies, both active and passive (self-referral), is encouraged. Recruiting trial participants via self-referrals has been shown to be more cost effective compared to other methods and can provide information about the demand for the treatment under consideration and patients' motivation to participate in the trial. However, critics of self-referral argue that it attracts different patients to those who would be referred by clinicians and the "worried well", hence it is essential to compare characteristics of patients recruited via each method to establish representativeness of the sample.
Using data from the HI-LIGHT vitiligo trial, this study will compare the following characteristics of patients recruited via self-referral to those recruited via other methods:
i) patient baseline characteristics including age, sex, ethnicity, medical history, and duration of vitiligo.
ii) severity of vitiligo at enrolment
iii) treatment adherence
iv) follow-up rates
v) number of adverse events
vi) treatment success
vii) trial eligibility rates

Methods
The HI-LIGHT trial recruited 517 participants aged ≥5 years with active vitiligo (a condition causing patches of skin depigmentation) affecting approximately 10% or less of skin. It tested the effectiveness of home-based light therapy and topical steroid cream, used alone or in combination, for the treatment of vitiligo. The primary outcome was treatment success at 9 months at a target patch assessed using the participant-reported Vitiligo Noticeability Scale. Participants were identified through secondary care dermatology clinics (118/517;23%), general practice mailouts (213/517;41%), and by self-referral (186/517;36%). Self-referral recruits were made aware of the study through direct local advertising.
We will use descriptive statistics and regression methods to compare between the two groups of patients.

Results Structure and Timelines
Results will be presented as differences in mean or proportion (and 95% confidence intervals) between patient recruited through self-referral pathway compared to other pathways or between self-referred and all screened patients, as appropriate.
The HI-LIGHT vitiligo trial is completed; we are waiting for the requested data to be released and expect to complete the analysis by early September 2022, ahead of the conference.

Potential Relevance and Impact

Results will demonstrate the impact of self-referral recruitment method on generalisability of the sample, adherence, attrition, and engagement, and will provide evidence to support or refute the common criticisms of self-referral. Recommendations will encourage or discourage use of self-referral pathway in dermatology RCTs.

P-163

Recruitment, consent and retention of participants in individually randomised controlled trials: review of trials published in the National Institute for Health Research Journals Library (1997-2020)

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Introduction
Conducting a randomised controlled trial (RCT) requires major financial investment and substantial amounts of public funding is spent in this area each year. A leading reason for premature discontinuation of RCTs is poor recruitment of participants with accrual taking longer or being more difficult than expected. The aim of this review was to describe the rates of consent, recruitment and retention in publicly funded trials published in the National Institute for Health Research (NIHR) Journals Library.

Methods
Reports of RCTs, that randomised individuals, published in the NIHR Journals Library from January 1997 to December 2020 were reviewed. A team of five reviewers extract information relating to the trial characteristics, sample size, recruitment, consent and retention. The primary outcome for the review was the recruitment rate for each trial defined as the number of participants recruited and randomised per centre per month. The secondary outcomes were the target sample size and whether it was achieved, the consent rate (percentage of eligible participants that consented and were randomised) and the retention rate (percentage of randomised participants that were assessed for and included in the analysis of the primary outcome).

Results
This review identified 388 RCTs from 379 reports published in the NIHR Journals Library. The median recruitment rate (participants per centre per month) was found to be 0.95 (IQR: 0.42-2.60), the median consent rate was 72% (IQR: 50%-88%) and the median retention rate was estimated at 88% (IQR: 80%-97%). The final recruitment target sample size was achieved in 63% (245/388) of the RCTs but 32% (79/245) of these trials required an extension to their recruitment period to meet the target. A further 22% (86/388) of trials recruited to within 80% of their final recruitment target. The original recruitment target was revised in 30% (118/388) of RCTs (downwards in 67% (79/118)).

Discussion
This review found considerable variation in the consent, recruitment and retention rates in publicly funded trials. Although the majority of (6 out of 10) trials achieved their final target sample size; 3 out of 10 revised their original target sample size (downwards in 7 out of 10 trials). This should be taken into account at the planning stage of an RCT and investigators should not be overly optimistic about their recruitment projections.

P-164

Measuring the quality of proxy consent decisions for adults who lack capacity to consent: development of the Combined Scale for Proxy Informed Consent Decisions (CONCORD)

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Introduction
Recruiting adults lacking capacity to consent in trials is complex as it requires the involvement of a 'proxy', usually a family member, to make a decision about participation on the person's behalf. Proxy consent decisions can be challenging for family members, with some experiencing an emotional and decisional burden as a result. Although numerous interventions have been developed to improve informed consent processes for people giving their own consent, interventions to support proxy consent decisions in non-emergency settings are still in their infancy. Evaluation of these interventions is limited to date due to a lack of measures to assess proxy decision quality. We report the development of the first such instrument, the Combined Scale for Proxy Informed Consent Decisions (CONCORD scale).

Methods
Building on a previous core outcome set (COS) which identified the outcomes of agreed importance, and using established measure development principles, we developed and refined a new measure of proxy decision quality. The process consisted of four stages: 1) findings from a recent scoping review and COS were reviewed to ascertain items for inclusion in the scale and to identify any existing outcome measures; 2) the content coverage by existing measures was assessed to identify areas of (in)sufficiency; 3) a novel scale was constructed; 4) cognitive interviews with family members of people with impaired capacity explored comprehension of the scale and assessed its content adequacy.

Results
The scoping review identified a number of outcome measures associated with both healthcare and trial participation decisions. When mapped against the key constructs identified in the COS to assess content coverage, insufficient coverage of areas such as proxy-specific satisfaction and knowledge sufficiency by existing instruments indicated that a novel measure was needed. An initial version of the combined measure was developed. It was tested during cognitive interviews with eleven family members over two phases, with revisions made to the scale following analysis of phase one. The interviews established comprehension and content adequacy of the scale. Participants suggested re-phrasing and re-ordering some questions, leading to the creation of a revised version.

Discussion
CONCORD is acceptable and feasible and has sufficient content adequacy to assess the quality of proxy consent decisions made on behalf of an adult who lacks capacity to consent in non-emergency trials, thus enabling the evaluation of interventions to improve proxy decision quality. Further work to concurrently validate the scale in a 'Study Within a Trial' (SWAT) is being undertaken.

P-165

Conducting clinical trials during COVID-19 pandemic: experience from a trial in dengue patients in Ho Chi Minh City

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The COVID-19 pandemic overwhelmed most hospitals in Vietnam as well as leading to many difficulties for clinical research. In this presentation, we will discuss about our experience in conducting an open label clinical trial using Metformin as an adjunctive therapy for dengue patients with obesity during the COVID-19 pandemic.

The trial started in July 2020 at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City (HCMC), Vietnam, aiming to recruit 120 obese/overweight dengue patients within two dengue seasons to assess the safety and tolerability of metformin in dengue patients with obesity. The clinical and laboratory findings of patients treated with metformin will be compared to patients receiving standard of care. The primary outcome is safety and tolerability and secondary outcomes consist of several clinical, immunological and virological markers of disease severity (ClinicalTrials.gov: NCT04377451). The first ten patients (out of 24 screening cases) were recruited within three months in 2020 for initial safety review.
Vietnam was one of the few countries that initially succeeded in controlling COVID-19 well in 2020 due to strict border controls and contact tracing. However, the few cases were identified in the city and hospitalized at HTD. The fear and stigma of the disease resulted in patients with other diseases like dengue seeking healthcare elsewhere or not at all. As a result, we could only recruit eight more patients (out of 12 screening cases) within the next seven months. Then in June-September 2021, a large delta wave occurred resulting in HTD transferring all their services for COVID-19 patients and all non-COVID studies conducted at this hospital had to be suspended. The strict city lockdown strategy prevented patients with other illnesses from accessing health care systems. Many strict pandemic control policies, including the requirement of COVID-19 screening in all patients, also led to hesitancy of presenting to hospitals. Subsequently a large omicron wave occurred in early 2022 resulting in less hospitalization but was associated with healthcare staff shortages due to illness or isolation policies.

In summary, during the pandemic period, conducting clinical research has been challenging due to strict lockdowns, fear of accessing healthcare services and staff shortages. Key lessons included; adapting to rapidly changing pandemic policies, diversifying study sites, public and community engagement and communication with local healthcare staff allowed us to continue research despite the overwhelming challenges of the pandemic.

P-166

Optimising recruitment in clinical trials for progressive multiple sclerosis: observational analysis from the MS-SMART and MS-STAT2 randomised controlled trials

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Background
Slow recruitment is a major factor contributing to the delay of randomised controlled trials, or their failure to report on time. There is a limited evidence base regarding the optimisation of recruitment strategies. Here we performed an observational quantitative review of our experience in recruitment for two large randomised controlled trials for people with secondary progressive multiple sclerosis. We aimed to explicitly determine those factors which can facilitate trial recruitment in progressive neurodegenerative disease.

Methods
Quantitative recruitment data from the sequential MS-SMART [NCT01910259] and MS-STAT2 [NCT03387670] UK randomised controlled trials was reviewed from the largest recruiting site, University College London (UCL). Similar eligibility criteria for both trials allowed comparisons over the two recruitment periods of 2015-2016 (MS-SMART) and 2018-2021 (MS-STAT2). This included sources of referral, progress through stages of recruitment, reasons for participant ineligibility and the impact of publicity events upon recruitment.

Results
176 participants were recruited at UCL for MS-SMART, and 315 for MS-STAT2. In MS-SMART, 18% of patients contacted were enrolled, compared to 27% for MS-STAT2. Online registration of interest portals provided the greatest number of referrals (76% in MS-SMART, and 51% in MS-STAT2), with publicity in national media outlets producing a demonstrable increase in the number of trial volunteers. The introduction of an online self-screening questionnaire for MS-STAT2 resulted in 67% of UK-wide volunteers (3080 of 4605) automatically determining their own ineligibility. In both studies, however, around 60% of those directly telephoned to discuss the trial were not eligible, with difficulties related to travel to trial visits, or excluded medication, being the most common issues. 84% of those deemed potentially eligible following telephone calls were enrolled in the MS-STAT2 trial, compared to only 55% for MS-SMART. The introduction of formalised pre-screening checklists and regular appointment reminders for the MS-STAT2 trial may have led to this improvement.

Conclusions
Through a detailed quantitative review of recruiting participants at the largest centre into two large randomised controlled trials with similar entry criteria, we have identified a number of approaches that may improve recruitment efficiency. We highlight here the importance of a mandatory online self-screening questionnaire, a coordinated publicity campaign, and simple interventions such as eligibility checklists and appointment reminders. These should be further assessed through a studies within a trial (SWAT) design.

Trial registration

MS-SMART (NCT01910259) and MS-STAT2 (NCT03387670)

P-167

Identifying resident-related barriers and facilitators to recruiting UK care home residents in research: a scoping review

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Introduction
Care home residents have been recognised as an under-served group in research. COVID-19 has had a devastating impact on care home residents, yet they have been widely excluded from COVID treatment and vaccine trials. Increasing opportunities for care home residents to be included in trials is urgently needed, including the 70% of residents who have cognitive impairment and may lack capacity to consent. Adequate representation of the population who are likely to benefit from the research is important in order to support the generalisability and application of research findings in practice. To better understand why older adults living in care home are often excluded, and therefore underrepresented, in care home research, this scoping review aims to identify resident-related barriers and facilitators to including older people living in UK care homes in research and identify potential interventions for modifiable barriers.

Methods/Approach
This scoping review follows Arksey and O'Malley's scoping review methodology. Relevant studies have been identified through searches of five electronic databases: MedLine, Web of Science, Scopus, CINAHL and PsychINFO. Reference lists and key journals of included studies have additionally been hand-searched to identify further relevant studies. Grey literature has been searched for relevant unpublished literature (e.g., EthOS), and a relevant organisations' website search (e.g., NIHR ENRICH (Enabling Research in Care Homes)). Initial synthesis has summarised the scope, amount, and nature of available evidence.

Timing of Potential Results
Synthesis is underway and will be completed by summer 2022. Key information collected during the data extraction stage will be summarised in a tabulated format. Alongside this information about the characteristics of included studies, a narrative discussion will be undertaken to map and contextualise extracted data. This presentation will present the findings and discuss implications for future trials in care homes.

Potential Relevance and Impact
This review represents a step forward in understanding how to include this under-served group in trials through identifying resident-related barriers and facilitators to research participation. The findings of this scoping review will be used to develop a survey and in-depth interviews to explore the views and opinions of residents, family members, and care home staff about factors they perceive to be barriers or facilitators of research participation, with the goal of developing an intervention to improve the recruitment of care home residents in research.

P-168

Implementation of the UK national data opt-out scheme across clinical trials requiring deferred consent

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Introduction
The UK national data opt-out will come into force 31.07.22. This service permits patients to have confidential information withheld from use in planning and research unless they explicitly provide consent. We aim to review the factors which should be considered when implementing the national data opt-out in trials requiring deferred consent with a key focus on randomised trials encompassing emergency care where survival rates are extremely low.

Methods/Approach
AIRWAYS-3 anticipates that patients who have a national data opt-out in place will be inadvertently enrolled into the trial due to the emergency nature of a cardiac arrest. This study aims to set precedent and proposes to withdraw from the study all patients who have registered a national data opt-out as soon as possible after enrolment. The total number of patients withdrawn from each arm will be recorded.
PARAMEDIC-3 proposes to use a ''consent overrides opt-out'' model, where survivors who have a national data opt-out will be approached for consent. If consent is given, participants will be opted into the trial.
POSED obtains anonymised data and will adopt the same approach as PARAMEDIC-3. However, ''national data opt-outs do not apply where information being disclosed is anonymised in accordance with the Information Commissioner's Office (ICO) anonymisation code of practice".
SIS, a trial investigating spinal injury, proposes to adopt the same approach as PARAMEDIC-3 and POSED, where surviving patients will be approached for consent. This is expected to have a higher survival rate than cardiac arrest trials.

Timing of potential results
Implementation strategies may vary depending on desired study outcomes and trial design. We will gain results by the end of 2024.

Potential relevance and Impact
Ongoing and pending research methods have been analysed to establish factors effecting ways the national data opt-out is applied. Identified considerations include: the level of bias introduced, type of data collated, survival rate, percentage of sample population thought to have a national data opt-out, sample size, study sensitivity and the consideration of patient burden when being informed. Conversations with ethics committees and patient advisory groups have consolidated the importance of adherence to the national data opt-out scheme. Establishing a framework of methods which respect the participants wishes while obtaining representative and unbiased data (especially where survival rates are extremely low) is of the greatest importance to allow the ethical advancement of medical research.

P-169

Successful implementation of Electronic Consent (E-Consent) in an Australian perinatal clinical trial (the LEAP1 Study)

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Background
Informed consent processes play an integral role in the ethical conduct of clinical trials. Yet, a requirement for in-person consent discussions and consent form signing may be barriers to trial participation for both sites and participants. These existing barriers have been exacerbated by the COVID-19 pandemic, increasing the risk of recruitment failure. LEAP1 is an Australian trial investigating 200mg bovine lactoferrin (bLF) vs 80mg iron sulphate (FeSO4) once daily until delivery in women with iron deficiency anaemia in pregnancy. The study opened in May 2017 and aimed to recruit 900 participants over 54 months. The option for electronic consent was introduced in response to the pandemic and aimed to reduce barriers to recruitment.

Methods/Approach
From May 2020, sites were offered two electronic options for seeking consent from potentially eligible people; (i) Adobe Sign, an e-signature platform which allowed for streamlined collection of electronic signatures, and (ii) fillable PDF consent forms, in which fields on the form were manually completed, the forms were saved, and then emailed to the next recipient for completion. Electronic methods of consent received ethical and governance approval prior to implementation, and no concerns from the lead ethics committee or site governance offices were raised. Site trials staff issued informed consent documents to participants via email (using fillable PDF forms) or through Adobe Sign, which allowed participants to read through and sign electronically following the informed consent discussion via face to face or telehealth consultation. Fully signed informed consent documents were kept electronically on site, and copies were also provided to participants in accordance with GCP principles.

Results
Of the 13 sites, 5 implemented electronic consent (1 site implemented Adobe Sign and 4 implemented a fillable PDF consent form). In sites adopting electronic consent, average monthly recruitment rates substantially increased (from 0.65 participants per site per month before e-consent approval to 1.75 participants per site per month after e-consent approval). This compared to a slight fall in recruitment from 0.83 to 0.79 in sites that continued to use in-person consent processes. The trial reached full accrual in October 2021.

Discussion
Electronic informed consent was found to be an acceptable, practical, and effective tool in supporting study recruitment in a perinatal context, particularly during the COVID-19 pandemic. Future trials may benefit from adopting similar methods of informed consent for their participants.

P-170

A Hybrid Approach to Seeking Consent for Trial Participation in a Care Home Study, Including Consent from Care Home Residents with Dementia

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Introduction
The COVID-19 pandemic has expedited the adoption of online processes in clinical trials. This has resulted in adaptations to the way many studies are implemented. The NightCAP study (NCT04373668) aims to improve night-time care in people living with dementia in care homes. The study was set-up during the pandemic and required a flexible process for taking consent from care home residents, directly or by proxy opinion from their next of kin (NOK), and from care home staff for separate participation.

Approach
We developed a consent system using REDCap Academic that enabled both electronic consent (e-consent) and the secure storage of scanned paper consent forms. For e-consent, forms were created as surveys that users accessed from a link within an email. A researcher countersigning form was developed to ensure validity of the consent form. The participant information leaflets were embedded into the e-consent forms and preceded by an identity check. For the paper consent approach, a separate form was created for scanned copies of the paper consent/opinion forms to be uploaded to. A survey was used to obtain feedback from users on the consent process.

Results
After thorough testing by the trial team, a hybrid consent system was developed, with five potential scenarios: care staff e-consent or postal consent, NOK electronic or postal proxy opinion and care home resident postal consent. Of 133 care home resident participants, 131 (98.5%) were consented by proxy, of whom 117 (89.3%) opted for e-consent. Two residents consented themselves using the paper approach. All 39 care staff used e-consent. Survey data indicated the e-consent system was easy to use, but highlighted some areas for improvement, including that the email address from REDCap could be more recognisable.

Discussion
The consent system is user-friendly, maintains a clear audit trail and is efficient as e-consent reduces the requirement for source data monitoring. One challenge with e-consent is for potential participants/NOK who do not have a personal email address. This was overcome with the hybrid paper consent approach. Depending on demographics of the target population, studies may not be able to exclusively use an e-consent process, making a hybrid consent system a valuable approach. Feedback suggested that despite some (addressable) limitations, there was a strong preference for using e-consent. The results show that e-consent is possible in a care home study with an older target population, but that it should not be the only available method of consent.

P-171

Design and implications of a two-stage consent process for an RCT in the police setting

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Introduction

Gateway was an NIHR Public Health Research funded randomised controlled trial (ISRCTN11888938) conducted together with Hampshire Constabulary. The trial aimed to recruit 18-24 year olds who had committed a low-level offence and randomise them to a conditional caution consisting of an out-of-court, police-led, multi-agency intervention called Gateway, or to usual process (court appearance or a different conditional caution). Follow-up took place at 4-weeks, 16-weeks and 1-year post-randomisation. The primary outcome was mental wellbeing measured by the Warwick-Edinburgh Mental Wellbeing Scale, completed by the participant via interview with a researcher.

Randomisation had to take place at the police station before the participant was discharged, as the police are legally required to know the criminal justice destination of offenders. For legal reasons it was not possible for a researcher to be present in the custody suite to obtain full consent, and as a result a two-stage consent process was devised.

Methods

At stage 1, eligible individuals were identified by police investigators, given information about Gateway and asked for consent to be randomised to the study and have their contact details passed onto the research team. If stage 1 consent was given, the participant was randomised and their contact details were passed to the research team. At stage 2, participants were given further information and asked to consent to data collection and use of personal information.

Results

The two-stage consent process was associated with both recruitment and retention issues. Challenges with recruitment included potential participants being missed at stage 1 or declining to take part in the study. Retention was mainly affected by participants being uncontactable on the phone number and other contact details given to the police. A number of strategies were implemented to improve recruitment and retention, however, ultimately the issues proved insurmountable, and the study was closed prematurely.

Discussion

Gateway was one of the first large-scale RCTs working with young adults committing low-level offences, a study population that is underserved and can be challenging to both recruit and retain. Although the trial was closed early, meaning the question of the effectiveness of the intervention remains unanswered, much valuable learning was gained by the study team while working with the study population. There is a need for further research into how to recruit and retain in this area, and in particular, how to gain the trust of young people in similar settings.

P-172

Boosting recruitment rates in trials with complex recruitment pathways spanning acute and community healthcare: experiences from the HERO trial in older adults with frailty

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Introduction
A large proportion of publicly funded UK health trials struggle to recruit to time and target. Recruitment from services spanning acute hospital and community settings, often provided by multiple NHS trusts or other agencies, is particularly challenging and time consuming due to complex patient pathways. We reflect on strategies employed to maximise recruitment in the HERO trial, a complex community rehabilitation trial, recruiting older people living with frailty on discharge from an acute hospitalisation +/- intermediate care rehabilitation in the NHS in England.

Methods
A range of approaches were implemented to increase recruitment:
- Regular (≈2monthly) individual site meetings to problem solve, share best practice, review screening data, and streamline local processes.
- Central trial team engagement with site clinical teams to facilitate potential participant identification.
- Monthly research team teleconferences, newsletters and website provided avenues for sharing best practice, seeking/disseminating information and for peer support.
- Local researcher capacity boosted through in-reach of central trial research personnel.
- Local clinical research network (CRN) support either via targeted funding to support research capacity in key local clinical teams where screening/recruitment activity occurred, or via the CRN flexible workforce team in-reach.
- Intervention delivery capacity maintained through monthly communications to foresee capacity issues and plan additional therapist training.

In-reach strategies were not implemented uniformly, but as deemed appropriate by site. A key facilitator was having trial sites in two regions (Yorkshire and South West England), enabling trial team researchers to efficiently and responsively in-reach to multiple sites simultaneously.

Results
National Institute for Health Research RCTs (1997-2020) recruit a median 0.95 (IQR: 0.42-2.60) participants per site per month. The HERO trial recruited to target (n=743) over 38 recruiting months (45 months including COVID pause). Varied recruitment rates across and within sites are presented with links drawn to strategies implemented. The median recruitment rate was 1.67 (IQR 0.93-2.36) participants per month per site, compared to an average of 1.8 (SD 1.3).

Discussion

Regular communication with sites enabled early identification of recruitment barriers. While difficult to infer cause and effect, boosting researcher capacity to support sites appeared consistently impactful, particularly to support recruitment in community settings. The central trial researcher model was instrumental in allowing many sites to reopen while remaining under COVID-19 pressures. In-reach need/cost varied by site, but were most efficiently implemented across sites in close proximity. We recommend central resource to support site recruitment in trials with complex recruitment pathways.

P-173

Evaluation of recruitment pathways in trials conducted in primary care: example from a large national priority adaptive platform trial for COVID-19 (PRINCIPLE)

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Introduction
Recruitment has always been a challenge in clinical trials conducted in the UK primary care setting. Evidence has shown that just 31% of studies recruited to target. PRINCIPLE was a national urgent public health adaptive platform that required rapid recruitment from people with SARS-CoV-2 positive and have symptoms in the community.
The PRINCIPLE trial has provided us an unique opportunity to evaluate different recruitment pathways as the trial progressed during the pandemic, and helped to inform the PANORAMIC trial.

Methods/Approach
Recruitment pathways in PRINCIPLE ranged from the traditional site centric GP recruitment pathway, to working with ambulatory trusts, care homes, regional recruitment, partnership with health apps, NHS digital referrals, NHS111 referrals and enabling the direct self-registration of the public via our website with public outreach and engagement. Information on screening, registration, and randomisation of participants, as well as other operational data were collected. Results will be reported descriptively.

Results
Between April 2020 and May 2022, the trial has successfully randomised 11036 participants across 7 treatment arms. There was a total of 9 recruitment pathways introduced at different times of the trial.
Numbers screened/randomised (% out of total randomised) from each pathways were:
Website Self-screening: 37168 / 6864 (62%); Zoe App: 5456 / 1268 (11%); NHS Digital Pillar 2: 2303 / 1288 (12%); GP site-based eligibility: 9079 / 1215 (11%); Devolved Nations: 761 / 99 (1%); NHS111: 1511 / 163 (1%); Ambulance Trusts: 1243 / 74 (0.9%) Other: 127 / 12 (0.1%) Carehome: 28 / 3 (0.03%);
Results suggested that there is a large variation in the different recruitment pathways. However, this variation is also time dependent. Although, a large proportion of participants were enrolled from self-screening via the website, the most efficient method was referrals from NHS Digital Pillar 2, with a conversation rate at 56% from screening to randomisation. Some of the recruitment pathways have very few numbers randomised, and the reasons could be due to the nature of the pandemic (e.g. national lockdown) or infrastructure cannot not be implemented in time.

Discussion
Experience from PRINCIPLE enabled the exploration of a large variety of recruitment pathways. The results were used to inform the design of future large scale national priority trials in PANORAMIC. Applying the most successful outreach and decentralised recruitment strategies combined with a streamlined process.

utilising drug delivery and IT systems enabled the rapid recruitment of over 25500 participants between December 2021 and May 2022.

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Structured Approaches to Informed Consent for Randomised Controlled Trials with Usual Care Comparators: A Review of Use

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Introduction
The most common approach to informed consent involves a conversation with the potential participant where the study and their role is explained in one session. Those seeking consent describe the study purpose, trial procedures (random allocation, measurement tools) and the intervention risks and benefits. This type of informed consent approach is required for trials where all participants will receive something other than usual care i.e. an experimental intervention or placebo. However, for trials with usual care comparators, this 'everything in one session' approach is not always required or beneficial. Little is known about alternative approaches.
The Trials within Cohorts (TwiCs) design supports an alternative structured approach to informed consent. This innovative approach to informed consent ensures that the information provided and consents sought are (i) relevant to the study stage, and (ii) tailored to the patient's group allocation (continued usual care or experimental intervention). Initially, all potential participants are asked for consent to take part in the observational element of the study. Then for any randomised trial embedded within the cohort, those who agree to provide observational data are asked for consent to be contacted if selected to a trial intervention group. Only those selected to the experimental intervention group are informed about the experimental intervention. The usual care group is not informed about treatments that they are not going to be offered.

Methods
We are conducting a review of studies using structured approaches to informed consent. We are reviewing publications of methods or reports of protocols or results from randomised trials that use cohorts to recruit. Data sources for this review include Medline and Cochrane Methodology Register and are limited to English language. This is supplemented with information from topic experts. We report design features (including terminology) and experiences and recommendations of trialist using structured approaches.

Timing of Potential Results
The results of this review will be complete by the end of August 2022. Interim results show that studies using structured approaches are being conducted in diverse areas including population health, oncology, mental and behavioral disorders, musculoskeletal conditions, and surgery.

Potential Relevance and Impact
Some triallists using structured approaches report better recruitment (faster and more representative), reduced expectation and disappointment bias and cross-over between arms. The findings from this review will support the development of guidance on informed consent approaches for pragmatic trials with usual care comparators.

P-175

Introduction of a centralised screening and recruitment database: optimising efficiency and maximising recruitment potential across multiple trials within a single speciality.

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Introduction
Multiple clinical trials recruiting within a single speciality, with a high patient throughput, requires efficient management of screening and recruitment processes. A screening and recruitment database within the speciality of cardiac surgery was introduced to facilitate centralised management of these processes.

Methods
The cardiac surgery trials database was introduced by the Bristol Trials Centre(BTC) and held on an NHS hospital server at the Bristol Heart Institute(BHI), where multiple university led studies recruit simultaneously
within the cardiac surgery speciality. Administrators add patient details such as name and hospital ID number, operation type and surgeon, with further patient demographics streamed from hospital electronic records. The database auto allocates patients to trials, based on baseline characteristics, operation type and participating surgeon. Administrators, then send study information, before passing details to qualified nurses for further screening. Auto allocation is used to assign multiple trials to a single patient in order of priority, based on surgeon preference and recruitment status of individual trials. A co-enrolment function highlights potential multiple 'within patient' approaches. Further recruitment details are populated by recruiters, indicating patient approaches and consent or decline, with reasons given.

Results
Up to eight cardiac surgery operations per day are performed and by maintaining the list daily, 100% of patients within the cardiac surgery speciality are consistently pre-screened for trials centrally, removing any subjectivity in the pre-screening process.
The trials database has improved efficiency by reducing the need for multiple trial specific screening lists and the burden of screening activity has been reduced for trained nurses, by enabling administrators with little or no medical knowledge to perform basic pre-screening.
As surgery lists are confirmed, database reports flag recruitment status of all listed patients, including patients for whom outpatient approach has not been possible. Those admitted the evening before surgery can then be approached, thereby maximising recruitment potential.
Aside from nuanced reports of consent rates and reasons for ineligibility and non-consent, broader extracts such as types and number of operations by surgeon has proven useful in future trial planning.

Discussion

The use of a dedicated speciality based patient screening and recruitment database has been shown to optimise patient recruitment potential and improve efficiency, as well as helping to embed research in routine care. With recent unprecedented challenges in trial recruitment, implementation of a centralised trial screening database such as this may be extremely beneficial.

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Going viral: Utilising online advertising in a sexual health trial

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Background
Recruitment for the DEVA trial (dequalinium vs antibiotics for treatment of bacterial vaginosis (BV)) coincided with the start of the COVID-19 pandemic, which halted trial activity. COVID-19 lockdowns and social distancing measures caused significant changes to the delivery of sexual health services in the UK, with a move towards remote, rather than face-to-face appointments with priority given to those with more serious health conditions.
To compensate for the reduction in BV patients attending sexual health clinics and to provide care to patients with symptoms of BV, in addition to face-to-face recruitment, the DEVA trial developed two remote recruitment pathways. One of these pathways invites women across the UK to self-refer, using an expression of interest (EoI) form on the trial website as an initial eligibility screen. For those deemed eligible, 100% of their screening, randomisation and follow-up is conducted remotely. As screening and recruitment is online, rather than in-clinic, online advertising was required to raise awareness of the trial to the patient population.

Methods
We collaborated with a marketing agency to develop the adverts and identify the most appropriate marketing strategy for the trial. Two advertising campaigns were run on Facebook and Instagram (campaign 1: 4 weeks and campaign 2: 12 weeks) with Google Ads used from the start of the first advertising campaign throughout the trial.
Activity was reviewed on a weekly basis, using information collated by Facebook and Google Tags as well as information on EoI form activity, collected by the trial randomisation system.

Results
To date, remote randomisations account for 50% (88/175) of trial participants. 57% patients who were deemed eligible on completion of EoI went on to consent for the trial. Patients clicking on Google ads were more likely to complete eligibility than those from Facebook/Instagram with conversion from click to EoI far higher for Google at 8.68% compared to Facebook/Instagram at 2.2%. Costs for the advert creation and two online campaigns to date is £34,000.

Conclusion
For trials recruiting remotely, advertising is key to publicise the existence of the trial however targeting relevant patient populations can be difficult, especially on Facebook/Instagram. Although Facebook/Instagram adverts reached a larger audience, restrictions prevent adverts targeting specific demographics (other than age and sex) or health conditions and result in fewer conversions than Google Ads. Facebook/Instagram adverts were more expensive to create, with additional expertise required to support the successful launch and maintenance of the trial ad campaigns.

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Design Characteristics of Public Health Intervention Trials: Review of NIHR Public Health Research Funded Trials

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Introduction
The NIHR Public Health Research (PHR) board funds research to inform the delivery of non-NHS interventions to improve public health and reduce health inequalities. The PHR funded Fresh Street study is testing offering weekly vouchers for local supplied fresh fruit and vegetables to all households in randomly selected streets and collecting data using repeated cross-sectional surveys with all households.
The aims of this review were to identify (i) the methods used to recruit study populations, (ii) the types of recruitment settings and eligibility criteria, and (iii) studies similar in design and conduct to our PHR funded community-based intervention trial Fresh Street.

Methods/Approach
We searched the NIHR journals library for randomised controlled trials funded by the UK NIHR PHR between January 2018 and March 2022. One reviewer extracted data from the included studies (n= 33) which was then sense checked by a second reviewer. Results were summarised by narrative review.

Results
33 studies were eligible for inclusion. Most intervention trials were described as either feasibility studies (n=14, 42%) or pilots (n=8, 24%); 12/33 (36%) were cluster randomised trials.
The majority recruited solely from schools (14/33, 42%) or health and/or social care settings 13/33 (39%). The remainder (6/33, 18%) supplemented their school/ health/ social care-based recruitment strategy by approaching the general population either online using targeted social media adverts or in person (e.g., stalls in shopping centres). All these studies applied eligibility criteria relating to status (e.g., school child, ex offender) and/or condition or unmet need (e.g., obesity, binge drinking). None recruited solely by geographical location. 15/33 (45%) of studies were supported by a Clinical Trials Unit, all of which used NHS settings to recruit.
No studies similar in recruitment setting or eligibility criteria to Fresh Street were identified.

Discussion
Although the PHR board funds research to inform the delivery of non-NHS interventions almost all PHR intervention trials recruit from health or other care services (social or educational services).
This review highlights the paucity of PHR funded studies that recruit from general population settings or with few eligibility criteria constraints, and the implicit bias towards specific population groups. Moreover, the high proportion of CTU supported trials privileges biomedical research methods which may not always be appropriate for research with the general population.
New initiatives to fund public health research collaborations, e.g., based in local authorities may support the design and conduct of public health interventions delivered in the wider general population.

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Evaluating the introduction of a remote electronic consent system in the CO2 study

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Introduction
The CO2 study (ISRCTN30671536) is a randomised controlled trial evaluating the efficacy and safety of carbon dioxide insufflation as protection against brain injury and dysfunction during open heart valve surgery. The study opened to recruitment in October 2021 and aims to recruit 704 participants aged 50 years and above undergoing planned left sided open heart valve surgery.
Remote electronic consent (e-consent) was introduced, alongside in-person and remote paper consent, due to COVID19 changes to the surgical pathway. E-consent is administered using the REDCap e-consent module which was adapted to mirror the paper consent process for consistency across methods.
Uptake of remote e-consent has been lower than anticipated with around half of sites declining to use e-consent in CO2 when asked in set up. This study aims to identify what makes a successful remote e-consent system.

Methods/Approach
An eight-item questionnaire was designed and will be distributed in June 2022, using REDCap, to staff from six sites who have undergone the CO2 site initiation visit and are delegated to obtain consent i.e., medically qualified doctors or research nurses.
All respondents will provide their centre, study role, length in role and age and answer four questions evaluating their opinion of e-consent, previous experience using e-consent and preferred consent method.
Respondents at sites that received CO2 e-consent system training will answer four additional questions evaluating the system, training and guidance and other systems used.
Responses are given as free text, Likert scales, multiple and single answers. Three questions use branching logic depending on the respondents' experience.
The questionnaire was piloted by trial managers and a research nurse who do not work on CO2. Feedback will be incorporated into the questionnaire before being finalised and disseminated.

Results Structure and Timelines
Data will become available when the questionnaire closes in August 2022. Data will be downloaded, analysed, and presented descriptively (number%). Thematic analysis may be used if enough participants provide free text comments.

Potential Relevance and Impact
The adoption of remote consent methods continues post-COVID19. Understanding users' preferences, concerns, and experienced issues are key to the successful development of an e-consent system sites are confident using with clinical trial participants. The results of this questionnaire will inform the specification of a user-friendly e-consent system that can be used in appropriate settings, trials, and populations.

P-179

Central management of follow-up visits for healthcare professional participants in the BRACE COVID-19 trial

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Introduction
The BRACE trial is an international trial comparing Bacillus Calmette-Guérin (BCG) with placebo in healthcare professionals (HCP) to determine if BCG vaccine reduces the incidence and severity of illness caused by SARS-CoV-2 (NCT04327206). During recruitment and follow-up, the UK experienced two national lockdowns, several waves of SARS-CoV-2 and the introduction of the SARS-CoV-2 vaccination trials and programmes. It was a busy and changeable time for participants and sites. We aimed to make it easy for HCPs and sites to participate by managing many of the trial processes centrally.

Approach
Exeter Clinical Trials Unit (ExeCTU) coordinated recruitment and follow-up of HCPs in the UK at five sites in Devon. Potential participants self-screened and consented online. Participants were directed to a third-party appointment website to book a baseline visit at a site of their choice.
Three sites opted for central coordination of follow-up visits at 3, 6, 9 and 12 months. The remaining two sites chose to manage their own follow-up. ExeCTU staff coordinated invitations and reminders and provided support to participants with booking follow-up visits through the appointment website. Participants were able to select a follow-up appointment at any of the five sites, irrespective of where they attended at baseline. The appointment website did not allow participants to cancel or re-schedule an appointment unassisted.

Results
Of 175 UK participants, follow-up was coordinated centrally for 157 participants. Overall, 661 initial invitation emails, 264 reminder emails, 151 reminder phone calls and 63 final reminder emails were sent by ExeCTU. While a majority of participants were able to book follow-up visits online unassisted, ExeCTU staff were required to support booking, re-scheduling and cancelling appointments on 93 occasions. Follow-up visits were attended by 160 (91.4%), 149 (85.1%), 143 (81.7%) and 140 (80.0%) participants at 3, 6, 9 and 12 months, respectively. 131 follow-up visits were at a different site from the baseline visit.

Discussion
The BRACE trial procedures were designed to provide flexibility for participants and minimise burden on sites. This was achieved by ExeCTU staff coordinating the majority of the follow-up management and support to participants. Most participants were able to book follow-up visits unassisted, suggesting the appointment website was a useful tool. Sending invitations and reminders and providing support to participants had substantial human resource implications for ExeCTU. Enabling participants to attend follow up at any site likely contributed to the high retention rate.

P-180

OPT out versus OPT in – Controversial or common sense?

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Introduction
OPT-out procedures can be used instead of OPT-in consent to enable individuals to exercise their autonomous preferences regarding research participation while reducing participant/researcher burden. In one study, 14.5% of participants did OPT-out showing the process empowered patients to decline participation (1) and a significantly lower recruitment rate was found in an OPT-in arm (2). There is minimal evidence to inform the decision on what approach (OPT-out/OPT-in) is most effective for a questionnaire follow up in trials extended beyond their original duration. Recently REC reviewed plans to use an OPT-out process for an existing consented cohort of participants to complete one additional 4 year questionnaire in the TOPSY trial (RCT to determine the effectiveness of self-management of vaginal pessaries on the quality of life for women with prolapse) (3). The REC's view was that OPT-out was not ethical and was an additional burden on participants. We will present our findings on OPT-in and OPT-out response rates for participants invited to complete a 4-year questionnaire.

Methods
Trial participants previously consented to completing a questionnaire at baseline, 6, 12 and 18 months. They were approached about the 4-year follow up at the time of being sent summary results. REC stipulated women had to OPT-in therefore we asked participants to let us know if they wanted to be sent the 4-year questionnaire and they could do this via an expression of interest form, an email or a telephone call. We also said they could let us know if they did NOT want to complete the questionnaire (OPT-out). 308 women were sent information about the 4 year follow up by 31st May 2022. We will present data on:

- % of OPT-in and OPT-OUT and non-responders
- % of OPT-in/ OPT-out responses by paper, email or phone
- Comparisons based on clinical characteristics such as; pessary type, continuation of pessary use.

Timing of potential results
We will provide further evidence on the process of OPT–in and OPT-out for low risk research activity such as questionnaire follow up. In an era where trials are becoming more efficient, we need to add to the evidence pool on the benefits, harms and acceptability of OPT-out options.

Potential relevance and impact
Increasing the evidence for OPT-in and OPT-out response rates for a long term follow up would support RECs in making decisions about opt out in future studies.

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Adherence to automated email/text requests to complete electronic questionnaires in different trauma populations

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Introduction
Poor retention in trials can reduce power and affect generalisability, validity and reliability of results. Routine clinic appointments are frequently used by research teams to obtain patient-reported outcomes and to maintain a level of contact with participants. In orthopaedic trauma trials, clinical follow up appointments are often limited, which increases the risk of loss to follow up or incomplete research data. Previously participants were contacted via postal questionnaire or telephone interview, however both of these methods are resource intensive. Electronic completion of questionnaires is anecdotally seen as the solution to this issue and is becoming increasingly popular without high quality data underpinning its use.

Aim
To assess the compliance with automated email/text requests to complete electronic trial questionnaires in different trauma patient populations.

Methods
Compliance data were collected between Dec 2019 and May 2022 from four large multi-centre trials recruiting; humeral fracture patients over 18 years; unstable ankle fracture patients 18-60 years; wrist fracture patients over 50 years; and ankle fracture patients over 18 years. Follow-up schedules varied, with initial weekly assessments for two trials, whilst two others only required contact after three months post-randomisation. All trials were conducted by the Oxford Trauma and Emergency Care group at the University of Oxford. An electronic system monitored the percentage of participants completing questionnaires following a link via email/text without trial management input.

Results
Electronic questionnaire completion without trial team input varied from approximately 60 per cent in two studies to 90 per cent in two other studies. Both studies with initial weekly follow-up found high return rates, with longer term follow-up remaining high in one study yet tailing off to 75 per cent in the other.

Discussion
Analysing how data is being completed by trial participants provides a foundation for trial managers for improving retention in follow up, furthermore it will allow for more accurate resource requests from funders. An initial finding is that the trials who had high compliance with the electronic questionnaires send questionnaires to the participant weekly for the first four to eight weeks, whereas the studies whose first follow up point was three months after baseline needed more input from the trial team.

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Participant choice of response mode for self-report outcomes in clinical trials: a comparison of baseline characteristics and questionnaire return rates between paper and digital

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Introduction
Retaining participants throughout follow-up is key to the efficiency and validity of trials. Offering participants a choice of how to complete questionnaires is increasingly common, but will increase the complexity of trial delivery and, potentially, trial costs. It is therefore important to establish whether offering this choice is beneficial to the trial, increasing questionnaires return rates in an efficient manner. Previous research (women only) has suggested that participants who choose to respond online rather than on paper tend to be younger and more highly educated. In a trial of women and men in work, we investigated whether baseline characteristics were related to chosen mode of questionnaire completion, and whether the mode chosen impacted on return rate.

Methods
WORKWELL is a pragmatic, multi-centre, individually-randomised trial of job-retention vocational rehabilitation for employed people with inflammatory arthritis. Participants were given the choice of follow-up via online or paper-based completion of questionnaires. Chosen mode of response and questionnaire return rate were analysed using univariable and multivariable logistic regression.

Results
Of 249 participants (Mean [SD] age 48.6 [9.9] years; 45 [18.2%] male), 114 (45.8%) chose to complete their outcome questionnaires online. Univariable regression analysis showed that younger participants, those who had been educated to diploma or degree level, and those working in higher-skilled jobs (Standard Occupational Class sub-major groups 3 and 4) were significantly more likely to choose to complete online. When multivariable logistic regression including these factors was performed, only age (OR=0.84 per 5 years older, 95%CI 0.74-0.97) and education level (OR=2.00, 95%CI 1.06-3.77) remained significant. Questionnaire return rates were significantly lower amongst those who chose online completion at both 6 months (82% versus 91%, OR=0.43, 95%CI 0.20-0.92) and 12 months (75% versus 87%, OR=0.44, 95%CI 0.23-0.86). Adjustment by age and education level slightly reduced the estimated effect of chosen mode of completion on return rate (6-month questionnaire: OR=0.52, 95%CI 0.23-1.16; 12-month questionnaire: OR=0.49, 95%CI 0.24-1.00).

Discussion
Findings were consistent with previous research, confirming that younger and more educated participants were more likely to choose to respond online. However, questionnaire return rates were lower for those who chose online completion, although this did not remain significant after adjustment for age and education level. Further research is needed into whether return rates differ by response mode, how enabling participant choice of response mode impacts on overall trial efficiency, and in what circumstances it is most important to offer participants this choice.

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Participant retention in paediatric randomized controlled trials: systematic review and meta-analysis

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Introduction
More randomized controlled trials are conducted involving children than ever before, however the factors which influence retention to these trials are under-researched. This systematic review and meta-analysis aimed to explore the factors which may influence retention.

Methods
Using the MEDLINE database, paediatric randomized controlled trials published between 2015 and 2019 were reviewed from five journals. The inclusion criteria were that the trial involved young people aged less than 18 and the intervention targeted the young people. The outcome was retention of participants for the primary outcome. Pre-specified trial context and design factors were extracted. To investigate potential sources of heterogeneity between trials, a univariate random-effects meta-regression analysis of the overall proportion retained in each trial by each of the trial context and design factors was used. This analysis was carried out in Stata 16.1.

Results
Ninety-four trials were included in this review. Higher estimates of retention were seen for trials with more follow-up assessments before the primary outcome, and those that had a shorter length of time until primary outcome. Trials that involved older children and those that did not include other participants (parents or teachers) also had higher retention. There was also evidence that using engagement methods such as reminders of the trial or incentives also increase retention.

Discussion
Paediatric RCTs should include multiple, regular follow-ups with participants specifically focusing on follow-ups before the primary outcome to reduce attrition. Retention is highest when the primary outcome(s) is collected up to six-months after a participant starts in a trial. Further research is needed to investigate how to improve retention when trials involve multiple participants such as young people and their parents or teachers. Those designing trials also need to consider the use of appropriate engagement methods such as incentives or reminders when planning a paediatric trial. This review was limited by the lack of reporting of key information about trial design and methods in published reports, and we are therefore unable to suggest specific methods of engagement to increase retention.

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How much is the lack of retention evidence costing trial teams in Ireland and the United Kingdom?

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Introduction
Evidence to support the use of many retention strategies in clinical trials is lacking. Despite this, trial teams still need to have some form of retention strategy in their trials to try and avoid high attrition rates. This study aimed to estimate how much this lack of retention evidence might be costing trials in Ireland and the United Kingdom.

Methods/Approach
We selected the top ten most routinely used retention strategies by Clinical Trial Units in the United Kingdom and made assumptions as to how each of these strategies was most likely to be implemented and the costs involved in doing this. We applied our costing model to a hypothetical trial scenario in both Ireland and the United Kingdom as well as to three published trial protocols. We developed the costing model and calculated the costs in Microsoft Excel.

Results
Retention strategies were often poorly specified, meaning we had to make assumptions about implementation and in some cases about the strategy itself. Based on our assumptions, some retention strategies can be extremely expensive; some of the costliest strategies included "data collection scheduled with routine care" (€900 - €32,503.25), "a timeline of participant visits for sites" – with integrated participant reminder (€304.74 –€14,803.70), and "routine site visits by CTU staff" and "investigator meetings face to face", both costing (€777.67 - €14,753.48). Others such as "telephone reminders for questionnaire response" (€34.58 - €568.62), "a timeline of participant visits for sites" – site reminder alone (€79.18 - €112.23), and "targeted recruitment of sites/GPs" (€30 - €1,620) were less costly compared to the other strategies.

Discussion
The cost of some of the strategies that are currently routinely used are significant, and so is the lack evidence to support their use. The evidence to support the ten most-used trial retention strategies by CTUs in the United Kingdom is weak or lacking entirely. Where benefits are currently unknown, evaluation should be a priority. We recommend the wider use of SWATs to evaluate the effects of retention strategies used in clinical trials to avoid persistent and widespread research waste.
Without evidence regarding the effectiveness of trial retention strategies, trial teams will continue to put substantial amounts of money into strategies that potentially have no beneficial impact on participant retention. More evaluation of the effectiveness and cost of trial retention strategies is needed to avoid widespread use of strategies that are both expensive and ineffective.

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Grip strength measurements at home: are self-administered measurements feasible?

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Introduction
Distal radius fractures are common fractures that are treated surgically or non-surgically, followed by several weeks in a cast or splint. Reduced grip strength is common after this injury, affecting daily tasks, like cooking. The WISE study is assessing the feasibility of a full-scale trial evaluating upper limb exercise for adults aged 50 years and over after distal radius fracture. Grip strength is a planned full-scale trial outcome. Normally, this requires face-to-face measurement by a researcher, which can be burdensome for participants. To help determine if self-administered grip strength measurement by participants is feasible for the full-scale trial, we are measuring the proportion of participants sent hand-held dynamometers that 1) return dynamometers, and 2) record grip strength measurements as instructed.

Methods
WISE is a parallel, three-group, feasibility randomised controlled trial. Participants are aged ≥50 years with a distal radius fracture recruited from six NHS hospitals. Allocation was 1:1:1 to usual care, independent exercise (usual care plus one session of advice and exercise with a therapist), or supervised exercise (usual care plus three sessions). We originally planned to measure grip strength face-to-face at study sites six months after randomisation. Due to COVID-19 restrictions, we decided to post hand-held dynamometers (CAMRY EH101) with written and video instructions to participants who complete six-month follow-up questionnaires to independently measure grip strength. Participants are asked to record grip strength on two consecutive days then return the dynamometer using a freepost envelope. A bespoke questionnaire assesses participants' difficulty recording grip strength, satisfaction with the dynamometer and instructions provided, and the perceived importance of grip strength.

Timing of Potential Results
We recruited 117 participants. Six participants withdrew. 95/103 (92%) participants who have reached the six-month time point have completed follow-up questionnaires and 92 were sent a hand-held dynamometer. Currently, 70/92 (76%) dynamometers have been returned – all undamaged. 67/92 (73%) participants provided grip strength data for two consecutive days as intended. Questionnaire responses indicated that participants thought grip strength measurement was easy to perform, grip strength was important, and the dynamometer and instructions provided were satisfactory.

Potential Relevance & Impact
A high proportion of participants posted hand-held dynamometers returned these and recorded grip strength measurement as intended, suggesting self-administered grip strength measurement by participants could be a feasible outcome assessment method. Validity of this self-administered grip strength measurement method needs to be assessed.

Trial registration: ISRCTN12290145
Funding: National Institute of Health and Care Research (NIHR200458)

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Including a theoretically informed leaflet in a participant take-home pack to improve questionnaire response rates.

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Introduction
Ensuring adequately high levels of participant response rates for patient reported outcomes collected by questionnaire is a common challenge for clinical trials. The evidence on strategies to improve retention to clinical trials is sparse – none of the 52 comparisons in the most recent update of the Cochrane review on strategies to improve retention provided high certainty evidence of effectiveness [Gillies et al 2021]. One area of interest is to develop approaches informed by behavioural science – in effect retention behaviour change interventions. The participant targeted actions involved in retention are behaviours i.e. returning a questionnaire or not. Therefore, leveraging the science of behaviour change to develop theory informed retention interventions offers promise. Developing behaviour change techniques into intervention to target retention has demonstrated that a theoretically-informed letter sent with questionnaires improved response rates compared with a standard letter [Goulao et al. 2020].

Methods
This Study Within a Trial (SWAT) aimed to increase response rates to the PUrE trial [McClinton et al., 2020] participant reported questionnaires by randomising half of the participants to receive a theoretically-informed leaflet outlining the importance of questionnaire response delivered in the participant pack. The leaflet was developed using the Theoretical Domains Framework (TDF). The salient domains for the target behaviour (returning questionnaires) were identified from qualitative studies in the literature. Recurring theoretical targets were categorised and strategies known to influence these salient domains were identified using Behaviour Change Technique taxonomies. These strategies were operationalised into a participant leaflet which was further developed with input from patient partners in the trial patient group. PUrE trial participants (N=255) were randomised 1:1 at the time of the PUrE main trial randomisation to receive the theoretically informed leaflet in their questionnaire take-home packs (n=125) or the study compliment's slip (n=130) which was included as standard. Sample size was determined by the number of PUrE trial participants available.

Results
Results will be available for presentation at the conference. Data will be analysed according to the intention-to-treat principle and will compare the overall response rate at each time point between the groups and the difference in response rate with 95% confidence intervals and p values.

Impact
Findings from this SWAT will be considered in the context of the existing evidence on intervention to improve retention to trials. Lessons learnt from the operationalisation and implementation of this SWAT will also be shared alongside transferable learning for the development of retention interventions.

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Developing theory-based text messages to support retention in clinical trials: A mixed methods approach

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Introduction

Returning a trial questionnaire is a behaviour affected by a range of psychological and contextual factors. Previously tested Short Message Service (SMS) interventions to prompt questionnaire return have not addressed these factors, are atheoretical, and have not been characterised by established taxonomies of behaviour change techniques (BCTs). Research suggests people often fail to recognise the contribution they are making to trials through questionnaire return. Such beliefs about the consequences of their behaviour could be targeted to support questionnaire return. We aimed to develop theory-based SMS messages to support participant understanding of the consequences of not returning trial questionnaires, that are acceptable and show fidelity to BCTs addressing beliefs about consequences.

Methods/Approach

Four members of the research team generated 32 messages based on four BCTs identified to address beliefs about consequences of questionnaire return. We used an iterative set of studies to refine the messages. In Study 1, 10 experts in behaviour change rated how well each message reflected the target BCT, on a scale of 1 (not very well) to 10 (very well). We stipulated messages scoring below the midpoint would be removed. Study 2 involved a focus group to discuss message acceptability, involving five women affected by breast cancer, as this population was the target of a future Study Within a Trial (SWAT). In Study 3, 60 breast cancer survivors rated each message on acceptability, from 1 (completely unacceptable) to 5 (completely acceptable), with messages scoring below the midpoint removed. In Study 4, 12 new experts in behaviour change rated the remaining messages on their fidelity to the intended BCT (scale of 1 to 10).

Results

In Study 1, all 32 messages had adequate fidelity to the intended BCT (mean=6.8/10 [SD=0.6) to 7.5/10 [SD=0.3]). In Study 2, patients recommended removing the BCT 'Comparative imagining of future outcomes' (4 messages) and two further messages, and requested amendments to 5 messages. In Study 3, 60 breast cancer survivors rated all remaining messages as acceptable (mean=3.8/5 [SD=1.2] to 4.3/5 [SD=0.8]). In Study 4, experts rated all remaining messages as having adequate fidelity to the intended BCTs (mean=6.1/10 [SD=2.4] to 6.9/10 [SD=1.4]).

Discussion

We developed a pool of 26 acceptable SMS messages with fidelity to intended BCTs. This approach could be used to design interventions supporting behaviours needed for trial delivery. We are evaluating two messages within a SWAT. The message pool is available to researchers interested in undertaking their own SWAT.

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Safety Reporting and reconciliation in large complex studies, experiences from the AML19 trial

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Introduction
Safety reporting in clinical trials must be performed in a timely manner and reconciled between the clinical and safety databases to ensure all events are captured appropriately. This can be difficult in complex, fast-moving, multi-arm trials and new approaches are needed.

Methods/Approach
AML19 is a complex phase III multi-arm international trial in leukaemia, with >100 hospitals and >2000 patients. Patients can have several courses of chemotherapy across both standard-risk and high-risk arms and may be exposed to several different Investigational Medicinal Products. Patients experience a large number and wide range of severe toxicites, some of which do not require reporting, and as such Serious Adverse Event (SAE) reporting criteria is very complex- increasing the risk of events being missed and going unreported. Reconciliation between databases is complicated for reasons such as differing event terms and events not meeting SAE criteria for several days which results in dates differing between records. Therefore, instantaneous reconciliation concerning a small number of events is more manageable than retrospective reconciliation of a large number of events.
The AML19 team developed a system in the trial database whereby emails would fire following completion of a Course Form in which toxicites are reported. If any toxicities potentially met SAE criteria, an SAE reference number was requested within the database. Following form submission, an email would fire to the Pharmacovigilance team, trial team, and site team to flag events which may meet SAE criteria and their SAE reference number (if given). If an SAE reference number was not provided, this would be apparent and queries would be sent to site immediately, to request an SAE be submitted or reason provided as to why it was not required.

Results
The email system has been useful for flagging potential unreported SAEs and minimising the risk of a delay between the event occurring and event being reported. SAE reports are reported in a timelier manner, and it allows for easier reconciliation and checking between databases.

Discussion
Trial teams should consider during database set-up which email triggers would be useful for reconciliation and querying for potential SAEs, and include these where possible. Bespoke database systems allow much more flexibility with this and may be worth the expense due to time-saving benefits later in the trial. However, these methods do rely on timely data entry from site and more needs to be done to improve upon this.

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How are Safety Data Reported in Publications? – A Systematic Review of Phase III Cancer Trials

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Introduction
To fully evaluate a new treatment, safety data are required alongside efficacy data. Trials typically collect 'severity' and 'seriousness' of safety data, but it is anticipated that publications may only report the former. We performed a large systematic review to identify how safety data are reported in phase III cancer clinical trials.

Methods/Approach
A literature search was performed in the Medline database using OVID, limited to studies published in 2019/20, with keywords including 'cancer', 'malignant neoplasm', 'clinical trial', 'randomised clinical trial', 'randomized clinical trial', 'RCT', 'trial', 'safety' and 'pharmacovigilance'. Title screening was performed (without prior sight of abstract), followed by abstract screening. Double screening was performed for a sample of title and abstract screening. Data including trial setting and size, description of the safety data to be collected and analysed as recorded in the methods, details of any safety analyses included in the results (such as number of patients with at least one adverse event of a specified grade, number of serious adverse events, or most common adverse event) will be extracted from each paper included in full text review. Analysis plans for safety data, inlcuding whether this was prespecified in methods section of paper will also be extracted. These data, as well as any further safety analyses included in the papers' supplementary material, will be summarised using descriptive statistics.

Results Structure and Timelines
19,102 records were identified for title screening, of which 16,198 were excluded based on title alone. A further 2195 records were excluded based on abstract screening, for reasons including conference abstract only, not a randomised controlled trial, early phase trial, trial not in cancer, pooled trials paper, paper describing post-hoc analyses only, and trial in progress paper (no results). 709 records were identified for inclusion for full text review. Full text review of manuscripts is ongoing, and results will be known in September 2022.

Potential Relevance and Impact
The results of this comprehensive systematic review will provide a view on current practice and inform recommendations for the inclusion of safety data in clinical trial publications.

P-190

A description of training accessed and gaps in provision identified by trial managers – a survey from Ireland and UK

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Introduction
Trial managers (TM) have a central role in the clinical trial team and provide skills essential for a successful trial. Such a role requires training and qualifications.
However, TMs are often overlooked members of the team and have no standardised career development. In 2022 trial management was called a profession in crisis by the UK Trial Managers' Network. A 2020 UK survey of trial managers highlighted relevant training, help in the design of trials and gaining qualifications relevant to trial management as being key to a rewarding trial management career. We wanted to supplement this with more detailed trial manager views on what they need to do their job effectively and progress their careers in Ireland and the UK.

Methods/Approach
An online survey was circulated using relevant networks and social media, between August and September 2020. The survey contained 44 questions, both closed and open-ended, arranged in three sections, with 'Training and experience' reported here.

Results Structure and Timelines
A total of 218 responded to the survey, n=34 from Ireland and n=184 from the UK. The majority of respondents had extensive experience managing single centre, multi centre and multinational trials (n=143). Analysis is ongoing but initial findings show that respondents listed 52 job titles, with 170 saying they fulfilled the role of TM while 12 listed oversight of TMs or other roles. Fifty-three individuals reported having either a professional management or clinical trial qualification, while nine areas of training (e.g. practical trial management with case studies and research governance including trial setup, monitoring and closedown and archiving) were identified as lacking. Most additional training mentioned was delivered by the UKTMN (n=91) to which few TMs in Ireland have access (n=5).
Findings will be reported in terms of frequencies of responses to closed questions and responses to open-ended questions will be content analysed and themes presented. Differences between the UK and Ireland will be highlighted, as will gaps in need of action in the UK/Ireland.

Potential Relevance and Impact
To develop a clear career development path for TMs, information about current training levels and gaps in training supply is needed. We will give a description of the kind of training and qualifications that TMs themselves have identified as missing in the UK and Ireland. This knowledge will enable employers and training providers to design and offer more appropriate training and highlight where the countries might collaborate.

P-191

Running a CTIMP during COVID restrictions

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The USTEKID trial is evaluating the impact of administering ustekinumab (STELARA™) to 12-18y olds newly diagnosed with Type 1 Diabetes (T1D) in a 2:1 randomised, double blind trial running in 16 hospitals across the UK. We aimed to recruit, randomise and dose 72 participants and administer either active treatment or placebo (saline) to them at weeks 0, 4, 12, 20, 28, 36 and 44, with the main follow up visit at week 52.
When COVID restrictions were first implemented in March 2020 and we had to pause recruitment, having only consented 32 of the 72 participants needed. Four months later we were ready to reopen to recruitment in sites happy to give approval (n = 6 / 16). Other sites were either prioritising COVID research or were far slower issuing approval.
The trial managed to continue treatment visits and data collection throughout the restrictions for three reasons:

1. a few sites did not stop trial treatment or follow up visits on site
2. we obtained approval to ship blinded drug to the participant's home
3. some outcomes could be measured using proxies

As the participants were all diagnosed with T1D, they were used to daily subcutaneous injections. The blinded treatment was prepared by Pharmacy at the site and immediately shipped to the participant's home within the four hour expiry date by an approved courier. The parent would typically oversee or administer the injection and we also had an unblinded research nurse video call the family prior to administration to check that everything was done correctly.
We had a few participants who lived too far away from the site to work with the four hour expiry of the syringe. In these cases, we opted to overlabel the vial to blind the user to its contents and prepared a box containing all the relevant materials for the family to make up the syringe themselves. Again, the unblinded research nurse video called to oversee the preparation and administration of the syringe.
The week 28 dose and week 52 follow up involved MMTTs. At sites, this would require regular venous blood draws at time 0, 15, 30, 60, 90 and 120 mins using a cannula but for home-based MMTTs, we opted to use dried blood spot cards to collect blood for c-peptide analysis.
The trial has completed recruitment only four months later than planned and is expecting last patient last visit in Sept 2022.

P-192

Strategies to increase retention of participants in a definitive RCT: aiming to retain power in a study impacted by COVID-19

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Introduction
Recruitment of participants to non-COVID clinical trials has been a challenge over the last couple of years. It is important to maximise recruitment in clinical trials but retention is of equal importance to study validity, and loss to follow-up rates also have a direct effect on the study power. Sample size calculations usually include adjustment for expected loss to follow-up rates, and if retention can be improved this can help to compensate when studies do not recruit the target number (1).

Method
REDUCE (REviewing long term antiDepressant Use by Careful monitoring in Everyday practice) study is a two-arm, 1:1 parallel group randomised controlled trial, with randomisation clustered by participating family practices. The study aimed to recruit 402 patients to have 90% power, assuming 20% loss to follow-up (2). Due to the pandemic and resulting pressure on primary care this target was not met. We needed to achieve six month follow-up rates above 80% to maintain sufficient power.
The COVID-19 pandemic also made follow-up challenging, and multiple strategies were employed by the study co-ordinators to maximize retention rates. Our main strategy was to identify suitable modes of communication with the patients e.g. regular contact via phone, email, sending multiple requests to non-responders, and discussing potential or anticipated barriers to survey completion (3). We implemented the following approaches:
1. The three coordinating centres (Southampton, Liverpool and Hull) worked together through weekly meetings to share ideas and find a best way to improve retention rate.
2. Southampton and Liverpool sentg the iSurvey links for follow-up questionnaires through an email. In Hull a text message was sent after the email which included a reminder of ID and password. All centres subsequently used the same method.
3. During the 6-week survey completion window, a reminder was sent every two weeks and patients had the option to complete the survey by phone.

Results
We recruited 330 patients (178 randomly allocated to the intervention arm and 152 controls), from 105 general practices. To date, 230 patients have reached 6 months follow-up and retention rates are above 80%. Being reactive to the need for improved retention and implementing new approaches and methods in all three centres has improved retention rates.

Conclusion
Retaining participants is vital to study success and exploring different communication strategies with patients can help to improve this.

Trial Registration: ISRCTN 12417565

P-193

Implementation of a novel site training process incorporating pre-recorded training in lieu of traditional site initiation visits.

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Introduction
Site initiation visits (SIVs) are traditionally conducted face-to-face or remotely, to deliver training before opening a site to recruitment. This can be burdensome during the resource-intensive trial set-up period, particularly for multi-centre trials with a high number of sites. Arranging a time when all relevant site and clinical trials unit (CTU) staff are available can be problematic, often delaying site opening. This has been further exacerbated by the COVID-19 pandemic which has led to a reduction in NHS staff resource. Streamlining the pre-trial training process could positively impact trial set-up and therefore recruitment timelines, though little research has been conducted to determine the most effective approach.
For the RE-ARM trial we developed a new training process, incorporating face-to-face and pre-recorded sessions, for increased efficiency and convenience.

Methods
RE-ARM is a multi-centre clinical trial assessing an immunotherapy/radiotherapy combination in metastatic urothelial cancer, aiming to open 20 UK sites. Sites were given the option of attending a remote launch meeting, taking the format of a traditional SIV, describing trial rationale and impact, detailing protocol-related procedures, and providing the opportunity for questions. Recorded presentations were subsequently made available to site staff as short videos. Prior to site activation, the Principal Investigator (PI) and Data Manager/Trial Coordinator were required to have either attended the launch meeting or confirmed they had watched the videos (2/6 videos were deemed mandatory). To mitigate the concern, based on previous research, that pre-recorded training is less effective than face-to-face, a structured informal discussion was held between the site and CTU team 1-2 months after activation, providing an opportunity for questions and to discuss any local recruitment issues.

Timing of Potential Results
The launch meeting was held in July 2021; 11 PIs and 47 site staff attended. To date, seven sites are open to recruitment. Of these, four (57%) had staff members who either could not attend the launch meeting or chose to watch the videos instead. Feedback from site staff will be presented. Expected benefits of the approach include staff being able to undertake training when convenient, fitting around competing clinical demands, and training being readily available for refresher or new staff training as required.

Potential relevance and Impact
Streamlining the training process prior to site opening may expedite site activation and trial recruitment and reduce CTU and site staff resource. Informal discussions after site opening allows opportunity to discuss trial progress and practicalities, identifying any recruitment barriers.

P-194

Does the burden of collecting investigator CVs and mandating up-to-date GCP certificates in large multi-centre trials outweigh the potential benefit? Experience from the TICH-2 Trial.

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Introduction
TICH-2 was a large multi-centre international pragmatic trial to assess whether tranexamic acid reduces death and dependency after hyperacute (within 8 hours of onset) spontaneous intracerebral haemorrhage (ICH). TICH-2 was run in accordance with the principle of International Conference on Harmonization (ICH) and good clinical practice (GCP). We aim to explore the impact of investigator curriculum vitae (CV) collection and the mandating of up-to-date GCP certificates on investigators, sites and the trial's coordinating centre.

Methods
We retrospectively reviewed the electronic delegation log and investigator account manager for TICH-2. As part of study set up it was necessary for investigators to provide their CV and an up-to-date (<2 years) GCP certificate before being given an account.

Results
Enrolment of 2325 participants took place at 124 hospital sites in 12 countries from 14th March 2013 to 29th September 2017. Overall, 1,613 TICH-2 investigators were added to the electronic delegation log during the period 18th February 2013 until 12th July 2017. Of these, 1,333 (82.6%) were attached to UK sites and 280 (17.4%) to non-UK sites. 1,341 (83%) investigators indicated via the online system that they had completed trial training and would comply with GCP. Of those 1,341 investigators, 50 (3.7%), were central site staff and 1,291 (96.3%) were attached to the other recruiting sites. There were 98 (7.3%) investigator accounts set up for the on-site pharmacists. Of the 1,333 site investigators attached to UK sites, 754 (56.6%) indicated via the online system that they had undergone consent training. As for non-UK sites, 213/280 (76.1%) investigators indicated they had consent training. A formal training assessment for trial investigators was introduced on 17th November 2014. From this date, up to the end of recruitment, 361 (27.1%) UK site investigators and 62 (22.1%) non-UK site investigators took the training assessment. Further data collected from the delegation logs and account manager will be presented at the time of the conference.

Potential Relevance and Impact
The data presented highlights the large number of investigators involved delivering a hyperacute stroke trial. Steps should be taken when setting up new clinical trials to streamline methodology and reduce burden on sites and clinical trial units to be proportionate to risk. We suggest focusing on trial specific training is likely to be of greater benefit that routine collecting CVs and training certificates.

P-195

Comparing two different models of Research Nurse deployment to a multi-centre clinical trial in primary care: experiences from the CANAssess 2 Trial

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Introduction

Recruitment to multi-centre trials in primary care is challenging. We compare the effects of two different models of Research Nurse (RN) deployment on set-up processes and timelines, recruitment rates and research efficiency within a multi-centre cluster Randomised Controlled Trial (cRCT).

Methods

Our ongoing CANAssess trial, funded by Yorkshire Cancer Research, evaluating a needs assessment tool for people living with cancer, aims to recruit 1,080 participants from 54 general practices, within four geographical recruitment hubs. One hub accessed practice-based RNs to recruit participants and conduct data collection (Model 1). Three hubs each employed a study-specific RN to recruit participants, conduct data collection, and provide additional support to trial set-up at practices (Model 2). Each hub has a target of recruiting 270 participants from 13-14 practices (Model 1 = 270 participants, 14 practices; Model 2 = 810 participants, 40 practices).

We compare the two models in terms of number of practices open, participants recruited, length of trial set-up at practices, average time to recruit first participant, and RN costs.

Results

In Model 1, the first practice opened in October 2020 vs January 2021 in Model 2. By 12 May 2022, CANAssess has recruited 390 participants from 29 practices: 185 in Model 1 (12 practices, 69% participant target, 86% practice target, mean 15/practice) and 205 in Model 2 (17 practices, 25% participant target, 43% practice target, mean 12/practice). The mean recruitment rate/practice/month was similar between Model 1 and Model 2 (1.2 vs 1.1). The mean trial set-up time was longer in Model 1 (249 days vs 186 days). The mean time to first participant recruited was longer in Model 1 (88 days vs 46 days). The RN estimated cost per participant recruited was lower in Model 1 (max. £144 based on activity vs £531.69).

Discussion

Study-specific RNs (Model 2) allowed practices to open and recruit their first participant quicker due to less training involved at the practice and the RN working full-time on the trial. However, practice-based RNs (Model 1) could commence immediately, three months earlier than Model 2, due to employment process delays in Model 2 and incurred lower costs per participant recruited. We recommend a hybrid recruitment approach to maximise recruitment in primary care trials, allowing some practices to open more quickly and others to recruit over a longer period of time with less cost involved, all at a similar recruitment rate.

P-196

Challenges and lessons learnt from implementing a master screening protocol as part of a platform trial in metastatic castrate resistant prostate cancer: the MAESTRO study

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Introduction
Platform trials are an efficient way to evaluate multiple treatments under one protocol or overarching framework. MAESTRO is a screening protocol for downstream trials within the MAESTRO-PERSEUS platform, investigating interventions in metastatic castrate resistant prostate cancer (mCRPC) with specific genetic aberrations. The primary objective of MAESTRO is to determine the frequency of targetable molecular aberrations in archival and fresh tumour tissue.

Methods
MAESTRO is a separate protocol from downstream trials, allowing flexibility for sites with regards to participation; removing agreement complexity with multiple stakeholders; and enabling research into mutation prevalence. PERSEUS1 is the first downstream trial, with more in development. Multiple downstream trials will maximise targeted treatment options for participants, with a hierarchy based on mutation rarity.
MAESTRO biopsies have provided an operational challenge; insufficient tumour for analysis has meant some participants could not be molecularly profiled. Where appropriate, re-biopsy has been permitted with consent, however timing is critical and the patient could miss the window to be profiled. To reduce burden to patients and centres, a protocol amendment was submitted allowing use of biopsies taken within 6 months of study entry if the patient had not had any subsequent treatment.

Results
This modular approach to delivering a platform trial has been challenged by the COVID-19 pandemic, with resource issues at sites due to competing priorities, and a pause in recruitment between March and May 2020. There is a risk of MAESTRO recruitment outpacing downstream therapeutic trials, due to lengthy set-up times. Some sites expressed interest in MAESTRO but not PERSEUS1 where capacity prevented both opening. This modular approach increased ease of set-up at the start, however a unified protocol could have maximised the delivery of this platform in the long run.
MAESTRO opened to recruitment on 28/11/2019 and as of 16/05/2022 had recruited 140 patients out of a target of 600.

Discussion
There are both benefits and challenges to conducting a platform trial with separate protocols. Despite its challenges, MAESTRO benefitted from being able to have its own objectives, allowing patients' data to be used regardless of whether there are suitable downstream trials. It also allows sites to select which of the downstream trials they have the capacity for. MAESTRO permits robust tumour molecular stratification for participants and will enable a better understanding of the molecular landscape of mCRPC.

P-197

An eTMF implementation in Microsoft SharePoint

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Introduction
During the COVID-19 lockdown with staff based at home, maintaining a central paper-based Trial Master File (TMF) in a Clinical Trials Unit (CTU) was impractical. A way of electronically managing and approving TMF documents was needed. With resources too limited to spend on a commercial document management system, the Nottingham CTU decided to implement a solution using MS SharePoint, which is included with Microsoft Office 365.

Methods
A document library was created to host the eTMF documents and configured for version control using check-out/check-in features. A folder structure to organise documents was made, but the ability for users to create new subfolders was disabled, to prevent folder structure growth. To mitigate this restriction, a managed term-set (meta-data) was configured to enable users to tag documents. Tags were categorised by document type (e.g. Protocol, PIS, CRF), stage (e.g. Design, Approvals, Archive), and group (e.g. PPI, GPs, Statisticians).
Power Automate was used to create the approval process (known as a flow) to replace the paper-based sign off process. These allowed multiple approvers to be assigned to approve the document for which the flow was started. Approvers were able to approve or reject the document, and add comments which were recorded in the document version history audit log and approval log, along with copies of documents made at time of approval.

Results
Although staff found the SharePoint environment familiar, there were many novel steps that required extra training. How-to training videos and reference documents were created to help. Meta data tagging was not enforced, and was often left off. Creating sub folders therefore became essential, so the restriction on this was removed.

Discussion
Whilst the solution implemented met all the basic document management system requirements at no extra cost to the trials unit, it did present some usage challenges. The ability for multiple users to simultaneously edit a document was needed. As check-out/check-in version control precluded this, documents were instead initially drafted outside of the eTMF and later uploaded and approved.
Using a meta-data only with no folders to organise eTMF documents was considered but rejected as it was felt this would be too big a step for users already acclimatising to a new platform. A hybrid approach left staff always using the familiar folders rather than the tags.

P-198

Delivering a process evaluation alongside trial set-up – a Trial management perspective (NIFTy Trial)

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A common complication of thyroid surgery is damage or accidental removal of parathyroid glands, which can cause post-surgical hypoparathyroidism (PoSH). The NIFTy trial is looking at whether the use of fluorescence during surgery can help with identification and preservation of these glands to reduce the incidence of PoSH. Early phase trials have demonstrated the feasibility of fluorescence as an intra-operative tool but NIFTy will be the first large-scale trial looking at efficacy in this setting, therefore this is a relatively new technique.

Surgery is a complex healthcare intervention as there are multiple components that can be delivered in different ways by different surgeons. MRC guidance suggests where possible RCTs should standardise content and delivery of the intervention. This, coupled with the novel technology under investigation, informed the decision to incorporate a qualitative process evaluation (PE) into the trial.

The integrated PE set out to use case study observations, surveys and expert panel consensus approach to identify and describe key components of the operation, agree the operative protocol including timing of fluorescence, and inform trial data collection. The PE was planned to take place during set-up of the main trial and was submitted as a separate protocol/ethics application, aiming to observe thyroid (benign and malignant) operations at 3 sites. Setting up the main trial in parallel with the PE, rather than delivering these components consecutively, reduced overall set-up time. Consideration was given to how findings of the PE would be implemented into the main trial in a timely manner.

Unexpected delays with the PE were experienced due to unforeseen circumstances e.g. availability of devices, Excess Treatment Cost issues and COVID-19. To minimise the impact of delays adjustments were made including observations at a single site, and only cancer operations (non-cancer operations had not been re-started since the pandemic), which would result in smaller variance between operations; to mitigate this impact we drew on the expertise of the expert consensus panel and data from the surgeon surveys to gather a wider view.

We will describe our experience of incorporating a PE from a trial management perspective, including steps taken to minimise set-up time and coordination of the 2 parts of the project. It will also describe the purpose and design, how we adapted to unanticipated problems and discuss the lessons learnt and considerations for incorporating similar work in future trials.

P-199

Evaluation of a clinical trials training package in a neonatal trial in Kenya and India

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Introduction

Training is essential before working on a clinical trial, yet there is limited evidence on effective training methods. Training was the second highest priority identified in a trials methodology priority-setting exercise in low and middle income countries (LMICs). The aim of this study was to evaluate a clinical trials training package in two LMICs.

Methods

We explored whether an enhanced training package in a neonatal trial in LMICs, utilising elements of the "train-the-trainer" approach, altered clinicians and researchers' clinical trials knowledge. The study was conducted in two large teaching hospitals in Nairobi, Kenya and Varanasi, India. The training package included a lead "trainer" attending an introductory course on clinical trials in the UK and other staff attending a 2-day in-country training session. Training included good clinical practice (ICH-GCP), protocol and data collection, informed consent and practical training of running the study in the neonatal units. To assess effectiveness of the package, several questionnaires, including ICH-GCP and Informed Consent freely available from The Global Health Network (TGHN) were completed by staff attending training at the start and end of the study. Questionnaire data were analysed in Stata and reported descriptively. For participants who completed questionnaires at both timepoints, mean differences in scores and 95% confidence intervals are reported.

Results

Thirty participants (doctors, nurses, research staff) received training and completed baseline questionnaires. Around three quarters had previously worked on a research study, yet only half had received training. Participants who self-reported having prior research experience, scored higher in each questionnaire before the start of the study. Nineteen participants (63%) completed questionnaires at the end of the study period. Only marginal increases were seen in questionnaire scores at the end of the study period. Very few participants 'passed' the informed consent and ICH-Good Clinical Practice (GCP) modules (pass mark >80% in accordance with TGHN).

Conclusions

This is the first report evaluating a clinical trial training package in a neonatal trial in LMICs. Due to the Covid-19 pandemic, there was a significant time lapse between training and study start, which likely impacted upon the scores reported here. The training package did not improve questionnaire scores. Given the burden of disease in LMICs, developing and evaluating high-quality training is critical.

P-200

Is clinical trial remote comparable to on-site monitoring? Comparing before and after the COVID-19 pandemic lockdown in the UK via a single site case study

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Background
During "lockdown" restrictions imposed in the COVID-19 pandemic, on-site monitoring was often not possible in the UK and more experience with remote monitoring was gained. On-site monitoring is time-and-resource intensive whereas remote monitoring requires no travel time or travel costs (1). Remote monitoring may replace the more expensive on-site monitoring if it shown to have a similar performance. To assess the relative efficiency and effectiveness of these monitoring methods, our study compared during lockdown remote monitoring to pre-lockdown on-site monitoring.

Methods
We considered a trial from CRUK & UCL Clinical Trials Centre which changed during restrictions from mainly on-site monitoring to mainly remote monitoring. The trial was a prospective, open-label, non-randomized phase I clinical trial of an advanced investigational medicinal product in oncology. All the remote monitoring visit (MV) reports from one site for this trial were compared with enough pre-pandemic on-site MV reports to give a comparable monitoring workload as assessed by subject visits. The MV reports were reviewed to compare monitoring efficiency (in terms of subject visits source data verified per MV), monitoring effectiveness (number of monitoring findings identified per MV), and site performance (in terms of clearance rate of monitoring findings). This study was not research defined by the UK Policy Framework for Health and Social Care Research and therefore did not require ethical approval.

Results
Eight remote and 17 on-site MV reports were reviewed. Compared to on-site monitoring, the monitoring efficiency of remote monitoring was greater: 29 vs 16 source data verified subject visits per MV. The monitoring effectiveness of remote monitoring was comparable to on-site monitoring: 1.0 vs 0.6 identified monitoring findings per MV. The site performance of remote monitoring was comparable for solving the monitoring findings: 75% vs 70% clearance rate.

Conclusion
The performance of remote monitoring was comparable to on-site monitoring at a single site, in a single trial during an enforced COVID-19 pandemic change. Though limited to a single site in a single trial, the findings are encouraging and further exploration to supplement or replace on-site monitoring is warranted.

(1) Monitoring of Clinical Trials: A handbook https://ukcrc-ctu.org.uk/guidance-for-ctus/ [accessed 30May2022]

P-201

RCTs in Follow-up: A Remote Intervention to Maintain Site Engagement and Improve Data Quality during the Covid-19 Pandemic

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Introduction
Longitudinal studies which involve follow up and data collection beyond 24 months are known to be challenging due to the attrition rates of the recruited participants. Maintaining patient engagement, ensuring that follow ups are completed and data queries are resolved relies on effective communication with the research team. With the emergence of the Covid-19 pandemic site visits became impossible and techniques to maintain engagement with the local site investigators proved even more challenging. We designed a standardised, site-specific remote intervention to maintain site engagement, improve data quality and prevent researcher led attrition.

Method
The intervention was conducted via videoconference and each meeting required the mandatory attendance of the PI and site investigators. Each meeting followed the same format with a structured agenda and standardised site-specific data extracts (including an update on data completion, data quality and safety reporting). The sites' workload and capacity were also discussed. Where necessary, repeat meetings were organised to monitor progress and resolve ongoing issues.
The intervention was applied to two large, surgical, multi-centre RCTs* managed by the Bristol Trials Centre with up to 8 years of follow up. By-Band-Sleeve (BBS) is a bariatric RCT with 1351 participants recruited from 12 hospitals in England. MARS2 is an oncology RCT with 335 participants recruited from 23 centres across the UK. In both BBS and MARS2 the sites to engage with were selected and prioritised based on each study's specified data collection objectives.

Results and Discussion
Between 2020 and 2022, a total of 54 remote meetings were held across the two studies. In MARS2 the percentage of missing forms improved from 14% to 4% and the percentage of completed forms with no unresolved queries went from 75% to 94%.
In BBS completion of the two primary outcomes at the primary endpoint rose from 75% to 86% and 75% to 80% respectively in the period between March 2020 and April 2022. In addition, once sites had capacity to resume non-Covid research they were able to resolve at least 500 data queries a month.
The detailed, site-specific remote intervention improved data quality and query resolution. We noted improvements in communication from our sites and Covid-related capacity issues were flagged. We recommend that similar studies prepare regular, remote monitoring meetings to achieve these benefits as a standardised practice.

P-202

Can patient and public involvement (PPI) representatives serve as independent members on Data Monitoring Committees?

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Background
There has been an increasing, appropriate focus on deepening patient and public involvement (PPI) within clinical trials. PPI representatives are now routinely members of Trial Management Groups or Trial Steering Committees (two types of oversight committee) for many trials. However, one oversight committee that rarely has PPI members is the Data Monitoring Committee (DMC). Our previous global survey of 375 clinical trialists found that 57% supported a role for independent PPI representatives on DMCs, and 24% highlighted the need for further research. Accordingly, we conducted a new online survey to focus specifically on the experiences and opinions of PPI representatives on DMCs.

Methods
This survey was aimed at individuals who self-identified as PPI representatives, with experience of PPI in the field of clinical trials. It was advertised via professional associations involved in patient engagement and clinical trials nationally and internationally via mailing lists and newsletters, and via Twitter. Descriptive analyses were performed for all responses.

Results
132 respondents completed the survey. The majority identified as being highly experienced with clinical trials, with 53% having been a member of at least one committee relevant to trials including research ethics committees, trial steering committees and trial management groups. Although not an unexpected finding, the majority of respondents (83%) reported no prior experience being an independent member of a DMC. Despite lacking in direct experience, there was a high willingness to be involved, with 85% believing that an independent PPI representative could or would always be beneficial for a DMC. Challenges acknowledged were how best to acknowledge the role of PPI representatives and how to handle the potential conflict between financial payment to PPI representatives and the need for independence of DMC members.

Conclusions
This survey provides the largest work to date specifically focusing on experiences and opinions on DMCs from PPI representatives. The responses underscore that PPI individuals are now routinely members of most clinical trial oversight committees but only rarely independent members of DMCs despite a high willingness to contribute. The most commonly highlighted benefit was the presence of a "patient voice" on the DMC. These findings may help inform future work on this topic, including how to involve PPI representatives on DMCs, how to measure the added value of PPI representation, the most appropriate methods to select and train PPI representatives, how to present information to PPI members and how to recognise their service to DMCs as independent members.

P-203

Lack of transparent reporting of trial monitoring approaches in randomised controlled trials: a systematic review of contemporary protocol papers

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Background
Monitoring is essential to ensure patient safety and data integrity in clinical trials as per Good Clinical Practice. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist guides authors to include monitoring in their protocols. We investigated the reporting prevalence and detail of monitoring in published "protocol papers" for contemporary randomised controlled trials (RCTs).
Methods: A systematic search was conducted in PubMed to identify eligible protocol papers published in key journals. Articles were further classified by whether they reported monitoring. Descriptive data were summarised for the reporting prevalence of monitoring and the reporting extent.

Results
Of 811 protocol papers, 386 RCTs (48%; 95% CI: 44% to 51%) explicitly reported monitoring information. In particular, 20% (77/386) of RCTs reporting monitoring information described an approach consistent with on-site monitoring, 39% (152/386) with central monitoring, 26% (101/386) with a mixed approach, whilst 14% (54/386) did not provide sufficient information to specify an approach. Only 8% (30/386) of RCTs reported complete details about scope, frequency and organisation, and the monitoring frequency was the least reported. Moreover, 6% (25/386) of protocol papers interchangeably used "audit" to describe "monitoring".

Discussion
Monitoring information was only reported in half of the published protocols. Suboptimal reporting of monitoring, as shown in this study, hinders the clinical community from having the full information on which to judge the validity of a trial externally and jeopardises the value of protocol papers and trial credibility. Greater efforts are needed to promote the transparent reporting of monitoring to journal editors and authors.

P-204

Temperature monitoring and excursion reporting in clinical trials: Experience from the Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH) trial.

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Background
DASH assessed the feasibility of a definitive trial testing the investigational medicinal product (IMP) desmopressin. The SmPC stipulates storage between 2 and 8°C and Desmopressin used in clinical practice requires fridge storage with temperature monitoring in accordance with local policy. Based on information from the manufacturers, DASH trial pharmacy manual required sites to complete a temperature excursion report for deviations outside of the temperature range. Sites were instructed to destroy IMP exposed to temperatures of (i) <2°C, (ii) ≥25°C, or (iii) >8°C but ≤25°C for ≥672-hrs (cumulative total). Here we assess the impact of temperature monitoring and excursion reporting of DASH IMP treatment packs.

Methods
DASH recruited 54 patients with intracerebral haemorrhage who were taking antiplatelets at time of onset, from 10 sites across the UK. Temperature excursion information provided by sites was collated to establish the number of excursions, numbers of IMP packs exposed, quarantined and destroyed, and the number of patients receiving IMP that had previously been exposed to an excursion.

Results
During the trial recruitment period (15th February 2019 to 31st March 2022), 60 excursions were reported. The majority of excursions were reported by sites (98%), with one reported by the pharmacy that produced the packs. 14 (23%) excursions reported temperatures of <2°C, 4 (7%) reported temperatures of both <2°C and >8°C but ≤25°C, and 42 (70%) reported temperatures of >8°C but ≤25°C. No treatment packs reached the time limit of 672-hrs between >8°C and ≤25°C. Of 140 treatment packs produced, 101 (72%) were exposed to at least one temperature excursion. Of these 101 packs, 70 (69%) were quarantined and 60 (59%) were destroyed. 3 (6%) participants received a treatment pack previously exposed to temperatures of both <2°C and >8°C but ≤25°C. 22 (41%) participants received a treatment pack previously exposed to temperatures of >8°C but ≤25°C.

Conclusion
The majority of IMP packs were exposed to at least one temperature excursion, and a significant number quarantined and destroyed. Most of the reported excursions did not affect the quality of the affected packs. The requirements for temperature monitoring and management of excursions needs to be considered at an early stage. Clear guidance via a pharmacy manual on what constitutes a reportable excursion is essential. Reporting minor excursions is time consuming and is unlikely to be beneficial in larger studies where the burden appears out of proportion to the risk, particularly in IMPs routinely used in clinical practice.

P-205

Detecting outliers and patterns amongst trial data

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Introduction
The aim of this work is to identify outliers using the structure of the data, by considering correlations across visits within a patient. We want to create a value per person that can be used to create a covariance matrix that can then be used to detect outliers, without using any further specific context or study knowledge.

Methods
The first step was to choose variables that are collected over various time points. For this example, vital signs and visit dates will be used. A value per person is created by grouping the vital signs to create an average which is then subtracted from the initial value.
Since missing data is an issue in many trials with various visits, methods to deal with missing data include:

- Looping over visits
- Replacing missing values with 0 (mean value imputation)
- Removing missing values (complete-case analysis)
- Multiple imputation

For each method, a robust covariance matrix will be produced. Robust methods are favourable to use here as they can handle and produce results that are not affected by outliers. The Mahalanobis distance and a cut-off (using the chi-squared distribution) will be calculated. The data will be filtered to only include the outliers that can then be looked into for further inspection. Values with $p<0.001$ are considered to be outliers.
The visit calendar dates for each person will be ordered by nominal visit number and a variable will be produced that counts the number of days between consecutive dates. Anomalies can be detected by visual inspection.

Results structure and timelines
The output will contain the subject identifier, the variables and time points where the outlier has been detected. The results of each method will be compared and any differences will be assessed in terms of whether they actually are outliers or not. Correlation matrices will be plotted as well as spaghetti plots of the vital signs over time with the outliers highlighted. The best method will be selected for dealing with missing data, as this is a potential problem for all studies.

Potential relevance and impact
This work can be generalised across studies with multiple visits where we want to detect any data entry errors. The output would be in terms of an excel spreadsheet that could be sent to data managers for quick review, which could ultimately speed up the process of data cleaning and querying.

P-206

Using Power BI and Automation to Modernise Monitoring

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Since moving to a remote working environment, with an increased reliance on electronic resources, study oversight has evolved to depend on remote and central monitoring. Due to this, central monitoring practices have had to become more robust. Previously, data managers extracted raw data from the EDC monthly, which was provided to trial managers who manually created tables, line graphs and other visuals using MS Excel which then had to be organised and formatted into multiple reports. This process was time consuming, prone to human error, and was unsuitable for the new level of oversight required.

To facilitate this new approach, Power BI was used to remove the manual element of the reporting process. Central Monitoring reports can be automated using Power BI, as once a template of the report is designed, the program takes extractions from the EDC system and inputs manipulates the raw data using the same logic every time it is refreshed. This means the time taken each month to produce these reports is reduced significantly. It also removes the chance of human error, as after validation, all the calculations are completed robotically for every row of the extraction, so all that is required is a quality check before each report is published.

This automated method of data manipulation and visualisation has been extended to other areas of reporting, such as Study Oversight Committee reports, Clinical Research Network and other stakeholder reports, and a live recruitment graph available on study websites. Using a weekly email extraction from the EDC system and Power Automate, another program in the “Power” series from Microsoft, the extractions are automatically saved and archived, then an automatic scheduled refresh within Power BI keeps the recruitment graph up to date. The live graph removes the need for the study team to either request a manual recruitment update from the data management team or log into the EDC.

Power Apps and their use in clinical trials are both constantly evolving. Currently, most reports are published to static PDFs, however this is not using the full potential of the program. In future these reports will evolve into live dashboards, allowing for more interactive meetings and the use of triggers. Triggers can send emails automatically to the study team based on predefined criteria in each report, allowing for real-time insight into study KPIs and targets.

P-207

Systematic Completeness Reporting as a Quality Assurance Tool for Protocol, Schedule of Assessments and CRF Design

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Introduction
Systematically reporting the completeness of submitted and expected CRFs is a vital part of data quality assurance but is all too often implemented late in a study's life cycle when it becomes apparent that there are significant quantities of missing data, uncertainty about levels of completeness prior to statistical analysis or the scale of the task has outgrown manual checking.
Early adoption of systematic completeness reporting using appropriate tools that support a scheduling rules-based approach aids study teams in maintaining high completeness levels with minimal effort compared to traditional manual checking routines, assures statisticians that the data is up to date and complete at all times and provides a readily usable input for missing data reporting to data monitoring committees. This should be considered good practice and we are adopting this as a standard approach for new studies.
Further benefit may be had if the development of the subject pathway scheduling rules for the completeness report become an integral part of the study development process and we are developing a methodology to realise this.

Approach
Taking the draft protocol, schedule of assessments and CRF set as inputs, our process will elaborate a set of subject pathways and a testable completeness check rule set and chronology during the design phase to highlight any logical and chronological inconsistencies in the protocol or schedule, processual dead ends and blind spots, duplicated or missing data points, broken dependency chains and incorrectly specified or missing triggers. The rule set will also be used in the generation of outline test plans to ensure comprehensive testing coverage and be used as the framework for building a completeness report; we can further develop this process to automatically generate SQL statements to speed writing of the completeness report.

Timing of Potential Results
The new process will have been piloted before conference and an initial evaluation undertaken.

Potential Relevance & Impact
In conjunction with realistic dummy data sets, the early development of a completeness rule set can identify problems at the study design stage and provide feedback to the study team to help ensure a high quality CRF set, schedule of assessments and study database design. With a set of completeness rules already established and validated against study documents and with a report designed before data collection begins, we can have a high degree of confidence from the outset that a study will be fit for analysis.

P-208

Timely Review of Ultrasound (US) Scans leading to High Rate of Data Completeness

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Introduction
For trials involving pregnancy, such as the multi-site, international, IMPROVE and IMPROVE2 studies in Kenya, Tanzania, and Malawi, outcomes often relate to premature birth or small infant size relative to gestational age (GA) at delivery. Screening ultrasound (US) scan is the best method for determining GA but needs operator expertise for accurate scans. Out of range and missing values typically result in missing data, potentially impacting study outcomes. There is a risk of erroneous results being recorded and endpoint data being inaccurate or biased if US measurements are unavailable. Alternative methods of estimating GA have more variability leading to increased ascertainment of premature birth and small infant size outcomes potentially biasing results.

Methods/Approach
IMPROVE and IMPROVE2 had clear Standard Operating Procedures for performing US scans, comprehensive quality control, and reporting results. Early during the study scans were submitted bi-weekly and every scan was reviewed, with new scans performed if unacceptable quality in the original. After this start up period, 10% of scans per operator were randomly selected for review. For data-checking prior to analysis, detailed acceptable ranges, and combinations of ranges, for US measurements were supplied by an obstetrician. Stata code was written which raised queries if any of the following observations (or combinations of them) were outside expected ranges:

- Femur Length
- Head Circumference
- Crown Rump Length
- GA reported in the database
- GA recalculated from reported US measurements
- Dates related to screening, enrolment, and delivery if GA or time on study had unexpected values

The data management team resolved discrepancies resulting from transcription errors and mis-reported dates, followed by remaining queries undergoing obstetrician review of the original US scan. Importantly, this exercise was performed well in advance of the anticipated study data lock, allowing adequate time for query resolution and scans to be reviewed by the obstetrician if necessary.

Results
Valid GA at enrolment was available from screening US results for 4671/4680 (99.8%) of IMPROVE and 904/904 (100%) of IMPROVE2 participants.

Discussion
The timely review of US scans meant that missing data for GA were minimal for the IMPROVE and IMPROVE2. A clear set of criteria for defining out of range values; review of data well in advance of analysis; and close communication between the trial statistician, data manager, staff members at participating centres and the reviewing obstetrician all contributed to this successful minimisation of missing data and hence potential bias.

P-209

Identifying methods, principles, or frameworks to assist recording adverse events in behavioural change trials: a scoping review

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Introduction
Adverse event (AE) recording is inconsistent and problematic in behavioural change intervention (BCI) trials. Since no other guidance exists, definitions and approaches designed for drug trials are often used. However, applying the standard AE definition ("untoward medical occurrence") might mean important harms or unintended consequences are missed. Examples of harms arising from well-intentioned behaviour change interventions include stigma, feelings of failure and risk compensation (that is, replacement of one unhealthy behaviour with another).
One issue is considering what harms might plausibly be expected from BCIs. The aim of this review was to identify frameworks and possible mechanisms of harms arising from BCIs, and suggested methods or considerations in recording harms.

Method/Approach
A scoping review was undertaken to identify articles, which met the following criteria:
Sample: Interventions intending to modify behaviour for e.g. psychological therapies, public health interventions (e.g. weight management, physical activity), peer or social support.
Phenomenon of Interest:
1) Frameworks of harms caused by BCIs, including mechanisms of harm.
2) Principles, methods, definitions of or approaches to harms recording.
Study design: Empirical research, literature reviews and editorial/opinion pieces
Three databases (Medline, PsycInfo and CINAHL) were searched. Reference list checking and citation searching of included articles was performed.
One reviewer reviewed titles, abstracts and full-texts against the inclusion criteria above. All queries were checked with another reviewer.
Data were extracted and synthesised descriptively by one reviewer and checked by another reviewer. A thematic map was developed.

Findings
[Numbers may change slightly when 2nd reviewer checked in July]: The review identified 3 frameworks of harms, 7 articles describing mechanisms of potential harms, 3 articles describing ways to identify potential harms, 10 articles describing general considerations on recording harms. Exemplar case studies were identified which demonstrated harms arising from specific interventions e.g. peer support in inflammatory bowel disease, social and emotional learning for adolescents and meditation and mindfulness.

Potential Relevance & Impact

BCIs might be considered low-risk interventions in that they are unlikely to cause serious events (defined as resulting in death, hospitalisation, life-threatening episodes etc). However, consideration of unintended consequences which do not meet standard AE definitions may be required.
The thematic map developed from this literature review can 1) Raise awareness that unintended consequences, that might be considered harms, are possible from BCIs. 2) Signpost to literature which may help triallists design AE recording so that it is more appropriate to the context of behaviour change and more efficient.

P-210

Recording adverse events on behavioural change trials: a qualitative study to inform guidance development

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Introduction

Unintended harms arising from behaviour change interventions (BCI) may not be adequately captured by Adverse event (AE) definitions originally designed for drug trials. Well-intentioned BCIs can cause unintended consequences such as stigma, replacing one unhealthy behaviour with another (risk compensation) and feelings of failure. There is often a high burden in recording harms that are not related to BCIs or trial procedures- reducing trial efficiency.

Deciding what AEs to record and what might plausibly be expected from BCIs is difficult. A review of NIHR protocols identified wide variation in how AEs were recorded.

This study aims to explore the experiences and perspectives of individuals involved in designing and delivering BCI trials in relation to harms recording. This will allow an understanding of how the approach taken to AE recording in BCI trials is decided, including what has worked or was problematic.

Methods/Approach

In depth qualitative interviews (n=15)) and focus groups (n=3) were undertaken with multi-disciplinary experts who design and deliver trials. This included oversight committee members, Patient and Public representatives, Chief Investigators, Trial managers, data collectors, Sponsors, and statisticians.

Topics included:

- views on the need for monitoring harms in BCI trials
- perspectives on how AE recording should be undertaken
- exploration of successful practice or challenges

Thematic analysis, using an inductive/deductive approach, was conducted in accordance with Braun and Clarke's standard methods. Open coding and categorisation of transcripts was undertaken by two researchers. A third researcher open coded a sample of transcripts as an initial cross check, and resolved differences as required.

Findings

Initial themes identified include factors considered for AE recording approach (e.g. population and burden, intervention risk, research team and sponsor views, purpose); perception of harms (patient perspectives, harm is possible, what constitutes harm); who is involved (multidisciplinary, differing opinions and conflicts), approach (default/robotic, lack of alternative, need for flexibility), language/terminology (definitions mismatch, move away from medical terminology) and should we record harms (not fear finding harms, resources as a barrier, overwhelming data collection). Patient and public representatives consider it important to thoroughly record harms from these types of interventions.

Categories and themes will be developed by refining the coding scheme. Final themes will be triangulated for inter-method convergence, discrepancy, or complementary information.

Potential relevance & impact

Currently, no guidance exists on how to record harms in BCI trials. The study findings will be used to develop operational considerations for monitoring harms in BCI trials.

P-211

Blinding Of Trial Statisticians: A review of current practice

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Introduction
There is good empirical evidence that blinding any of clinicians, participants and outcome assessors does reduce the likelihood of bias the final outcomes in clinical trials. However, there is little empirical evidence about the practice of blinding statisticians and whether this could have a meaningful effect on the final outcomes. As part of the Blinding of Trial Statisticians (BOTS) study, a review of recently published randomised trials was conducted to determine the practice of blinding of statisticians and to identify whether there was any association between blinding status of trial statisticians and the reported outcomes.

Methods
The NIHR Evaluation Trials and Studies Coordinating Centre database was used to identify reports of randomised controlled trials between 2016 and 2020. Data were extracted regarding trial characteristics, the blinding status of statisticians, clinicians, outcome assessors and participants, and whether a statistically significant finding was reported. Study authors were contacted whenever the blinding status of the trial statisticians could not be determined from the report. The proportion of statistically significant findings for the primary outcome was compared between the studies where the trial statistician was blinded versus not blinded, adjusting for potential confounders using logistic regression.

Results
A total of 179 trials were included in this study. The reporting of blinding methodology was often absent or of low quality in the included studies. The blinding status of the statistician remained unclear for 106 (59%) of the included studies. After contacting study authors, blinding status of the statistician was determined in 152 (85%) of included studies. There was no evidence that the blinding status of the statistician influenced the likelihood of significant findings being reported, OR 0.98 (95% CI 0.47 to 2.05). However, there was strong evidence that blinding any of clinicians, participants and outcome assessors reduced the likelihood of statistically significant findings being reported, OR 0.33 (95% CI 0.13 to 0.86).

Discussion
There was no evidence found to show that the blinding status of the statistician influenced the likelihood of significant findings being reported in clinical trials. While there remains some uncertainty in the risk of any bias that might be introduced by unblinding trial statisticians, the risk certainly appears smaller than that associated with not blinding clinicians, participants, and outcome assessors. This finding calls into question existing guidelines which recommend routinely maintaining the blinding of statisticians to treatment allocation until the final analysis.

P-212

Applying case study methodology in the operating theatre to develop a surgical intervention protocol.

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Introduction
The Medical Research Council guidance on the development of complex interventions states that the randomised controlled trials should standardise the content and delivery of the intervention. In surgical trials, it is important to establish standards for both the standard and 'novel' procedure that ensure interventions are delivered as intended, and still reflect real world practice. Aim: To identify and agree the key components of a surgical intervention to be tested in an RCT.

Method
This study used a case study, survey and expert panel approach. Qualitative case studies of surgeries were undertaken prior to a surgical RCT for post-surgical hypoparathyroidism (the NIFTy trial). Each case study involved non-participant observation and video recording of total and completion thyroidectomies, and interviews with surgeons. Video and observational data were used to construct a typology of the steps and components of the operation, and identify when to use near infrared imaging (NIRF) and ICG fluorescence. Interviews with surgeons provided additional context. Results informed two surveys; (1) to understand current practice around parathyroid identification; (2) to assess willingness to make specific steps in the surgery mandatory. Findings were taken to an expert panel.

Results
Ten qualitative case studies from four surgeons at one centre were undertaken. The video, observation and interview data identified few differences in surgical approach. A typology detailing the constituent surgical components and points where imaging could be used was developed. Sixty-four surgeons responded to survey 1; only 47/64 always looked for parathyroid glands when operating. Few had experience of using NIRF imaging. Forty surgeons responded to the second survey; capsular dissection of the thyroid lobe, preservation of parathyroid pedicle, and clinical assessment were viewed as important to parathyroid preservation. The expert panel concluded that surgical steps contributing to parathyroid preservation would be recorded for the trial, but few steps would be mandated. NIRF (without ICG) must be used during thyroid mobilisation, and ICG must be used at the end of surgery to assess parathyroid viability.

Conclusions
The study adapted an approach used by Blencowe et al (2015) to determine how the intervention could be standardised and delivered within an RCT. The methods allowed the identification of key components of the intervention. The inclusion of the survey and expert panel approach provided greater certainty about the acceptability of the surgical protocol, and confirmed the data items to be collected to inform the analysis of surgical decision making.

Trial registration ISRCTN59074092

P-213

Rapid qualitative analysis of recruitment obstacles in the FORVAD (Posterior Cervical Foraminotomy surgery versus Anterior Cervical Discectomy surgery in the treatment of cervical brachialgia) trial

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Background
The COVID-19 pandemic prompted an increase in interest in rapid qualitative methods in health research, both because of the urgent need for evidence to inform decision making and because the shift to virtual data collection has the potential to make rapid methods more feasible. However, rapid methods have not previously been used extensively for qualitative research in trials.

Methods
A rapid qualitative study was conducted over three months during the early closedown of the FORVAD trial to understand why recruitment had been challenging, with the aim of informing future research in this area. Semi-structured interviews were conducted remotely with 18 healthcare professionals and two patients. Data analysis was conducted using rapid analysis techniques and was informed by Normalisation Process Theory (NPT).

Results
The analysis suggested that surgeons at participating sites supported the trial and recognised collective clinical equipoise, however many had individual preferences for one or other procedure linked to their usual practice. Organisation of the recruitment pathway varied, with some sites directing potentially eligible patients to dedicated clinics and other sites taking a more ad-hoc approach. The dedicated clinic approach appeared to facilitate more eligible patients being identified and recruited, although staff at other sites explained that dedicated clinics did not fit easily with their clinical pathways. Randomisation on the day of surgery presented legal, ethical and organisational challenges which appeared to have had a negative impact on recruitment.

Discussion
The rapid approach enabled the study team to rapidly pinpoint several factors that had contributed to poor recruitment, most of which are potentially modifiable and could be addressed in the design of future trials. Conducting this analysis so quickly whilst also ensuring it was both robust and relevant was achievable because of a combination of four factors: 1) existing experience and expertise in qualitative research and trials within the team; 2) use of a framework (NPT) to help focus data collection and analysis; 3) the contextual knowledge and experience of the FORVAD Trial Management Group; 4) buy-in from the central team and site staff.

Conclusion
Compared with more traditional thematic analyses, rapid qualitative methods offer the potential to more rapidly identify and address trial implementation challenges, as well as potential efficiencies in study

conduct. We recommend that researchers consider using rapid qualitative methods more often in trials, particularly during the set-up, internal pilot and recruitment stages.

P-214

Integration of Qualitative Research Into Surgical Trials to Optimise Trial Conduct

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Surgical trials often face issues with implementation and more recently, qualitative research has been integrated into projects to try and mitigate potential issues in trial conduct. Often research teams may be aware of anecdotal reasons for difficulties with trial conduct, however qualitative research allows a formal way to document learning to inform the trial design and to increase the chances of successful trials in future.

Qualitative research in surgical trials has tended to focus particularly on patient recruitment, however qualitative research is broad and can take on many forms with wider impact. Such research allows identification of improvements to make to the trial design, development of rescue plans and to understand and interpret the results once the trial is complete.

Qualitative research can be incorporated at various timepoints. It is crucial that it is understood what data/evidence is required to change practice to inform the trial design. Surgery is a complex intervention; a process evaluation involving observations of a procedure can help to identify key components within its original setting to inform trial protocols and related data collection.

Staff interviews during set-up can provide a detailed insight into the patient pathway and during recruitment can identity any issues with clinical equipoise and recruitment challenges. Patient interviews can be undertaken to explore randomisation acceptability, understanding of treatments and reasons for non-participation. Recruitment encounter recordings/observations may reveal issues with information presentation which can be used identify training needs.
Clinician and patient views can also be used to feed into the dissemination plan to ensure maximal impact from the trial results and inform post-trial scalability information rollout. Where trials fail to recruit, qualitative research means that specific reasons why recruitment was unsuccessful can be published, hence guiding any future research that may take place in this area.

Whilst valuable information can be gained from qualitative research, inclusion of this research brings some disadvantages, for example additional costs, complexity of protocol/consent documents, extension to trial timelines, and increased patient burden. Although some surgical trials therefore may not warrant the inclusion of qualitative research, e.g. where successful recruitment has been previously demonstrated, it can be difficult to predict in advance which trials will experience difficulty in conduct.

Our experience of implementing qualitative research within our surgical trials portfolio and the impact will be presented in addition to recommendations for inclusion in future trials.

P-215

Exploring factors that can influence the planning, conduct and reporting of qualitative research in trials: A narrative synthesis

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Background
Qualitative research in trials (QRT) is commonly conducted. However, issues with visibility, recognition, and reporting of QRT have been highlighted. Challenges that can lead to the poor conduct and reporting of QRT as well as its potential value not being realised have been highlighted. Understanding these challenges and how they can be overcome can help researchers understand how to better implement and report QRT. This narrative synthesis aimed to understand what influences the implementation of QRT and make recommendations for those engaged with QRT.

Methods
We searched 10 electronic databases between 2011 and 2020. We included publications that explicitly discussed factors influencing the conduct and reporting of QRT or which made recommendations for good practice. We used tabulation of publication characteristics, reflexive thematic analysis, and conceptual mapping techniques to develop a preliminary synthesis and explore relationships within and between the data.

Findings
Of 5530 publications screened, 23 were included. Most were published in 2019 (n=7, 30.4%), 2013 (n=5, 21.8%) and 2014 (n=4, 17.4%). Multidisciplinary team working whereby qualitative team members were embedded within trial teams and understanding and consideration of all trial aspects within the team helped ensure QRT was recognised and encouraged. Resistance to qualitative research and greater credibility being given to quantitative research led to methodological tensions and favouring of quantitative trial components. Being mindful of how each approach could interact and early discussion, planning and documenting of QRT could help reconcile differences and assure the integrity of both qualitative and quantitative research. The integration of qualitative data and findings with other trial sets was believed to be important for maximising the benefits of using multiple approaches. However, meaningful integration was difficult and rarely achieved. Levels of knowledge and understanding of the value of QRT, negative attitudes towards qualitative research and reduced incentives to engage with it were key barriers to uptake and its conduct and reporting. Key research organisations such as Clinical Trials Units (CTUs) and reporting conventions play a role in reinforcing or changing ongoing perceptions of the value and credibility of QRT.

Discussion
Increasing understanding and appreciation of the value of QRT within the research community as well as promoting a supportive environment where qualitative research is integrated into the wider trial framework can ensure QRT is successfully implemented. Key stakeholders such as funding organisations, journals, and research organisations, such as CTUs, should consider how they can best encourage and support QRT.

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Exploring what influences the implementation and reporting of qualitative research in trials: a case study of three trials with a qualitative component

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Background
The benefits of using qualitative research in trials (QRT) have been demonstrated and it is commonly used. However, the prevalence of QRT and issues with its conduct and reporting have been highlighted. Understanding factors that influence the implementation of QRT can help researchers to develop strategies to increase the use of QRT and facilitate successful QRT. We aimed to understand how factors influence the planning, conduct and reporting of QRT and make recommendations for researchers undertaking QRT.

Methods
We used a multiple case study design which included 3 trials with a qualitative component (n=1 evaluating a drug intervention, n=1 surgical and n=1 behavioural). Nine semi-structured interviews with trial team members (Chief Investigators, trialists, trial managers and qualitative researchers) explored how QRT was planned, conducted, and reported and the roles and working practices of trial teams. 184 trial documents including funding applications, protocols, and trial outputs (publications, reports) were used to corroborate interview data and gain insight into trial discussions, decisions, and processes. Cases were analysed using a pattern-matching strategy that involved developing and testing propositions through inductive and deductive coding.

Results
Engagement with QRT depends on people including trial teams, site staff, funders, oversight committees and journal reviewers understanding it and seeing its value. This can be increased through the early promotion of QRT and its purpose within the trial. Having adequately resourced qualitative expertise embedded within multidisciplinary trials teams and good collaborative relationships is important. This can help raise the profile of the QRT and ensure successful implementation. Consideration of all qualitative research aspects and how these relate to other trial components, whilst remaining flexible, can help to ensure QRT is conducted and reported well. Activities that encourage this can help to overcome methodological tensions and ensure the validity and rigour of all approaches within the trial. Qualitative analysis and how to integrate qualitative data and findings with other trial components can be overlooked and poorly planned. Meaningful integration of methodological approaches, data and findings is believed to be important but may not always be appropriate or feasible. This may be due to the timing of findings being available, resource constraints, level of importance placed on the QRT and journal reporting conventions.

Discussion
Successful implementation and reporting of QRT require adequate resources, good planning, flexibility, and activities that foster an early shared understanding, and good working relationships and which promote the integrity and usefulness of all trial components.

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"I felt she had to fight her corner:" How qualitative researchers can become vulnerable when conducting qualitative research in trials

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Background
Qualitative research in trials (QRT) is commonly used and has many benefits. However, there are challenges to conducting QRT and its use has not gone uncontested. Qualitative researchers play a key role in the conduct of QRT but little attention has been paid to how the challenges of QRT can affect them. As part of a larger study exploring the conduct and reporting of QRT, the role of researchers and the degree to which they experience a sense of vulnerability were investigated.

Methods
Data were drawn from a narrative synthesis of publications utilising QRT and a case study of three trials using qualitative research. Thematic analysis was conducted on 184 pieces of evidence (26 publications - narrative synthesis: nine interviews and 149 trial documents - case study).

Results
The position of the qualitative researcher within the trial team and a range of noted challenges when conducting QRT indicated a sense of vulnerability for qualitative researchers. This included a lack of confidence, a sense of insecurity and heightened exposure within the multi-disciplinary trials (MDT) team. Inadequate funding for qualitative research led to a sense of pressure to deliver high-quality results with limited resources. Feeling undervalued within the team also led to study results being devalued by other team members.
Findings from the qualitative research aspect of data triangulation were sometimes unwelcome, and results were, at times, challenged, leading to tension within teams that was often seen to be difficult to negotiate. Qualitative researchers were expected to defend their discipline and felt compromised through the expectations that they should meet standards similar to those expected of quantitative researchers. However, facilitating increased knowledge and understanding of QRT, fully integrating qualitative researchers into trials teams, involving them in trials meetings, and ensuring open communication, was seen to negate some of these challenges.

Discussion
MDT teams need to be aware that the research environment can be challenging for qualitative researchers and ensure they are supported in their role. Fully embedding qualitative researchers in trials teams, throughout a trial, and further research into how best to support qualitative researchers who may experience a sense of vulnerability is now needed.

P-218

Blinding Of Trial Statisticians: A qualitative study to inform guidance development

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Introduction
Blinding is an established approach in clinical trials which aims to minimise the risk of performance and detection bias. There is little empirical evidence to guide UK Clinical Trials Units (CTUs) about the practice of blinding statisticians. Current guidelines recommend that statisticians remain blinded to allocation prior to the final analysis, but these guidelines are not based on empirical evidence. As part of the Blinding of Trial Statisticians (BOTS) study a qualitative investigation was conducted to explore when and how statisticians should be blinded in clinical trials from the perspective of those working in CTUs.

Methods
The data were collected qualitatively through online focus groups with various stakeholders who work in the design, management, delivery, and oversight of clinical trials. Recordings of the focus groups were transcribed verbatim and thematic analysis was used to analyse the transcripts.

Results
Thirty-six participants from 18 CTUs participated in one of six focus groups. Four main themes were identified, namely: statistical models of work; factors affecting the decision to blind statisticians; benefits of blinding/not blinding statisticians and practicalities. Factors influencing the decision to blind the statistician included: available resources; study design and types of intervention; outcomes and analysis.
Although blinding of the statistician is perceived as a desirable mitigation against bias, there was uncertainty about the extent to which an unblinded statistician might impart bias. Instead, in most cases, the insight that the statistician offers was deemed more important to delivery of a trial than the risk of bias they may introduce if unblinded. Blinding of statisticians was only considered achievable with the appropriate resource and staffing, which were not always available.

Discussion
This study found that there was wide variation in practice between UK CTUs regarding the blinding of trial statisticians. Therefore, the most important finding is that a 'one size fits all' approach is not practical in the process of deciding when/how the trial statistician should be blinded. A proportionate risk assessment approach would enable CTUs to identify risks associated with blinding and not blinding statisticians and identify appropriate mitigation strategies. The findings of this study were used to design guidance and a proportionate tool to support this risk assessment process.

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Impact of COVID pandemic on study participation

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Introduction
'Outcome Monitoring After Cardiac Surgery (OMACS)' is an observational study collecting tissue samples and outcome data from patients undergoing cardiac surgery at the Bristol Heart Institute (BHI) for use in future research.
During the first wave of the COVID-19 pandemic, NHS Trusts were directed to prioritise urgent public health research and clinical care, pausing recruitment to most ongoing research. OMACS was amongst the first studies to re-commence at the BHI in May 2020 and provides data to investigate the influence of the pandemic on participant engagement with clinical research.

Methods/Approach
Baseline characteristics were compared in two cohorts of OMACS participants: patients operated in the year before the first lockdown (pre-pandemic cohort) and year after (during-pandemic cohort). Consent rate was calculated for patients approached pre-pandemic and during-pandemic. Retention was measured by the number of quality of life (QoL) questionnaires returned at 3 months. Patients in the pre-pandemic cohort sent questionnaires after 16/03/2020 were excluded.
QoL was assessed using the Coronary Revascularisation Outcomes Questionnaire (CROQ) (patients who underwent coronary artery bypass grafting) or SF12-questionnaire (other cardiac procedures). QoL scores and missing data were compared.

Results
Consent rates were higher pre-pandemic (73% of those approached) than during the pandemic (66%). Cohort demographics were similar; 510/680(75%) of the pre-pandemic cohort were male, versus 357/496(72%) during-pandemic, the average age was 64 in both cohorts. Logistic Euroscores, a measure of predicted mortality based on pre-operative characteristics, were lower in the during-pandemic cohort (median [IQR] 1.65 [1.08, 3.08] versus 3.43 [1.96, 5.96]). More procedures in the during-pandemic cohort were urgent or emergencies (41.4% and 1.5% respectively, versus 35.2% and 0.8% pre-pandemic).
Pre-pandemic retention at 3 months was 67%(229/340) compared to 73%(293/399) in the during-pandemic cohort. Derived QoL scores were similar. Questions relating to social activities/outdoor exercise were left blank more often during the pandemic; SF12 questionnaires had missing responses for 5.5% of respondents during the pandemic compared to 1.8% pre-pandemic.

Discussion
Recruitment rates decreased during the pandemic, possibly due to changes in approach methods. Retention increased during the pandemic, indicating participants were more engaged with the study. Interestingly, despite a larger proportion urgent/emergency procedures during the pandemic, overall Euroscores were lower compared to the pre-pandemic cohort.
Analysis of QoL responses suggests that questions about socialising were less applicable during the pandemic due to social restrictions. Overall QoL scores were unaffected. This may need to be considered in analysis of QoL scores from this period.

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EXTENT OF SUCCESSFUL PARTICIPANT/CLINICIAN BLINDING AND IMPLICATIONS IN INTERPRETING RESULTS IN A MEDICAL DEVICE RANDOMIZED SHAM-CONTROLLED TRIAL (RCT)

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Background
Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by oral dryness (xerostomia). Associated salivary gland dysfunction reduces salivation, which compromises oral health and quality of life(1). Salivary electrostimulation devices are a promising therapy for xerostomia.
Importance of the placebo effect is well-known(2). Sham-controlled RCTs distinguish between true intervention, placebo, and possibly mechanical effects. Systematic reporting of participant/clinician blinding success remains rare(3), despite being considered essential by consensus(4).

Methods
SALRISE is a multicentre, Phase III, parallel-group, double-blind, randomized sham-controlled trial assessing clinical and cost-effectiveness of a salivary electrostimulation device (SaliPen) for pSS. SALRISE was conducted in Rheumatology/Oral Medicine departments managing pSS patients in National Health Service (NHS) hospitals. Clinical and patient-reported data were collected for up to 12 months.
The primary objective was to determine whether the active device reduced xerostomia symptoms as measured by the patient-reported Xerostomia Inventory (XI) score at 52 weeks post-randomization compared to the sham device. Participant-completed diaries captured data on frequency of device usage. Exit polls recorded which device type participants/clinicians believed they/their participants had received. James'(5) and Bang's(6) blinding indices (BI) were calculated to evaluate the success of blinding.

Results
11 NHS centres randomized 136 participants (active n=67, sham n=69). 51% of participants indicated which device type they thought they received; 27% stated they didn't know. James' overall BI (0.638) did not indicate participant unblinding. However, Bang's BI indicated active arm unblinding with over 20% answering correctly beyond a chance level (0.204), but not for sham arm (-0.054). Within arms, more participants predicted they received an active device rather than sham (active 33% vs 18%; sham 28% vs 23%). Frequency of participant weekly device usage was similar across arms (mean (sd): active 16.0 (10.82); sham 14.5 (7.36)). Clinicians indicated which device they thought participants received for 49% of participants, with device type not known for 43%. Neither James' (0.729) nor Bang's BIs (active 0.068, sham -0.030) indicated clinician unblinding. Impact of level of success in maintaining the participant/clinician blind on interpretation of trial results will be discussed.

Discussion
Previous studies investigating salivary electrostimulation devices have been open-label/uncontrolled(7), or else concealed treatment allocation via a sham device comparator(8) but did not report degree of blinding success. Where there are differences in efficacy/adverse effects some successful guessing of treatment allocation may be expected(9). In SALRISE, exit poll data quantify the extent of successful blinding via blinding indices, providing context for the interpretation of trial outcomes.

P-222

A mixed methods study to understand how surgical trainee collaboratives achieve success and develop strategies to increase clinician engagement in trials

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Introduction

Over 20 regional or speciality Surgical Trainee Research Collaboratives (TRCs) have been established across the UK. TRCs have conducted several randomised trials despite recruitment to surgical trials often being challenging. These networks can design trials, improve recruitment to ongoing trials and help develop a research-active consultant workforce. However, understanding the reasons for TRC successes could enhance them further and aid translation to other clinical specialities. We aimed to understand the role of TRCs and to develop strategies to enhance trainee engagement in clinical trials in a mixed methods study.

Methods

We used observation of 5 TRC meetings, 32 semi-structured interviews, and an online survey of trainees registered across UK regions to explore their motivations for engagement in trials and TRC experiences, including barriers and facilitators. Interviews purposefully sampled TRC members and linked stakeholders across surgical specialties and UK regions. Interviews were analysed thematically, alongside observation field notes. Survey responses (n= 73) were analysed using descriptive statistics. Strategies to enhance TRCs were developed in a workshop of 13 trial methodologists, trainees, consultants and research nurses and were disseminated in a digital animated story.

Findings

Of the trainees survey responses, 36 (49.3%) were involved in TRCs, 7 had been involved and 30 had never been involved (41.1%) The main reasons for trainees engaging with TRCs were an interest in surgical research (n = 43, 58.9%), publications (n = 39, 53.4%) and improving patient care (n = 37, 50.7%). The interview data also showed that trainees engaged with trials to progress their careers, improve patient care and surgical evidence. TRCs could mobilise trainees and gain wider access to patients. Challenges for trainees included competing clinical priorities, limited time, confidence, gaining recognition for their inputs and authorship. TRCs supported trainees through their infrastructure, research expertise and mentoring. Key strategies for successful TRCs were consultant support, simple rapid studies to launch the TRC, transparency of involvement and recognition for trainees, including authorship policies, and working with Clinical Trials Units and research nurses. A 6-minute digital story on YouTube utilising interview data disseminated these TRC strategies.

Discussion

Trainee surgeons are generally motivated to engage with clinical trials and TRCs. Trainee engagement in TRCs can be enhanced through building relationships with key stakeholders, maximising multi-disciplinary working and offering training and career opportunities. Further work is needed to determine whether these strategies can improve engagement in other areas such as primary care and with allied health professionals.

P-223

What impact could the estimand framework have on a trial of a complex intervention?

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Introduction

The intention-to-treat (ITT) principle is widely adopted in trials of complex interventions, and the effectiveness of treatment policies are central to decision-making. In 2019, the ICH E9 (R1) Statistical Principles for Clinical Trials addendum established the estimand framework, setting out a structured approach for considering appropriate strategies to answer trial research questions. The framework encourages trialists to focus on how the interaction of population, treatment conditions, outcomes, summary measures and intercurrent events informs study design and analysis. Our objective is to explore how this approach could impact on a trial.

Methods/Approach

As a motivating example, we use the recently completed TOPSY study, which included a trial of pessary self-management for women with pelvic organ prolapse. TOPSY opened in 2018 and was designed prior to the publication of the E9 addendum, and a treatment policy strategy using an ITT analysis was planned as our primary analytical approach, with an on-treatment strategy as a sensitivity analyses. There were many intercurrent events in the TOPSY study, including non-adherence fully to allocated treatment, participants seeking alternative interventions, and changes in how some participants received treatment, eg as a consequence of the Covid pandemic. We will therefore investigate the following:

1. Could the trial have been designed differently if it had been carried out within the structure of the estimand framework?
2. Would this change the trial results?

The investigators will consider alternative estimands, which could include hypothetical strategies (eg changing the intervention received on the basis that a major disruption to healthcare provision like the Covid pandemic had not happened), composite strategies (eg changing the outcome by defining a composite measure to incorporate symptoms and intervention received), or principle stratification strategy (eg changing the population to those who would not seek alternative treatment). Alternative treatment effect estimates for these strategies will be reported.

Timing of Potential Results

The findings will include re-analysis of selected TOPSY trial data. The primary TOPSY trial completed in March 2022 and this secondary analysis is ongoing. The findings will provide an illustration of how the estimand framework can be incorporated into the conceptualisation, design and reporting of a randomised trial.

Potential Relevance and Impact

Our findings will provide an insight into how the estimand framework could change the way in which a trial may be conducted and interpreted. This will also aid trialists by discussing a structured and practical approach to adopting important new guidelines in trial methodology.

P-224

Estimands in a large pragmatic randomised controlled trial of antivirals to treat covid-19 patients in the community

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Introduction (covering aims/objectives/settings)
In a randomised controlled trial, the estimand is the precise description of the treatment effect that the trial aims to estimate. They should be considered at the design stage to ensure relevant data are collected to be able to answer the questions of interest. For example, whether data that occurs after an intercurrent event will be included in the analysis determines whether it needs to be collected or not.
PANORAMIC (Platform Adaptive trial of Novel antiviRals for eArly treatment of covid-19 In the Community) is a large adaptive platform trial testing novel antiviral treatments for covid-19 in the community. The primary aim is to determine the effectiveness of selected antiviral agents in preventing hospitalisation and/or death in higher-risk patients with a confirmed positive PCR or LFT SARS-CoV-2 test result. Analysis will be on the intention to treat population. To date, over 25,000 participants have been randomised between 2 active treatments and the comparator arm usual care.

Methods/Approach (making clear the approach e.g. applications and implementation, mixed methods, opinion, qualitative, quantitative, review, simulation, survey, SWATs).
PANORAMIC was not designed using the estimand framework. Here we attempt to reframe the questions of interest from the point of view of estimands to see if our current analysis strategy aligns with the objectives of the trial and perform post hoc analyses where there are differences. As it is a pragmatic trial and the primary outcome includes all-cause mortality, the estimand will be a treatment policy strategy. However, this strategy cannot be used for the main secondary outcome of time to recovery as death is an intercurrent event for this outcome.

Results Structure and Timelines (what form would the results takes)
Estimands for the primary and main secondary outcomes will be described, highlighting challenges in the data collection.

Potential Relevance and Impact (why might the results be important or interesting)
Defining estimands from the conception of the trial ensures relevant questions of interest can be answered and relevant data is collected. In a time when CTUs are starting to embrace estimands in practice, the more examples and discussion the better.

P-225

What is the intervention effect in those that engaged? Estimation of treatment effects in app engagers in the SPARKLE COVID rapid response TwiC

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Introduction
Traditionally the unbiased randomisation respecting "intention to treat" (ITT) analysis is the main trial analysis. However, estimating the intervention effect in those who received it is also of interest. Recently the International Council for Harmonisation E9-addendum outlined the estimands framework to make the effects estimated in trials more explicit. One aspect is defining the population, an example being the subset that took the intervention as intended. Such estimands are of particular interest in trials of remote or app-based interventions, where uptake varies. Estimation of this type of principal stratification estimand including the Complier Average Causal Effect (CACE) requires specialised statistical methods (Dunn et al https://doi.org/10.3310/hta19930).

The SPARKLE randomised controlled trial within a cohort is evaluating an app (Parent Positive) to improve children's behaviour and parental wellbeing during the pandemic. Estimating the intervention effect in app engagers is a key secondary aim, in particular because the intervention is unblinded and evaluated in a non-clinical population where there could possibly be low uptake. We aim to apply principal stratification methods to compare effects in engagers with the ITT effect, and to illustrate these perhaps not yet widely applied methods.

Methods/Approach
The SPARKLE trial ITT effect is the mean Parent Positive versus control difference in child conduct, obtained by fitting a linear mixed effects model with a time by treatment interaction effect to two post-randomisation measures. We will obtain CACE estimates in those engaging with the app, and principal stratification estimates in those with high and low app engagement. The latter requires fitting discrete latent class models; we aim to fit a principal stratification version of the ITT model to retain power and so estimates can be appropriately compared.

Results Structure and Timelines
We specify these methods in the statistical analysis plan (https://preview-kcl.cloud.contensis.com/business/assets/sparkle-sap-v1.1.pdf), describing this as an exploratory analysis. The main analysis showed no significant ITT effect on the primary outcome, with simple individual time point instrumental variable CACE analysis providing larger, less precise estimates. The more complex model results will be compared with these and between those with different levels of usage. An ultimate aim is to produce a methods application guidance publication with code (to be disseminated via our departmental github).

Potential Relevance and Impact

More widespread exploration, application and development of methods for principal stratification estimands, and dissemination via analysis plans, publications and code repositories will help promote more use of this estimand.

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Are randomised trials addressing clear and useful questions? A systematic review of estimands

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Introduction

It is important to understand the precise questions individual trials address for the treatments under study. This is because asking different types of questions (e.g., what is the effect of treatment regardless of adherence, versus the treatment effect if fully adhered to) can lead to quite different conclusions about the usefulness of a treatment. Updated international trial regulatory guidelines (ICH E9(R1)) call for trialists to precisely describe the treatment effect a trial aims to measure by defining an estimand. As this is a new area of focus, whilst the guidelines were being adopted worldwide, we reviewed published randomised trials to evaluate how often the targeted treatment effect could be understood through the specification of estimands or using the information on the reported statistical methods (the estimator). We aimed to determine whether reporting of estimands in trial reports is necessary to fully understand the questions being addressed.

Methods

A systematic review of phase II-IV randomised trials published in 2020 in six leading general medical journals. The main outcome measures were: the number of trials which stated the precise primary question being addressed about an intervention (the estimand) or for which this could be unambiguously worked out from the reported statistical methods, and the strategies being used to handle post-randomisation events that affect the interpretation of patient outcomes, such as intervention discontinuations or uses of rescue medications (termed intercurrent events).

Results

Of 255 eligible trials, none fully specified the primary estimand and for 138/255 (54%) trials the precise treatment effect the trial addressed could not be inferred from reported methods. Most trials (242/255, 95%) reported intercurrent events, but the strategy for handling these could only be determined in 125/255 (49%) trials (4 stated strategy, 121 inferable). Where this could be determined, most trials (96/125, 77%) addressed the effect of the treatment regardless of adherence (treatment policy), whilst others addressed hypothetical questions (17/125, 14%), such as if participants continued treatment despite non-adherence due to adverse events or did not die.

Discussion

The precise question addressed in most trials is unclear. Reported statistical methods do not always enable one to unambiguously establish precisely what a trial has investigated. This is predominately due to lack of clarity on the handling of intercurrent events. Reporting of estimands in trial reports is necessary to fully understand the questions clinical trials address. CONSORT guidelines should be updated to mandate reporting of estimands.

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Rethinking intercurrent events when defining estimands: worked examples from tuberculosis trials

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Introduction
In randomised trials, the occurrence of intercurrent events (ICEs) happening post-randomisation can change the treatment effect being estimated. Before the introduction of the ICH E9(R1) addendum on estimands, ICEs and strategies for handling them were often inconsistently described, thus inhibiting clear interpretation and comparison across trials. These problems especially arise in trials evaluating treatments for tuberculosis (TB), where the primary outcome definition is often complex and involves components representing different ICEs.

Methods/Approach
Based on our understanding of the estimand framework and our experience of conducting large phase-III TB trials, we discuss considerations in handling common ICEs, including treatment changes and treatment extension, poor adherence to randomised treatment, re-infection with a new strain of TB which is different from the original infection, and death. We use two completed trials (REMoxTB and STREAM Stage 1) as illustrative examples.

Results
First, changes from allocated regimens should not necessarily be viewed as an unfavourable outcome: from the patient perspective, the potential harms associated with a change in the regimen should instead be directly quantified via a treatment policy strategy. Second, handling poor adherence to randomised treatment using a per-protocol analysis does not necessarily target a clear estimand; instead, it would be desirable to develop ways to estimate the treatment effects more relevant to programmatic settings. For example, it may be sensible to separate out non-adherence due to toxicity versus other reasons, and handle the former with the treatment policy strategy and the latter with the hypothetical strategy. Third, re-infection with a new strain of TB could be handled with different strategies (e.g. treatment policy or hypothetical), depending on whether the outcome of interest is the ability to attain culture negativity from infection with any strain of TB, or specifically the presenting strain of TB. Fourth, where possible, deaths could be separated into TB-related and non-TB-related and handled using appropriate strategies (e.g. composite or hypothetical). Finally, although some losses to follow-up would result in early treatment discontinuation, patients lost to follow-up should not always be classified as having an unfavourable outcome. Instead, loss to follow-up should be separated from not completing the treatment, which is an ICE and may be considered as an unfavourable outcome using a composite strategy.

Discussion
The estimand framework clarifies many issues but also challenges trialists to justify and improve their outcome definitions. Future trialists in TB and related areas should consider all the above points in defining their outcomes.

P-228

Cardiac events and time-varying treatment: incorporating causal analyses into the STATIC trial

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Introduction
STATIC is a phase III trial in patients with chronic lymphocytic leukaemia (CLL) that compares two treatment strategies. Patients either take ibrutinib continuously until they have active disease (control) or take it upon reaching specific criteria and stop, either when the criteria are reversed, or when they have active disease (experimental).
In emerging data from the FLAIR trial (ISRCTN01844152), an increased risk of sudden cardiac death was observed which may be associated with ibrutinib exposure and history of cardiovascular disease (CVD) (CVD vs. No CVD relative risk 18.1 (95% CI: 2.3, 146)).
To determine how to investigate this link, causal analyses are considered, with the estimand framework used to explicitly define the research question. This allows evaluation of individual treatment regimens and outcomes, in addition to consideration of intercurrent events and potential time-varying confounders.

Methods/Approach
To establish the estimands of interest, we consider the intercurrent events of changes to ibrutinib schedule and define hypothetical treatments of interest [consistency]. We then examine the identifiability of these estimands by using a DAG to represent our causal assumptions regarding time-varying treatment and covariates [exchangability], and considering the limitations imposed by the trial design on which Dynamic Treatment Regimes (DTRs) could be observed [positivity]. By ensuring these are accounted for in trial setup, we can do causal analysis to assess the estimand.

Results
Our causal question asks: “What is the effect of ibrutinib exposure on participants experiencing at least one grade ≥3 cardiac AE?”, where “cardiac AE” are used as surrogate endpoint for sudden cardiac death. This will output into a logistic regression model, which will account for our variables, including duration of exposure, defined as time spent on ibrutinib on STATIC trial, in yearly intervals (0-<1 year, 1-<2 years etc). Intercurrent events including ‘clinically significant’ treatment breaks were considered. All variables are defined as categories as otherwise data collection may be on too onerous for a secondary research question.

Discussion
Estimands and causal methods have allowed us to consider the research question in detail and provided an improvement on standard techniques by allowing patients to be assessed on an individual level and the inclusion of time-varying confounders. By establishing this whilst the trial is in set up, it allowed us to ensure everything we need to collect is, for a more accurate investigation, resulting in allowing an improved future analysis to be undertaken.

P-229

Comparison of statistical methods for the analysis of patient reported outcomes (PROs) particularly Short-Form 36 (SF-36) in RCTs using standardised effect size: an empirical analysis

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Introduction
Short-Form 36 (SF-36), a patient-reported outcome (PRO), is frequently used as a key outcome in randomised controlled trials (RCTs). The SF-36 generates eight domain scores that tend to be discrete, bounded, and skewed. Various statistical methods have been applied for the analysis of PRO data, but their estimated values, for the treatment effect, may not be presented on the same scale as the original outcome. This study aims to introduce the scale-invariant standardised effect size (SES) to unify and compare different statistical methods for the analysis of SF-36 domain scores with evidence from empirical analyses.

Method
Ten statistical methods included for comparison were linear regression, Tobit regression, median regression, censored absolute least deviation (CLAD) model, ordered logit model, ordered probit model, beta-binomial regression, binomial-logit-normal regression, beta regression and fractional logistic regression. Data analysis was conducted by fitting these methods to nine RCT datasets, which used the SF-36, in multiple clinical areas. SF-36 domain score at a specific follow-up time point in each trial was analysed by adjusting treatment group and its corresponding baseline score. The estimated values, SESs, and model fit were compared using Akaike information criterion (AIC).

Results
Marginal effects of the Tobit regression produced similar estimates of treatment effect as linear regression, while estimates from median regression and CLAD model deviated from the estimates from linear regression and tended to scatter around zero. Ordered logit model generated higher absolute estimates and binomial-logit-normal regression produced higher SESs compared to other statistical methods. When the number of possible scores of the SF-36 domain increased, the model fit of Tobit regression, ordinal regression and binomial regression became poorer, but the model fit of linear regression improved.

Discussion
SES is a handy measure that can be used to compare treatment estimates from different statistical methods. Linear regression is a classic and simple method to use when model assumptions are not significantly violated. Ordinal, binomial, and fractional regression may fit better to domains with a small number of possible scores, but they require recoding of SF-36 scores and transformation of estimates for model application and interpretation. This increases the complexity in practice. To what extent the increase in the precision of estimation outweighs the cost of simplicity of interpretation needs to be investigated. Future research will focus on simulation analysis to compare the estimation accuracy and model robustness of these methods.

P-230

Outcome Reporting Bias in Nephrology Randomized Clinical Trials: Examining Outcomes Represented by Graphical Illustrations.

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Background
Outcome reporting bias (ORB) is widely reported in the medical literature, but the contribution from published graphical illustrations is unknown. The aim of this study was to investigate the occurrence of ORB in contemporary nephrology clinical trials relating to the choice of outcomes reported through graphical illustrations.

Methods
An observational study was conducted using nephrology clinical trials searched from five high-impact medical journals from 2015-2020. Eligible trials reported a phase 2, 3 or 4 trial, contained at least one published outcome graphical illustration (graph or figure) and were registered on a clinical trial registry. The primary outcome was the occurrence of ORB based on the choice of graphical illustrations in published trial manuscripts, deemed to be present if a graphical illustration displayed a secondary or unregistered outcome ahead of a trial's primary outcome, or if any unregistered trial outcome was presented as a graphical illustration.

Results
In 75 eligible clinical trials, the primary outcome for ORB was present in 60% of the trials (n=45). Occurrence of the primary outcome did not differ significantly based on trial sample size, funding model, trial phase, individual medical journal or publication year. An unregistered trial outcome was graphically illustrated in 93% (n=42) of those clinical trials with ORB present.

Conclusion
Outcome reporting bias based on the choice of graphical illustration is common, driven primarily by graphical illustration of unregistered trial outcomes. More appropriate choice of outcomes for graphical illustrations by authors, coupled with both increased enforcement of CONSORT guidelines by medical journals and specific guidelines for graphical illustrations choice, are desirable to address these findings.

P-231

Improving the reporting of adverse events in randomised trials of complex interventions and digital therapeutics

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Introduction
Current methods of analysis and reporting of adverse events (AEs) within randomised controlled trials (RCTs) are suboptimal. A heavy reliance on frequency tables and subjective commentary fails to transparently convey both the extent of harms and their relevance to the intervention in question. Recently, efforts have been made to enhance the reporting of AEs in the context of drug trials. Both practical guidance and software packages for visualising harms have been extensively developed by Philips and colleagues (e.g., BMJ 2022), and extensions to the CONSORT statement have been made to improve standard reporting within publications. However, the extent to which this guidance translates to the reporting of AEs in RCTs of complex interventions and digital therapeutics is yet to be established. This work aims to apply and expand recent guidance to demonstrate their application in RCTs of these interventions.

Methods
We consider an RCT of a blended digital and psychological intervention compared to treatment as usual for people with psychosis (SlowMo Trial, N=362) and a trial of novel AVATAR therapy compared to an active control in people with auditory hallucinations (N=152). The impact of differential reporting of AEs due to increased contact with participants in the intervention arms is explored, and existing visualisation methods are applied to AE data from these trials with consideration of how to account for the AE reporting mechanism.

Results
There were 54 AEs in SlowMo and 22 in AVATAR. We show in both trials that a table displaying adverse events split by arm does not contain sufficient information to distinguish differential reporting mechanisms. Graphical visualisations of AE data will be presented, with extensions to account for how AEs were reported to the study team (e.g., during the intervention or routine data collection). The results of gap analyses comparing existing methods against considerations required for more complex intervention settings will be presented.

Discussion
The consideration of appropriate analyses and reporting of AEs within RCTs should not be confined to drug-settings only, but requires additional consideration for complex intervention and digital therapeutic trials. Such trials are usually open label and involve challenges such as increased AE reporting and data collection within the intervention arm. This work highlights important differences which need to be accounted for when reporting AEs from complex versus non-complex RCT settings and provides guidance for how to conduct this.

P-233

Cost effectiveness of assessment and intervention by a health and social care team in the emergency department in older adults: Trial-based economic evaluation

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Background
Over 65s are frequent attenders to the Emergency Department (ED) and more than half of these patients are admitted for overnight stays. Early assessment and intervention by a dedicated ED-based Health and Social Care Professionals (HSCP) team reduces ED length of stay, the risk of hospital admissions among older adults and the enhanced model may improve health-related quality-of-life and patient satisfaction. This study aims to evaluate whether augmenting the treatment as usual, for over 65 admitted to ED, is cost effective.

Methods
Cost-effectiveness analysis, conducted alongside the randomised controlled trial of 353 patients aged over 65 with lower urgency complaints compared the effectiveness of early assessment and intervention by a dedicated HSCP team in the ED, compared to treatment as usual (TAU). Economic analysis estimated the average cost per patient of contact with the HSCP team, over and above TAU, compare how contact with HSCP team changes health care use and associated total costs and estimate the effect of HSCP on Quality-Adjusted Life Years (QALYs). A series of deterministic sensitivity analyses were performed to ensure results were robust to a variety of scenarios.

Results
Within the OPTIMEND trial, the average cost of a contact with the HSCP team during ED admission is estimated to be €801per patient. Incremental QALY, compared to TAU, is 0.053 (95% CI: 0.023 to 0.0826, p<0.0001). Accounting for cost savings as a consequence of contact with HSCP team, the average incremental saving in the total cost, compared to TAU, is -€6,128 (95% CI: -€9,217 to -€3,038, p<0.0001). Given the incremental health gains and significant cost savings, base case CEA finds HSCP dominates over TAU in terms of value for money. As inpatient admissions is a major cost driver for the observed average cost savings, to test robustness within a far more conservative perspective, a sensitivity analysis omits all cost of inpatient stay from total cost equation and find the ICER to be €12,589 per QALY and, with reference to Irish guidelines on economic evaluation, the probability thast the ICER if less than €20,000/QALY 89.93% and less than €45,000/QALY is 99.40%.

Conclusions
The initial cost of deploying a HSCP in ED improves overall health and, by reducing inpatient length of stay, results in staggering cost savings. This economic evaluation conducted alongside the OPTIMEND trial provides convincing evidence that HSCP should be adopted as a routine part of treatment as usual in emergency departments.

P-234

Challenges of improving data quality for Machine Learning/Artifical Intelligence projects in Low and Middle Income Countries

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Introduction
Dengue is one of the most common mosquito-borne viral diseases globally. The employment of the machine learning/artificial intelligence (ML/AI) approaches can potentially improve diagnostics and management, but has not been adequately studied in low-and-middle countries (LMIC) [1]. In the VITAL project (vital.oucru.org), we aim to improve the management of dengue using a combination of clinical, laboratory and continuous physiological monitoring data. Diverse datasets from studies enrolling dengue patients have been collated from prospective observational studies at the Hospital for Tropical Diseases, Ho Chi Minh City, over the last 20 years. We would like to highlight three challenges in terms of data quality based on our observations and reflections on the project.

Challenges and opportunities
First, it may require significant human resources to collect, collate and format data used for ML/AI-embedded applications. Currently, the preparation for ML/AI projects is labour-intensive and mainly done manually by the research staff due to the lack of uniform data sources. The coexistence of hand-written and electronic medical records can make the data collection more complex and time-consuming, and possibly prone to errors and missing data. In addition, the lack of connectivity between hospital systems might hinder the automated integration ability of AI/ML-embedded tools.

Second, the heterogeneity of infrastructure within and between local hospitals can also make it challenging to apply the standard operational procedures for data collection across the study sites. For example, the monitoring devices used within wards and hospitals usually vary in terms of models and company; thereby, the data extraction procedure from these devices cannot be standardised. This highlights the need for flexibility in data acquisition procedures but also having measures to maintain the homogeneity of data quality.

Finally, it is important to have regular interim analyses to check for the data generalisability. Although the ML/AI approach can allow for continuous self-learning temporally, the performance of ML/AI models can be affected depending on data input variations over time [2]. The data collected should be evaluated and adjusted based on the preliminary findings, ensuring that diverse patient groups are included and represented.

Conclusion
As data quality is critically important that defines the performance of ML/AI approaches. The highlighted issues should be considered at the design stage as well as re-evaluated regularly during the trial period. The lessons learnt from our experience can be useful for the design and conduct of clinical trials evaluating the ML/AI models in lower resource settings.

P-235

DECIDE-AI. Development and validation of consensus reporting guidelines for early clinical studies of medical AI: Emerging themes.

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Despite considerable commentary on its potential, and numerous reports of in silico studies, few studies of machine learning systems have so far been evalauted in clinical practice. We noted considerable heterogeneity and low average quality amongst published studies of early clinical evalaution, and initiated a Delphi process to develop expert consensus guidelines to assist authors performing such studies.

The guidelines were developed by a multi-stakeholder expert panel over 2 rounds with a final expert panel to resolve persistent uncertainties, and were published in May 2022 (Nature Medicine [https://doi.org/10.1038/s41591-022-01772-9] and BMJ [https://doi.org/10.1136/bmj-2022-070904]. The current paper describes the themes which emerged from the development process and the research needs these identified.

Early clinical evaluation involved consideration of the human/machine interface, as fully automomous machine decision making is unlikely to find widespread applications in our healthcare systems in the near future. This necessary interaction poses challenges to evaluation because both expertise in using the system and trust of the system by the human are initially low and undergo fluctuation during early experience before reaching a stable state. Attempts to iteratively improve human/machine interaction involve attention to Human Factors issues, and effectively modify the nature of the AI intervention. A quality-improvement like approach to study design for early clinical evaluation is therefore likely to be appropriate. The need for a control group is debatable, given that the intervention studied will change during the study. Differences in clinician experience, patient population and clinical context between centres may result in outcome variability, and modifiers will need to be understood and accounted for before randomised trials can be undertaken with confidence.

These features of clinical AI systems mirror those addressed for surgery and medical devices by the IDEAL Recommendations, which should be carefully considered when designing early clinical AI trials. A number of initiatives are currently underway to test and validate the DECIDE-AI guidelines, and early experience will be reported on in the presentation.

P-236

Performance of multiple imputation using parametric and semiparametric imputation models for handling missing outcomes in cluster randomised trials

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Missing outcomes in cluster randomised trials (CRTs) are a commonly occurring problem, which may cause invalid inference if ignored or handled appropriately. Multilevel multiple imputation (MMI) has been widely recommended for handling missing outcomes in CRTs. Recently, multiple imputation (MI) by predictive mean matching (PMM) for continuous outcomes has been suggested as a semiparametric alternative to MMI. However, in that study, it was assumed that both the missingness mechanisms and the covariate effects are the same between the intervention groups, which is a strong assumption and unlikely to hold in practice. In this work, we performed an extensive simulation to compare the performance of MMI and MI by PMM when the missingness mechanisms and/or covariate effects are the same or different between the intervention groups. Results show that MMI outperforms MI by PMM when the missingness mechanisms and/or the covariate effects are different between the intervention groups. Based on the simulation results, we give guidance on the conditions under which each of the above two approaches give valid inference.

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How to reduce, handle and report missing data in trials involving participants with advanced disease: co-produced guidelines using nominal group technique

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Background
Missing data (MD) can introduce bias and reduce the power, precision and generalisability of trial findings. Guidelines on how to address MD are limited in scope and detail, and poorly implemented. Trials involving participants with advanced disease, such as palliative care trials, have been shown to have large amounts of MD due to modifiable and non-modifiable reasons.

Aim
To develop guidelines on how best to (i) reduce, (ii) handle and (iii) report MD in clinical trials. These guidelines will be relevant to all trials at risk of MD and especially those including participants with advanced disease, multimorbidity and/or frailty.

Method
Modified nominal group technique was used to develop the recommendations which allowed delegates to develop ideas, identify priorities and inform the guidelines in a structured manner. Patient and public research partners, clinicians, trialists, methodologists and statisticians attended a workshop and stakeholders worked in groups to develop the guidelines. Following the workshop, a multi-stakeholder guideline development group, which included patient and public research partners, co-developed the guidelines.

Results
1. Reducing MD
- Prepare and plan for how to reduce MD at the trial design and protocol development stage
- Resource the trial adequately to minimise MD
- Train all research staff to understand the risks posed by MD and how to minimise MD
- Discuss the value of complete data and how to reduce MD with participants
- Collect the reasons for MD
- Distinguish participants who want to withdraw from providing any further data from participants who wish to withdraw from part of the study protocol
- Monitor and address MD during the trial.

2. Handling MD
- Include a statistician in the trial team from the start
- Decide how MD will be handled in the design, conduct and analysis of the study and report these decisions
- Prepare for MD analyses at the trial design stage
- Inflate the sample size for expected MD
- Consider how to handle data truncated due to death

- Explore the nature of the MD
- Decide on plausible assumptions about the MD mechanism
- Conduct MD sensitivity analyses

3. Reporting MD
- Transparently report the points above
- Discuss the impact of MD on the validity of findings.

Conclusion
These guidelines are ready for wide implementation. Their use will address the issues considered most important by stakeholders including public research partners, clinicians and methodologists.

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Measuring quality of life in trials including patients on haemodialysis: how are transplants and mortality incorporated into the analysis? A systematic review.

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Introduction
Haemodialysis treatment causes significant reductions in quality of life (QoL). When enrolled on a clinical trial, some patients are lost prior to follow-up either because they die or receive a kidney transplant. It is unclear how these patients are dealt with in the analysis of QoL data. This review assessed the current practice of trials to understand how informative dropouts (those related to the intervention or disease) are dealt with in the primary data analysis. There are also questions surrounding the consistency of how QoL measures are used, reported and analysed in current practice. This review also looked at how closely trials adhere to the guidance for the Kidney Disease Quality of Life (KDQoL) Questionnaire, written by the developers.

Methods/Approach
A systematic search of electronic databases for clinical trials measuring QoL in haemodialysis patients, using any variation of the KDQoL was conducted.

Results and Discussion
We included 61 trials in the review. A third of trials had more than 20% dropout, despite the majority having a duration of 6 months or less. 76% of trials had some form of informative dropout (dropouts due to death/transplantation/adverse effects). Despite this, most trials used complete case analysis (CCA) to deal with dropouts, which is invalid when dropouts are informative. Other methods to account for missing data included single imputation (n=3) and multiple imputation (n=1). Single imputation was also used in sensitivity analysis, which, like CCA, is invalid in the presence of informative dropouts. There was also an inconsistency in the reporting of the KDQoL, with many papers (70%) either amending the validated questionnaires (leaving out specific questions) or only reporting domains with statistically significant results. Missing data due to dropouts are common in nephrology trials. There is currently little guidance on how to deal with informative dropouts in clinical trials. In the trials reviewed, informative dropouts were dealt with no differently to non-informative dropouts, despite CCA and single imputation being inappropriate under these conditions. The results of this review show that methods for dealing with informative dropouts in current practice are inadequate and could be biasing trial results. Inconsistencies in the use of patient-reported outcome measures, for example amending questionnaires and cherry-picking results also raises questions about the validity of these trials. Methodological issues such as those discussed in these nephrology trials could be a contributing factor as to why there are limited effective interventions to improve QoL in this patient group.

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Methods to address baseline data recorded 1 year apart due to logistical disruption attributed to the COVID 19 pandemic

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Introduction
The FibroScHot 18 trial is a phase IV, randomised superiority trial comparing the effect of 2x and 4x treatments annually with praziquantel to the standard 1x annual treatment on the prevalence of Schistosoma mansoni associated periportal fibrosis of the liver. Logistical disruption caused by the COVID-19 pandemic led to baseline data being recorded for half of participants in March 2020 and the remaining participants recorded in March 2021. In order to assess any potential change for participants with observations in March 2020 and March 2021, a random resample of 10% of participants was performed in March 2021 for the primary and secondary endpoint variables for participants who had baseline data recorded in March 2020.

Primary – Ultrasonography Score a 6 point ordered categorical scale dichotomised to a binary variable
Secondary – Mean faecal egg count – this is the mean eggs per gram calculated from a maximum of 6 Kato-Katz slides, 2 per stool from 3 stool samples per participant per time-point

Aims
To assess whether or not baseline data recorded in March 2020 would be considered valid as baseline data for 2021
Objectives
1. Measure the strength of agreement between the faecal egg counts recorded at baseline 2020 and baseline 2021
2. Measure the strength of agreement between the Ultrasonography scores recorded at baseline 2020 and baseline 2021

Methods/Approach
Conditional logistic regression will be used to assess the strength of the agreement for the dichotomised ultrasonography score baseline data.
In order to assess the strength of the agreement for the faecal egg count baseline data between the two time-points a Bland-Altman plot of the difference between the two baseline values (y axis) against the mean (x axis).

- Difference = baseline 2020 – baseline 2021
- Mean = (baseline 2020 + baseline 2021) / 2

A histogram to show the distribution of the differences will be produced to check that the assumption of normality is met.
Results
Conditional Logistic Regression:
Odds Ratio for paired data with 95% CI's and P value.
The Bland-Altman plot will detail:
Mean difference between the two baseline readings
95% CI for the mean difference
Limits of agreement calculated as: $\delta \pm 2s$ (where δ = mean difference and s = standard deviation of the differences)

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Calibrating a network meta-analysis of trials of sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor analogues and dipeptidyl peptidase-4 inhibitors to a representative routine population

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Introduction

Participants in randomised controlled trials are generally younger and healthier than individuals typically encountered in clinical practice. Consequently, the generalisability of trial findings is often uncertain. To address this problem one can calibrate trials to a representative target population. This ongoing systematic review will use a novel calibration methodology, based on multilevel network meta-regression, to calibrate trials of sodium glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) receptor analogues and dipeptidyl peptidase-4 (DPP4) inhibitors in type 2 diabetes to the Scottish population.

Methods and analysis

We selected a target population from the highly representative Scottish diabetes register comprising people in Scotland with type 2 diabetes potentially suitable for treatment escalation via any of the three drug classes of interest.

Medline and EMBASE databases, the US clinical trials registry (clinicaltrials.gov) and the Chinese Clinical Trial Registry (chictr.org.cn) were searched from 1st January 2002 to 22nd November 2019. Two independent reviewers applied eligibility criteria to identify relevant trials for inclusion in the network meta-analysis. Included trials were phase 3 or 4 randomised trials of SGLT2 inhibitors, GLP1 receptor analogues or DPP4 inhibitors, with placebo or active comparators, in participants with established type 2 diabetes. Trial outcomes included at least one of: glycaemic control (HbA1c), change in body weight or major adverse cardiovascular event (MACE). Unregistered trials were excluded.

We now intend to perform a calibrated network meta-analysis incorporating both individual level participant and aggregate-level trial data and routine healthcare data for the target population.

Results and discussion

134,008 people with type 2 diabetes suitable for escalation were identified (mean age 63.5 years, 60.7 % male, mean duration of type 2 diabetes 9.9 years, 2019 observed deaths 199 per ten thousand). A systematic review of Medline and EMBASE databases (n=9069) and two clinical trial registries (n=1716) yielded 596 eligible randomised trials of SGLT2 inhibitors, GLP1 receptor analogues or DPP4 inhibitors. IPD was obtained for 80 trials.

Using novel methodology, we will now perform a calibrated network meta-analysis to estimate the comparative efficacy of drugs from the 3 studied classes in a real world target population. This method uses all available data, retaining the strength of trial data (not breaking randomisation) while improving representativeness using routine healthcare data.

Our planned approach requires fewer assumptions than simple extrapolation and unlike many approaches to calibration which require IPD for all trials, allows inclusion of both IPD and aggregate-level trials potentially reducing bias.

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But are the mediator and outcome measuring the same thing? Discerning mediator and outcome measurement in clinical trials

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Introduction
Fields like psychology and psychiatry often measure unobservable latent outcomes via questionnaires. The study of mediation is of interest in these fields, where in a clinical trial an intervention is thought to influence the outcome via a third variable. Typically, the mediator is an intervention target (e.g., focusing on symptoms) whereas the outcome is a clinical measure allowing intervention evaluation. This implies that the mediator and outcome represent distinct theoretical constructs. The choice of mediator and outcome measures (and of questionnaire items to measure them) should be informed by theory and clinical experience. However, in practice, some items across questionnaires can be similar, raising the question of whether these questionnaires are measuring distinct constructs. Where items measuring the mediator and outcome overlap entirely, the mediator is closer to an earlier measure of the outcome rather than a third variable. This study (10.1016/j.jpsychores.2021.110595) used a theoretical psychometrics framework to quantify overlap between the mediator and outcome measures in the PACE trial of interventions for chronic fatigue syndrome.

Methods
Established psychometric methods were applied to quantify overlap between pairs of mediators and outcomes. Using confirmatory factor models, potential cross-loadings were identified based on modification indices. We tested whether the cross-loading with the highest modification index $\chi 2$, when added to the model, significantly improved model fit. We repeated this procedure for all potential cross-loadings in the modification indices. Selected cross-loadings were classified according to the strength with which they loaded onto the primary (i.e., theoretically defined) and secondary factors. R code is available (https://github.com/ewancarr/mediator-overlap).

Results
Out of 26 mediator-outcome pairs (13 mediators; 2 outcomes), only 6 had salient cross-loadings, all of which involved outcome items cross-loading onto mediator factors. Most salient cross-loadings involved 4 items from the fatigue outcome measure that cross-loaded on to the mediator factors for avoidance/resting behaviour, damage, fear avoidance, and symptom focusing.

Discussion
Using the PACE trial as an example, we showed that psychometrics methods can be used to quantify the extent of overlap between mediators and outcomes measured via questionnaire. We found minimal overlap, suggesting the mediator and outcome measures were distinct. As well as considering other important assumptions for a robust mediation analysis (e.g., no unmeasured confounding of mediator and outcome), we recommend that researchers assess overlap between mediators and outcomes assessed by questionnaire before conducting a mediation analysis to ensure they are measuring reasonably distinct constructs. Future work will focus on refining overlap quantification.

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Using pilot trials data to inform decision making in bioequivalence trials

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In the verification of bioequivalence between a generic drug and its branded counterpart, a pilot trial with only a few patients would often be conducted before a pivotal bioequivalence trial. The accrued pilot data are used to assess the feasibility and to estimate the range of possible effects. Due to limited sample sizes, it is not recommended to decide if a pivotal should occur based on significance tests at the conventional level of 5%. Whilst some authors suggest adjusting the significance level in hypothesis testing, Bayesian framework provides an alternative approach to inform a Go/No-go decision. Moreover, it brings about the possibility of incorporating pilot data in a prior for parameters that underpin the pivotal trial.
Consider two-sequence, two-period crossover designs that compare the test (T) and reference (R) treatments. We develop a robust Bayesian hierarchical model to accommodate the respective linear mixed-effects models fitted to the pilot and pivotal trials. The study-specific treatment effects ($\delta i = \mu Ti - \mu Ri$, i = 1, 2) can further be modeled with a random-effects distribution. Robust prediction is attained by including a prior mixture weight that reflects skepticism about the plausibility of an exchangeability assumption. We further stipulate a scaling factor based on the study sample sizes and intra-subject variances. This helps compute predictive probabilities of bioequivalence to inform the Go/No-go decision. Once a Go decision would be made, the assessment of bioequivalence in the final analysis can be yielded by the pilot and pivotal trial data jointly. The proposed Bayesian hierarchical model is illustrated using data examples and simulations. Simulation results show that our model is superior to traditional methods, such as the two one-sided tests (TOST) procedure or a modified version of the TOST.

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A Comparison of Methods for Bayesian Inference in Clinical Trials

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Introduction & Objectives

Bayesian statistical methods are increasingly used in clinical trials. Asymptotically exact simulation-based approaches such as Markov Chain Monte Carlo (MCMC) are usually required to perform Bayesian inference. However, they can act as a barrier to applying Bayesian methods in practice because of the high computational cost and software complexity. A less computationally expensive approximation method, Integrated Nested Laplace Approximations (INLA), which does not require simulations is available. We compared INLA and two MCMC algorithms (in the software JAGS and STAN) in terms of feasibility and accuracy using Bayesian adaptive clinical trial data.

Methods

Three algorithms, namely JAGS, STAN and INLA, were compared using data from an international Bayesian adaptive trial that investigated the treatment effect of therapeutic anticoagulation with heparin in non-critically ill patients hospitalized with COVID-19 compared to usual care. By fitting Bayesian hierarchical generalized mixed models for categorical, binary, and time-to-event outcomes, the estimated posterior distributions of the regression model coefficients and the hierarchical model variances were compared. The runtime of each algorithm was also investigated.

Results

INLA requires noticeably less computational time compared to STAN and JAGS as it is between 85 and 269 times faster than STAN and 26 and 1852 times faster than JAGS. Specifically, on average, INLA takes 9.63 seconds while STAN and JAGS take 19.23 minutes and 1.26 hours, respectively, to estimate the posteriors. Implementation of INLA is facilitated by a well-established package in the statistical software R. The average overlap of the 95% CIs for the posterior means of the treatment and gender effects estimated using INLA was 96% and 97.6% compared with STAN and JAGS, respectively. The density curves for the posterior distribution of these effects nearly overlapped for all three algorithms. The estimated posterior means for the hierarchical model variance are within the 95% CIs estimated using MCMC. However, the density curves of the posterior distribution of these hyperparameters approximated using INLA exhibit multi-modality which does not match the unimodal density curves estimated using MCMC.

Discussion

INLA has high feasibility of implementation and is substantially faster compared to the MCMC methods. The posterior distributions for the regression model coefficients are approximated well using INLA. However, INLA encounters challenges when approximating the posterior distributions of hierarchical model variances and future work should focus on determining the optimal adjustment for the INLA algorithm to improve this estimation.

P-245

Maximise the generalisability of two heart failure randomised controlled trials by calibrating the trials to a HF registry in Scotland.

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Background
RCTs are the gold-standard for determining therapeutic efficacy and safety, but the characteristics of patients participating in trials differ from those commonly encountered in clinical practice. Trial calibration involves re-estimating trial treatment effect estimates by accounting for these differences to better reflect target populations, while still preserving randomisation.

Method
Individual-level data from COMET, comparing carvedilol and metoprolol, DIG, comparing digoxin and placebo, and a clinical practice HF registry in Scotland comprising 8,012 patients predominantly with reduced ejection fraction, were obtained. Calibration using regression-based and inverse propensity score weighting (IPSW) approaches to estimate the treatment effects on the primary outcome (all-cause death for both trials) and composite outcome (all-cause death or hospitalisation for COMET, death or hospitalisation due to worsening HF for DIG) was performed. In the regression-based method we applied trial and registry-derived regression models to patients' characteristics in the registry. In the IPSW approach we performed weighted regression of the trial data based on trial inclusion probabilities derived from trial and register data. We then identified registry patients in the highest and lowest deciles of risk for each primary and composite outcome and performed regression-based and IPSW calibration for these sub-groups.

Results
Registry patients were older, had poorer renal function and higher-dose loop diuretics than trial participants (mean (standard deviation) age 73 (12) years compared to 62 (11) and 64 (11) years in COMET and DIG and for eGFR 59 (23) mL/min/1.73m² compared to 67 (21) and 62 (21) mL/min/1.73m² in COMET and DIG and for loop diuretics 62 (31) mg/day compared with 20 (46) mg/day in COMET). For each trial, the point estimates were similar for calibrated (IPSW) and uncalibrated analyses (e.g., OR 0.65 (0.45, 0.94) versus 0.83 (0.74, 0.93) for COMET all-cause death), with slightly greater uncertainty levels (reflected by wider standard errors (SEs), 0.19 versus 0.06). Treatment-effect estimates were also similar when trials were calibrated to high-risk (0.69 (0.51, 0.95), SE: 0.08) and low-risk patients (0.78 (0.65, 0.95), SE: 0.09) identified from the registry, with still wider SEs. Similar results were obtained using regression-based calibration.

Conclusion
Regression-based or IPSW approaches can be used to calibrate trial effect estimates to administrative/registry data, with only moderate reductions in precision.

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Approaches to address multiplicity in pragmatic RCTs: simulation studies to aid with the design and interpretation of RCTs with potential multiplicity concerns

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Introduction
We are seeking to determine optimal approaches to address multiplicity in pragmatic RCTs, and whether approaches should vary according to research questions and study design. The work reported focuses on simulation studies, with the following aims to:
-Describe how trial design factors affect Type I/II errors when testing hypotheses
-Recommend when statistical methods to adjust for multiplicity are advised, and the preferred method(s)

Methods
RCTs were simulated either with multiple primary outcomes or comparing multiple treatments with a control. Underlying treatment effects and trial design factors (e.g. correlation, sample size) were varied, and regression models fitted for each simulation. We also varied how the multiple comparisons were combined in the overall trial interpretation; e.g. trials that define multiple primary outcomes can be designed to require either: a) all primary outcomes, or b) at least one primary outcome to meet pre-defined effectiveness criteria for the new treatment to be declared effective. Finally, different multiplicity adjustment methods (e.g. single-step, step-up/down, hierarchical) were applied. The impact of design factors and adjustment methods on both Type I and Type II error rates is described.

Results
The key trial design factors that impact on Type I/II error rates are: 1) how the multiple comparisons are combined, and 2) the correlation/relationship between primary outcomes or treatment comparisons. The impact on overall trial Type I and II errors is often conflicting, e.g. if all primary outcomes are required to meet effectiveness criteria then Type I errors are low (below 5%), but Type II errors are higher than for each outcome separately. Increases in Type I/II errors are greater for weakly correlated outcomes/comparisons. Different adjustment methods also affect Type I/II errors variably; simpler adjustment methods can be conservative, particularly when outcomes/comparisons are strongly correlated. Definitive results will be presented at the conference.

Discussion
The next steps are the development of:
-Succinct guidance from the simulations and earlier literature review and surveys of experts, covering trial design factors to consider and recommended approaches in certain situations.
-R code to directly calculate (without the need for simulation) overall trial Type I/II error rates, according to trial design factors.

This will help statisticians and methodologists designing future pragmatic RCTs, and guide health professionals interpreting RCT findings.

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Bayesian information sharing methods for a longitudinal basket trial

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Introduction
Basket trials are a novel clinical trial approach whereby a single drug or intervention is investigated in multiple subgroups. Basket trials offer the opportunity to share information between baskets, thereby potentially increasing the power to detect a positive basketwise treatment effect. Basket trials can offer multiple advantages over running a series of separate trials, including reduced sample sizes, increased efficiency, and reduced costs. Primarily, basket trials have been undertaken in Phase II oncology trials, whereby patients are recruited by a common biomarker or genetic mutation which the treatment is aimed at, and then classified into baskets based on the location of their cancer. Basket trials would be an ideal design for investigating a novel treatment in other disease areas which share similar features, for example, chronic ageing related diseases. However, trials in this area frequently have longitudinal outcomes, and therefore suitable methods are needed to share information in this scenario.

Methods
In this paper, three Bayesian information sharing methods were extended to account for a longitudinal basket design. These methods were: the standard Bayesian hierarchical model (BHM), the Hellinger Distance (HD) method proposed by Zheng and Wason (2020), and the EXNEX method proposed by Neuenschwander et al (2016). These methods were then compared with standalone analysis to demonstrate the benefits of information sharing. This was done via a simulation study in a variety of scenarios in terms of bias, MSE, type I error rates, and power.

Results
Our results indicate that each method is suited well to different situations. The HD method may be more suitable to a Phase III confirmatory trial, as it relies on less assumptions than others in order to share information more sensitively between baskets, while still controlling type I error rates well. However, the BHM also performs well in scenarios where the treatment is broadly beneficial in all baskets. The EXNEX method works well when there is large heterogeneity in treatment effects between baskets. All methods that share information improve the power and lower the type I error rate (in general) over independent analysis.

Relevance & Impact
Our results demonstrate the benefits of information sharing over independent analysis for a longitudinal basket trial looking at treatment effect over time. This has the potential to provide many advantages including reduced sample sizes, increased efficiency, and reduced costs. This could have relevance in studies for chronic ageing related diseases, where longitudinal outcomes are routinely collected.

P-248

A win ratio approach for evaluating the average bioequivalence

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Introduction
A bioequivalence trial is a study of presumed therapeutic equivalence between the test and reference drugs based on pharmacokinetic (PK) parameters rather than on clinical, or other, endpoints. Bioequivalence is commonly evaluated using the two one-sided test (TOST) procedure at 5% significant level or the two-sided 90% confidence interval for the geometric mean ratio of primary pharmacokinetic (PK) parameters (e.g., AUC and Cmax) of the two drugs [1].

Methods
We propose the use of the win ratio method proposed by Pocock et al. as an estimand to assess average bioequivalence of PK parameters between two medicinal products [2]. For a PK parameter, a subject in test formulation will be compared with a subject in reference formulation. For each comparison, the test formulation is labelled a “winner” or a “loser” or “tied” according to the values of PK parameter. The win ratio is the total number of winners divided by the total number of losers. Variance can be estimated using the method proposed by Bebu and Lachin method [3]. The average bioequivalence can be claimed when the 90% confidence interval for the win ratio of two drug products lies within the bioequivalence limits of (0.8,1.25) [1].

Results Structure and Timelines
Using the real trial dataset and Monte Carlo simulations, this study will compare the statistical power and type I error of the win ratio method with other statistical methods such as TOST procedure and 90% confidence interval for assessing average bioequivalence of PK parameters under various scenarios. We already have real trial data analysis results and will perform the simulation studies and will have the results by the end of July.

Potential Relevance and Impact
We expect that the win ratio method will have similar power and type I error to other available methods for assessing average bioequivalence. Win ratio will offer an alternative method for evaluating bioequivalence between two medicinal products, especially when the normality assumption for the log-transformation PK parameters does not hold.

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P-249

Application and Implementation of Two-Part Models in Clinical Trial Data (of I-WOTCH)

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Introduction
Skewed distributions of outcome measures along with a high-occurrence of zero-values, are common in clinical trial data. There are standard methods to approach the analysis of these data that require careful judgement from the researcher. This feature is prevalent in substance abuse studies, such as I-WOTCH, an interventional study on reducing opioid use, where these data characteristics were found. The two-part model is statistically appropriate for this task but introduces interpretability issues as well as difficulty in its implementation. Thorough understanding is required to correctly apply this complex method.

Methods
In this research, I explore and compare different methods of statistical analysis using the I-WOTCH clinical trial data. This will be a total of four models. The statistical analysis plan proposed the use of mixed-effects regression models which were able to achieve the study objectives. I compare this original model along with two commonly used approaches, i.e., transformations and dichotomisation. Transformations is the recommended statistical tool when accounting for skewed distributions. Dichotomisation is another recommended method when encountering zero-inflated data. Finally, I compare these results with the application of the two-part model which is capable of accounting for both features.

Results/Timeline
The literature in healthcare research on statistical methods recommends the use of two-part models for this situation. Further study is required on the statistical costs and benefits of applying this model, as well as finding the correct approach for analysing model performance. Once the statistical theory is better captured and a method of comparison is established, I will apply the four models on the I-WOTCH data. I will report on each model's performance, and its difficulty on implementation and interpretability.

Impact
These results will help inform future studies of the recommended methods for statistical analysis of outcome measures. These will be particularly helpful in the ongoing area of research on rehabilitation, such as I-WOTCH. Development and clarity of statistical methods produces higher quality research which leads to better informed decisions for healthcare providers.
More specifically, this research will provide clearer insight and scientific enquiry in the potential differences between a patient that is no longer dependent on opioids and a patient that is less dependent on opioids.

P-250

Assessing the use of variational inference for large real-world clinical data

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Introduction
With growing acceptance by clinical regulators of the value of real-world evidence to supplement experimental clinical trials, there is increasing interest in the use of Bayesian analysis for real-world clinical studies.
This interest has been limited by the computational challenges applying the Markov-chain Monte-Carlo (MCMC) approach to large real-world clinical data (RWD) that incorporate missing and adulterated data along with many discrete variables.
MCMC is considered the gold standard for Bayesian inference because, in the limit, MCMC is guaranteed to eventually converge to the true posterior distribution. Approximate Bayesian inference via optimisation of the variational evidence lower bound, usually called Variational Inference (VI), has been successfully demonstrated for other applications. We investigate the performance and characteristics of currently available R and Python VI software implementations for large RWD.

Methods/Approach
Four R implementations and four Python implementations are compared. The implementations include several algorithms for VI: coordinate ascent mean-field VI, stochastic VI, automatic differentiation VI and two application-specific R packages. A Bayesian latent class approach for phenotyping paediatric type 2 diabetes mellitus from a large observational study (435,321 patients) was chosen as a real-world exemplar. The R package rjags was used to implement an MCMC baseline model for comparing with VI. Several cuts of the data with increasing complexity are separately analysed: continuous variables with no missing data, continuous variables with data missing at random and not at random and all data including discrete variables. We conclude the study with a simulation analysis to explore in more detail where particular differences occur.
Timing of Potential Results
We expect to have all results analysed by early September 2022. The most time-consuming aspect is running the MCMC baseline comparison on such large data.

Potential Relevance & Impact
The effective use of VI will enable the application of Bayesian inference for clinical studies with large data currently only suitable for frequentist statistical approaches. Our study will produce a detailed analysis of all aspects of VI methods clarifying how and when to use each VI approach. We also aim to contribute novel extensions to VI where necessary to make these methods widely effective (for example discrete and multi-modal latent variables).

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Analysis of cluster randomised controlled trials using MLE, GEE, GEE2 and QIF: an empirical study

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Background
Using four case studies, we aim to provide practical guidance and recommendations for the analysis of cluster randomised controlled trials (CRCTs).

Methods
Four modelling approaches (Generalized Linear Mixed Models (GLMM) with parameters/coefficients estimated by Maximum likelihood; Generalized Linear Models with parameters/coefficients estimated by Generalized Estimating Equations or GEE (1st order or GEE1, second order or GEE2) or Quadratic Inference Function (QIF)) for the analysis of correlated individual participant level outcomes in CRTs were identified from a review of the literature. These four methods were applied to four case studies of CRCTs (Ponder CRCT, Age-Gap CRCT, NOSH CRCT, Informed choice leaflets CRCT) with continuous and binary outcomes, and number of clusters ranging from 10 to 100 and individual participants ranging from 748 to 9,207; using the statistical packages, R and SAS.

Results
The intracluster correlation coefficient (ICC) for each of the case studies was small (<0.05) indicating little dependence of the outcomes related to cluster allocation. All the models fitted produced similar results for the treatment effect, including the simplest approach of ignoring clustering for the case studies considered. However, in some cases QIF produced differing estimates and results compared to the other three methods.

Conclusion
In most cases the four different modelling approaches produced similar results which is consistent with the original primary analyses, a plausible reason for this could be the negligible correlation (small ICCs) among responses in the four CRCT cases studied. However, QIF produced different results compared to the other three methods in some cases. This is noticeable for small to moderately sample sized trials.

Due to the small ICC values observed the generalisability of our results is limited. It is important to conduct simulation studies to comprehensively investigate the performance of the four statistical methods considered.

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Proposal for extension of estimation in subgroup analyses – moving on from p-values

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Introduction
Recommendations for analysing and reporting subgroup analyses in randomised controlled trials are well established and – if performed appropriately – can help us understand whether interventions are differentially effective in participants with distinct characteristics. Such guidance includes ensuring that the focus of attention is on tests of interaction, as opposed to hypothesis tests within subgroups which are at increased risk of both type I (false positive) and type II (false negative) error. Analyses are typically conducted through the addition of subgroup by treatment group interaction parameters into the regression model that has been used to produce estimates of the overall treatment effect. However, p-values from interaction tests are limited in as far as they do not help to quantify the difference between subgroup-specific treatment effect estimates. We propose a simple extension to the recommended practice for subgroup analysis that may aid in this respect.

Methods/Approach
Using recently published trials as motivating examples, we will estimate both absolute and relative measures of differences between subgroup-specific treatment effects (for continuous and binary outcomes). Estimates of uncertainty around these 'difference in differences' or 'ratio of ratios' measures will be produced along with a suggested visual display. Guidance will be offered on how such estimates could be incorporated into the study design and how they should be interpreted. Stata v17 will be used for analysis.

Timing of Potential Results
Results from these analyses will be available by August 2022.

Potential Relevance and Impact
To our knowledge such estimates are rarely presented in reports of clinical trials and we believe this work will provoke discussion on whether such additional measures may be useful in interpreting subgroup analyses.

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A systematic review of economic evaluations alongside Studies Within A Trial (SWATs) for improving recruitment and retention in Randomised Controlled Trials (RCTs)

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Introduction
The recruitment of potential participants and retention of existing participants in randomised controlled trials remain key challenges in achieving sufficient internal and external validity. Emerging trial methodology research has been attempting to identify strategies for improving recruitment and retention in RCTs, mainly through the adoption of a novel design, the Studies Within A Trial (SWATs). A recent Cochrane review has assessed the effectiveness of several strategies for improving recruitment to RCTs, and another Cochrane review has assessed the effectiveness of several strategies for improving retention in RCTs. However, a systematic review evaluating the cost-effectiveness of strategies for improving recruitment and retention in RCTs has yet to be undertaken. The aim of this review was to critically appraise the cost-effectiveness of strategies to improve participant recruitment and retention in randomised controlled trials (RCTs), within the framework of SWATs.

Methods
All included studies from the latest Cochrane reviews on recruitment and retention in RCTs were considered. To identify articles published since the Cochrane reviews, the following databases were searched until March 2021: MEDLINE, Embase, CINAHL, Cochrane Methodology Register, Science Citation Index and Social Citation Index, ERIC, PsycINFO, and Scopus. Hand searching of conferences databases and journals was also undertaken, including ClinicalTrials.gov, OpenTrials, EU Clinical Trials Register, CENTRAL, and ORRCA. The quality appraisal of the included studies was undertaken through the Cochrane risk of bias tool. The Centre for Reviews and Dissemination guidance was also used to assess the quality of economic evaluation of the included studies. Fixed-effect inverse-variance weighted meta-analyses were undertaken. The GRADE certainty of evidence was applied for each strategy, and Trial Forge Guidance 2 was used to evaluate the uncertainty of the findings. The cost-effectiveness of the recruitment and retention strategies was summarised via cost-effectiveness rankings.

Results
A total of 6,569 records were identified and 29 SWATs including more than 37,000 participants were included. The only cost-effective strategy, with high GRADE certainty of evidence, was providing trial-branded pens as a retention strategy, costing $6.98 for an additional participant to be retained in an RCT. There exists huge uncertainty regarding the cost-effectiveness of the remaining 13 identified strategies.

Discussion
Future SWATs should replicate existing recruitment and retention strategies, rather than evaluate novel ones. We recommend that economic evaluations be carried out alongside all future SWATs, costs and benefits be recorded clearly and transparently, and the cost-effectiveness of existing recruitment or retention strategies be evaluated.

P-254

Assessing correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection by COV002: a single-blind, randomised, controlled, phase 2/3 trial

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Introduction

An understanding of the immune response predictive of protection against infection and disease (i.e. correlates of protection) could facilitate rapid licensure of vaccines.

Methods

We calculated correlates of protection for SARS-COV-2 infection using data from a phase 2/3 randomised single-blind vaccine efficacy trial (COV002, NCT04400838), conducted across 19 sites and 11 groups in the UK. Participants in the study were randomised to receive ChAdOx1 nCoV-19 (ChAdOx1) or a MenACWY vaccine. Efficacy cohorts and immunogenicity cohorts were randomised in different ratios (1:1, 3:1 or 5:1) depending on the group. A subset of participants received low dose vaccines for first and/or second doses.

Immune markers included anti-spike, anti-RBD IgG, pseudovirus and live neutralising antibody. The outcomes included both symptomatic and asymptomatic infection separately, ascertained through PCR testing of both symptomatic participants and weekly self-swabbing of asymptomatic participants. We first assessed the immune response predictive of SARS-CoV-2 infection risk (i.e. correlates of risk) using a case-cohort design among participants who received ChAdOx1 and had antibody data available at day 28 post dose 2 (the cohort). All samples from infected participants (cases) were tested while a sub-set of samples from non-infected participants (non-cases) were pseudo-randomly selected for testing. To account for potential selection bias due to sample selection procedures, we predicted the probability of having samples selected for testing from participant and trial characteristics, and incorporated the inverse predicted probability weights when modelling correlates of risk. We predicted absolute risk of infection using weighted generalised additive models (cubic spline smoothed log antibody levels as predictor) adjusting for baseline risk of exposure to infection. The estimated absolute risk was compared to the overall risk of infection among MenACWY recipients to derive correlates of protection, weighted by the randomisation ratio for study groups not randomised 1:1. Confidence intervals were obtained by the bootstrap percentile method.

Results

Higher levels of all immune markers were correlated with a reduced risk of symptomatic infection but not asymptomatic infection. Using these methods, we were able to estimate antibody level associated with 50-90% vaccine efficacy against symptomatic infection for all immune markers. For example, 80% vaccine efficacy was correlated with 264 (95%CI: 108, 806) BAU/ml anti-spike antibody.

Discussion

Correlates of protection can be used to bridge to new populations using validated assays. We are using the approach to assess correlates for emerging variants. The methodologies could provide insights into correlates of protection design and analysis nested in randomised controlled trials.

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Dilemma of Sham Needles in Acupuncture Research: A scoping review

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Introduction
Great efforts have been made to conduct clinical trials that include the use of “sham” or “placebo” acupuncture procedures, but debates and skepticism arise regarding the effectiveness of acupuncture as studies yield negative and equivocal conclusions. This scoping review summarized the current sham acupuncture designs and their theoretical and practical feasibility to further promote rational and convincible clinical evidence.

Methods
Literature search was performed using MEDLINE/PubMed, EMBASE, Cochrane Central Register of Controlled Trials Library (CENTRAL) and Web of Science from their inception through Dec 31, 2019. We included clinical trials that identified comparative effect of acupuncture manipulation (or connected with electronic apparatus) versus sham/mock methods, or trials aimed at credibility or verification of sham needling patterns.

Results
601 clinical trials conducting “sham” or “placebo” acupuncture were retrieved over the past decades (from 1974 to 2019), consisting of 52,735 recruited participants of 35 countries. A total of 607 pseudo-needling groups were set up involving 11 types of combinations based on four elements: Location of points (L, 61.61% used), depth of needling (D, 25.54%), needling instruments (N, 45.47%) and stimulation (S, 28.01%), but with highly heterogeneous parameters that have been rarely addressed. Given its “self-limiting” and “peak-value” property, acupuncture works via multi-component and multi-target stimulation, along with individualized dose- & time-response factors, which has differentiated it from medication and other nonpharmacologic treatment like surgery. None of the “sham” element, when interpreted from their theoretical mechanism or clinical practice, is conducted unanimously with sufficient consensus regarding irrationality and reliability, and their potential specific effects have been disregarded to a great extent due to methodological heterogeneity. Rationality and heterogeneity between diverse “sham” designs should be verified and synthesized under pathophysiological process, and more studies are needed to optimize clinical outcomes and emerging evidence according to the characteristics of acupuncture treatment.

Discussion
To date, sham approaches in acupuncture research have been flawed by design theoretically and practically and are unlikely to equated with the “placebo”, hence the interpretation of clinical trials and systematic reviews (with meta-analysis) should be taken rigorously and critically. More comparative studies and pragmatic trials are encouraged, in line with clinical practice, to provide rational and robust evidence for the efficacy of acupuncture.

P-256

Subgroup reporting in clinical trials and its implications on subgroup analyses.

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Introduction
Subgroup analyses assess treatment effects in trial participants assigned into one or more categories based on baseline characteristics. Individual trials are rarely sufficiently large to reliably estimate subgroup effects, but subgroup reporting is useful for secondary research such as meta-analyses and health economic analyses. The proportion of trials reporting specific subgroups (eg age, sex, race/ethnicity, comorbidities) is however not well described. Therefore, we examined the reporting of all subgroups for a range of trial conditions and drug classes for trials registered on clinicaltrials.gov.

Methods
We identified phase 3/4 trials for a pre-specified set of conditions and treatment comparisons from clinicaltrials.gov (PROSPERO (CRD42018048202)). Papers for these trials were identified from clinicaltrials.gov database and a PubMed search of the trial IDs. We screened all papers manually and via automatic text searches (regex string "sub-group|subgroup|strata|(by baseline)|subpopulation") for any report of subgroups analyses).
One or more 'condition of interest' for each trial was obtained from clinicaltrials.gov. We collapsed these conditions, which had already been coded using Medical Subject Heading (MeSH) terms, into broader MeSH categories. We coded all interventions using the WHO Anatomic Therapeutic Chemical classification system. We created an interactive heatmap of subgroups for all trials. We have also produced summary statistics and the 5 commonest subgroups for each trial's (first recorded) condition of interest.

Results and discussions
1,778 trials were identified (2,427 papers). 945 papers reported subgroups corresponding to 609 trials. All subgroups can be visualised in our interactive heatmap (https://ihwph-hehta.shinyapps.io/subgroup_heatmap/). We summarised subgroup reporting for 36 conditions. Of these, 121 type 2 diabetes trials reported subgroup effects, the commonest (in order) being age, HbA1c, BMI, race and gender; 67 obstructive lung disease trials reported subgroup effects, the commonest being chronic obstructive pulmonary disease (severity/duration etc), followed by age, gender, steroids, and smoking status and 53 arthritis trials reported subgroup effects, the commonest being rheumatoid arthritis, tumour necrosis factor inhibitors, age, gender and immunosuppressive agents. Across conditions, age and gender were widely reported. Other patterns were evident, such as reporting subgroup effects by diabetes status among cardiovascular trials.
An overview of the patterns of subgroup reporting across conditions informs future trial reporting and guides the development of systematic review protocols.

P-257

Development of a statistic to assess the influence of an omitted study due to missing standard deviation on a fixed or random-effects meta-analysis

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Introduction
Good reporting of research findings in primary papers is crucial to allow meta-analyses to include all available relevant studies. However, key information in trial results is still commonly missing, such as standard deviations (SD) of continuous outcomes. Recommendations in the Cochrane Handbook and PRISMA statement, on handling missing data, includes retrieving all connected information and performing sensitivity analysis to challenge the missing data assumptions. These are not frequently followed, nor is there a simple method to evaluate the impact of omitting a study from a meta-analysis. We previously proposed a statistic to help reviewers assess the influence that a study without an SD estimate may have on the pooled effect of a fixed-effect meta-analysis. We then calculated this Z-statistic across multiple Cochrane meta-analyses. This current research sought to extend this for the random-effects meta-analysis case.

Methods
The data in Davey et al. paper was used to form a database of studies with unresolved missing SDs. It consisted of issue 1, 2008 of the Cochrane Database of Systematic Reviews, comprising 6672 meta-analyses of continuous outcomes. A transformation based on a connection between the inverse-variance weighted method for fixed-effect models and the DerSimonian and Laird method for random-effects models was identified. This was used to demonstrate and compare the influence of omitted studies on point estimates across meta-analyses whether fixed-effect or random-effects models were used.

Results
396 (6%) meta-analyses were affected by omitted studies. The previously proposed 'influence statistic' for fixed-effect meta-analyses tells us whether, and by how much, a study that does not report the precision of an effect could influence the overall meta-analysis estimate. A transformation to each omitted study's arm sample sizes, was identified to allow the random-effects meta-analysis to take on a fixed-effect model form. The influence statistic per meta-analysis was calculated and these were compared across the dataset of mixed fixed-effect and random-effects meta-analyses to identify those with point estimates most sensitive to having omitted studies.

Discussion
Incomplete reporting of variance estimates in continuous outcomes by study authors remains a reality. We proposed a tool that would help authors to determine the influence of a missing trial in the pooled meta-analysis estimate in both fixed and random effects models.

Reference
Davey et al. DOI https://doi.org/10.1186/1471-2288-11-160

P-258

A review of statistical analysis of cluster randomised controlled trials: a case study of the National Institute for Health Research Journals Library

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Background
A cluster randomised controlled trial (cRCT) randomises groups of participants (instead of individual participants) to the treatment arms. Interventions are usually administered at the cluster level while measurement of outcome is done at the participant level. Outcomes for individuals within a cluster are more likely to be correlated. Conventional statistical methods assumes that outcomes are independent, this might not be true in practice for a cRCT. An appropriate statistical method for analysing cRCTs should account for the correlation among outcomes from a particular cluster. The primary objective of this review is to investigate the statistical methods used in practice for analysing the primary outcomes in cluster randomised controlled trials and the secondary objective is to investigate the adherence to the CONSORT (Consolidated Standard of Reporting Trials) reporting guidelines for cRCTs.

Methods
We searched the National Institute for Health Research (NIHR) Journals Library, from 1st January 1997 to 15th July 2021 chronologically for reports of cRCTs. The title and abstract of each report were screened to determine if it contains a cRCT, when the information was not sufficient, we proceeded to screening the introductory and methods chapters of the report. Information on the statistical methods used in the primary analyses and the observed intracluster correlation coefficients (ICCs) were extracted. Reports on pilot and/or feasibility studies were excluded as these have separate design and analysis issues.

Results
This review identified 79 reports containing the results of 86 cRCTs with 100 primary outcomes. Two primary outcomes were analysed at the cluster-level using a generalized linear model. At the individual-level, the generalized linear mixed model was the most used statistical method (80%, 80/100), followed by regression with robust standard errors (7%) then generalized estimating equations (6%). Ninety-five percent (95/100) of the primary outcomes in the trials were analysed with appropriate statistical methods that accounted for clustering. The median observed ICC value was 0.02 (IQR, 0.001 – 0.060) and ranged from -0.02 to 0.63. However, 42% of the observed ICCs were not reported.

Conclusions
Our results support the evidence that in practice, appropriate statistical methods are being used in the primary analysis of cRCTs. Most of the analyses are done at the individual participant level using generalized linear mixed models. However, the inadequate analysis and poor reporting of cRCTs particularly the observed ICC for the primary outcome among studies published in United Kingdom is still happening in recent times.

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The pragmatism of randomised controlled trials (RCTs) of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs): retrospective analysis using the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool

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Background
Pragmatic randomised controlled trials (RCTs) aim to assess the effectiveness of interventions under usual care conditions. In contrast, explanatory RCTs aim to investigate interventions under ideal conditions. The PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool was developed to assess the pragmatism of RCTs during their design. It has also occasionally been used for the analysis of published RCTs, but relatively infrequently. Therefore, we used PRECIS-2 to assess RCTs of GLP-1 RAs in type 2 diabetes.

Methods
206 GLP-1 RAs trials from an existing systematic review (PROSPERO CRD42020184174) were assessed using the PRECIS-2 tool. We rated each trial for the nine domains of PRECIS-2; eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis (each domain is scored from 1-very explanatory to 5-very pragmatic) using published papers. We examined the proportion of trials for which adequate information was available to assess each domain. The association between the mean score of the PRECIS-2 tool and the registration of RCTs on databases was measured.

Results
Information needed for assessment was not reported only for recruitment, setting and flexibility (adherence) domains. Information about recruitment was mostly underreported in 154 (75%) of the RCTs; the setting was not reported in 68 (33%) of the RCTs, and flexibility (adherence) was not available in 110 (53%). The remaining domains were reported in all studies. The mean score of PRECIS-2 for all GLP-1 RAs trials was 3.5 (0.6) SD out of 5, indicating a medium level of pragmatism. The minimum mean score of all included RCTs was 1.3 out of 5, and the maximum score was 5 out of 5. There was a significant difference between the means of database registration groups ($p < 0.001$). The mean difference between RCTs registered on clinicaltrials.gov and RCTs registered on other registries was 0.63 (1.03, 0.21) and, was 0.60 (.97, 0.32) between RCTs registered on clinicaltrials.gov and unregistered RCTs. The mean difference between RCTs registered on other registries and unregistered RCTs was 0.02 (0.51, 0.55).

Conclusion
Published papers contain inadequate information to calculate all of the PRECIS-2 domains in the majority of RCTs.

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Challenges in Factorial Design Randomized Control Trials

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Introduction
Randomised controlled trials (RCTs) using a factorial design enable the assessment of multiple interventions within one trial. Compared to multi-arm, factorial RCTs are more efficient as they require fewer participants, assuming the interventions are independent (i.e., no interaction effect is present). This supposition creates specific challenges in the design, analysis, and reporting of a factorial RCT, and when ignored, can lead to biased results. In our methodological review, we evaluated current methodology and reporting of published reports of 2x2 factorial design RCTs and assessed how frequently trial design methods differed in reporting of results compared to those pre-specified in the protocol/statistical analysis plan (SAP).

Methods/Approach
We searched PubMed to identify primary reports of 2x2 factorial design RCTs published between 01 January 2018 and 04 March 2020. The corresponding trial protocol and/or SAP were collected, where available. Data from primary reports and protocol/SAP were extracted and compared on the trial characteristics (e.g., disease, sample size, funding) and approach to factorial design-specific methodology (e.g., account for interaction in sample size/analysis) as indicators of potential challenges.

Results
The review included a sample of 100 factorial RCTs. A larger number (23%, n=23/100) were conducted in cardiology; the median sample size was 258 (interquartile range 120 to 693); 44% (n=44/100) were multicentre; 61% (n=61/100) were non-industry funded. The rationale for a factorial design was often efficiency (43%, n=43/100); 12% (n=12/100) explicitly assumed no treatment interaction; 4% (n=4/100) reported a powered sample size to detect an interaction. The primary outcome analysis was conducted for the main effects in 48% (n=48/100). 59% (59/100) of articles reported assessing an interaction. Protocols/SAPs were available for 38% (n=38/100) of reports. 63% (n=24/38) intended to assess for an interaction in the analysis (as reported in the protocol/SAP) and 17% (n=4/24) of these did not present this in the primary results report.

Discussion
No studies have previously conducted a factorial design RCT review of both primary reports and their equivalent protocols/SAPs. Published protocols associated with factorial design RCTs results were low (38%). Factorial RCT-specific methodology was infrequently pre-specified in protocols. Where specified, inconsistencies between protocols and reporting of results were present. Reporting guidelines for factorial RCT protocols and primary results reports such as the Reporting Factorial Trials: development of extensions to the CONSORT 2010 and SPIRIT 2013 guidance statements (Equator Network, 2021) are timely.

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Can activity monitors accurately determine sedentary periods and sleep times in less active populations? Comparison of approaches in the RECREATE feasibility study in stroke survivors

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Introduction
Activity monitors are increasingly used in clinical trials to measure physical activity or sedentary behaviour to inform participant outcomes and/or intervention fidelity.
The RECREATE programme seeks to develop and evaluate strategies for reducing sedentary behaviour to improve outcomes after stroke. In the feasibility study, we summarised stroke survivors' outcomes as a proportion of waking time, so we needed to separate sleep time from waking time for participants.
Gold standards of calculating sleep times using participant observations or plethsmography are impractical for large-scale trials. Automated algorithms for the activPAL monitor can be used to identify sleep times based on long sedentary periods, however these may not be appropriate for less active populations. Alternatives include sleep diaries or assuming a set waking time across all participants.

Methods
In this feasibility study, participants were asked to wear the activPAL monitor for 7 days at baseline and again at follow-up. We compared sleep times derived using activPAL algorithm with self-reported sleep times from participant diaries using paired mean differences and 95% confidence intervals (CI).

Results
activPAL data was available for 26 participants at baseline and 13 participants at 4 months. Sleep times calculated from the activPAL algorithm were 2.2 hours longer per day (95% CI 1.3 to 3.2, n=115 days) at baseline and 0.8 hours longer (95% CI 0.0 to 1.6, n=75 days) at 4 months compared to the sleep diary. At baseline, daily sleep times ranged from 3.5 to 20.8 hours from the diary and 1.3 to 23.5 hours from the activPAL algorithm. At 4 months, daily sleep times ranged from 4.3 to 13.3 hours from the diary and 0.3 to 24 hours from the activPAL algorithm.
In the activPAL algorithm, periods of sedentary behaviour immediately before or after sleep could be incorrectly classified as sleep time, thus under-estimating the amount of sedentary time during waking hours.

Discussion
Although it is feasible to collect activity monitor data in stroke survivors, existing automated algorithms to summarise activity outcomes may be inappropriate due to incorrectly classifying sedentary periods as sleep

or incorrectly indicating that the activity monitor has been removed. The two proxy measures of automated algorithms and sleep diaries provided different results.
Further research is needed to adapt activity monitor algorithms for use in less active populations, such as stroke survivors. We plan to test this further on a larger sample size in a randomised trial as part of the RECREATE programme

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Sample size re-estimation in partial cluster randomised trials using Analysis of Covariance method

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Introduction
Sample size for a randomised controlled trial is usually determined based on the analysis of primary outcome measured after the implementation of treatment. By taking into account the baseline outcome measurement, the Analysis of Covariance (ANCOVA) can reduce the required sample size in parallel and cluster randomised trials (1-3) by the design factor (1-rho^2), where rho is the correlation between the baseline and follow-up outcome data. However, no study has shown the impact of ANCOVA on sample size in a partial cluster randomised trial (individual randomisation in one arm and cluster randomisation in the other arm). We aim to estimate the level of sample size reduction by the use of ANCOVA in this design.

Methods/Approach
The sample size for the partial cluster randomised trial is calculated using Moerbeek method (4). We will use simulation to demonstrate the potential sample size reduction using and verify the accuracy of the design factor. The outcome data are assumed to be continuous.

Results Structure and Timelines
We will present the relative change of sample size at different levels of correlation at 80% and 90% power. The work is anticipated to be completed by August 2022.

Potential Relevance and Impact
Many clinical trials have suffered from depleted funding and staggered participant recruitment due to the COVID-19 pandemic. The potential benefit of changing the analysis to ANCOVA may help the partial cluster randomised trials provide a solution to the analysis with reduced sample size when trial extension is less feasible.

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Investigating the presence of surgical learning in a randomised trial: the Timing of Primary Surgery for cleft palate (TOPS) trial

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Introduction

When conducting a randomised trial in surgery, it is important to consider surgical learning, where surgeons become more familiar with one, or both, of the interventions during the trial. If present, and unbalanced between groups, learning can compromise trial validity and may require further statistical investigation. We demonstrate an investigation into learning within a surgical trial of cleft palate repair.

Methods/Approach

TOPS was an international, two-arm, parallel-group trial, comparing primary surgery, using the Sommerlad technique, for cleft palate delivered at six- or twelve-months of age. Prior to participating, Sommerlad technique experience and routine age for primary surgery varied between centres and surgeons. All participating surgeons therefore underwent pre-trial surgical skill calibration, and the randomisation schedule was balanced on operating surgeon. We apply visual methods and statistical modelling to explore learning for two surgical outcomes: operation time and fistula formation.

Results

26 surgeons operated across 22 centres. As the trial progressed, operation time reduced for surgeons with no pre-trial Sommerlad experience (n=2), before reaching a plateau at approximately 30 trial operations, whereas it remained stable for those with prior experience. Fistula rates remained stable regardless of Sommerlad experience. Routine age for primary surgery did not impact selected outcomes.

Discussion

The TOPS trial attempted to reduce learning effects through design, by incorporating skill calibration and balancing randomisation by surgeon, but this was not fully achieved. This statistical investigation illustrates how surgeon skill can be explored using real trial data. These methods can be applied to alleviate specific concerns of surgical learning, or to aid trial interpretation and generalisability.

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Investigating the impact of clustering by surgeon on trial conclusions: to **adjust or not to adjust**

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Introduction

When conducting a randomised trial in surgery, it is important to consider clustering, where variation in outcomes may be smaller between patients treated by the same centre or surgeon than those treated by different centres or surgeons. The intraclass correlation coefficient (ICC) is the statistical measure of clustering. Although design can reduce the impact of clustering, it is important to consider any remaining impact on trial conclusions when analysing the trial. This is particularly important when the cluster (centre or surgeon) is used to balance the randomisation schedule. We aimed to explore the presence of surgeon clustering within a real trial dataset and determine the impact of clustering on trial conclusions.

Methods/Approach

This investigation reanalyses the TOPS trial (Timing Of Primary Surgery for cleft palate). TOPS was an international, two-arm, parallel-group trial, compared primary surgery, using the Sommerlad technique, for cleft palate delivered at six- or twelve-months of age. The randomisation schedule was balanced on operating surgeon. Using a secondary outcome (fistula formation) as a motivating example, we estimate the level of surgeon clustering and the impact on trial conclusions. This is determined by comparing two analysis approaches: an adjusted model (mixed effects logistic regression incorporating a random effect for surgeon) and unadjusted model (standard logistic regression). Finally, using Monte Carlo simulation methods, we explore the performance of these models by estimating empirical power and coverage under varying degrees of the ICC, treatment differences, sample size and distribution of trial cases within surgeon.

Results

73 (13.2%) of 552 patients had fistula formation. 26 surgeons operated across 22 centres (median surgeon cluster size=15.5, ICC=0.15). The treatment effect was not statistically significant at the 5% level using either model (adjusted: Odds Ratio (OR)=1.230 (95% Confidence Interval (CI)=0.743 to 2.036, 0.4203; unadjusted: OR=1.219 (95%CI=0.742 to 1.998, 0.4363). When simulating data, the empirical power was similar for both models for lower levels of ICC but adjusting improved power as the ICC increased. Similarly, as the ICC increased, the adjusted model provided better coverage for all ORs.

Discussion

The conclusions reached using the adjusted model matched those made with the unadjusted model when applied to the TOPS trial. However, under different scenarios, failing to appropriately adjust in the presence of clustering may be detrimental to trial conclusions. Researchers should be aware of the potential for clustering by surgeon, and the scenarios where the impact is most extreme, to ensure that trial conclusions are valid.

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Process evaluation of the daily pain-scores collected via two-way text messaging services: a statistical analysis of a prospective cohort study

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Background
Hidradenitis suppurativa(HS) is chronic, painful, inflammatory, and relapsing skin-condition. The quality-of-life of HS-patients is highly impaired and it is strongly associated with their pain. There is lack of formal studies investigating pain assessment and management in HS-patients. The aim of this analysis is to examine the feasibility of daily pain-scores provided by the HS-patients in daily-text-messages.

Methods
HS-patients' daily pain-score on a numerical rating of 0(no pain) to 10(maximum) via two-way text-messages-service were collected for up to twelve weeks(84-days) after treatment initiation in a prospective observational cohort study. The daily-text-messages were delivered at 6pm and the incoming messages were received in an Application Programming Interface. We used time-to-event analysis to examine patient's adherence to the daily text-messages-services over time and associated baseline factors. We examined consistency of the daily-pain-scores and its baseline correlates using linear-mixed-effect models and generalizability-coefficient(GC). Several mixed-effect models with daily pain-score as dependent, time(days/weeks/months) and its square as independent variables were considered to examine the consistency (generalizability) of the pain-scores over time.

Results
During the text-messages period(84-days), 4898 daily-messages from 100 patients (86% female, 80% white, and aged 19.4-67.1 years) were included the analysis. The mean pain-scores fluctuated over time with 4.24 (95% Confidence Interval-CI: 3.68-4.80) at the start and dropping to 2.77(2.13-3.41) at day-14. It was 2.79(2.10-3.48) at day-36 and was dropped to minimum, 2.23(1.36-3.09) on day-80. Adherence to the text-messages-service dropped exponentially, the median time of adherence was week-5(day-36), and adherence at the end of the period(day-84) was only 20%. Patient's age, ethnicity, HS Hurley-stages, medication choice, dermatology quality-of-life index and seeing nurse were significantly associated with the dropout. The mixed-effect-models showed a significant decrease of the pain-scores over time, $p<0.0001$. A higher consistency was observed in the model for daily pain-scores in the first 14 and 28-days, (GC/intra-class-correlation-ICC)=0.850(95%CI: 0.806-0.885), ICC=0.793(0.74-0.838), respectively. For the whole 84-days pain-scores, ICC=0.761(0.704-0.810). ICC for the initial 6-weeks weekly-pain-scores was 0.690(0.599-0.769) and it was 0.708(0.577-0.812) for the monthly pain-scores. The daily pain-score was significantly associated with the baseline variables of HS Hurley's stages, seeing a surgical doctor, dermatology quality-of-life index, pain item of EQ5D, HS quality-of-life scores, the number of abscesses.

Conclusion
Two-way text-message-service is useful to collect HS daily-pain-scores over four weeks. The daily-pain-scores for two-to-four weeks are highly consistent and valid. Patient's adherence to the daily messaging-services for a longer-period (>5 weeks) is less likely. Clinicians need to consider SH-severity and other baseline characteristics to examine HS-pain

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The CDISC Analysis Results Standard enables automation, reproducibility, traceability and re-use of analysis results

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Introduction
Large trials generate many analysis results in the form of tables, figures and written reports, but they are rarely output in a form that is machine-readable, and there has been no standard way of describing and organising these results. This makes it difficult to automate their generation, make them reproducible, trace their origin or enable them to be reused in other outputs.
The Clinical Data Interchange Standards Consortium (CDISC) develops data standards for clinical trials which have been widely adopted by industry, regulators, and, increasingly, academia.
The CDISC Define-XML standard includes structures to hold Analysis Results Metadata (ARM), but this is limited in scope and is generated retrospectively.
A standard way of representing and describing analysis results and associated metadata is therefore desirable.

Methods/Approach
CDISC set up a multi-national team of volunteers drawn from the pharmaceutical industry, academic trial groups, regulators and software providers to develop a new Analysis Results Standard (ARS). Through a number of use cases, principal requirements for the standard were identified as automation, reproducibility, reusability and traceability.
The ARS team's goals were to:
1. Define an Analysis Results Metadata Technical Specification (ARM-TS), to support automation, traceability, and creation of data displays.
2. Define an Analysis Results Data (ARD) structure, to support reuse and reproducibility of results data.
3. Illustrate and exercise ARD and ARM-TS with a set of common data displays.

Results
The ARD model defines data structures to contain the result itself together with a label and a description of the statistical method, and separate elements describing the analysis, comparison and grouping variables, the source dataset, population and other selection criteria.
The ARM-TS includes separate, linked elements describing attributes of the ARD elements and displays (e.g. tables and figures).
In combination, the ARD and ARM-TS contain all the information necessary to reproduce the analysis, and to understand precisely what each result represents. They also give other contextual information such as the reason and purpose of the analysis. The ARS as whole thus supports meta-programming and provides traceability.
The presentation will include examples of how the ARS can be applied to some common safety displays.

Discussion
The ARS holds great potential to improve the quality of analysis result data, and will be of value to investigators, statisticians, programmers, data managers and regulators.
ARS is currently undergoing CDISC consensus review and is expected to be published in mid-2023.

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A preliminary study to evaluate an adapted version of the International Trauma Questionnaire for use by people with intellectual disabilities (ITQ-ID)

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Aims

There is a growing interest in treating trauma in people with intellectual disabilities (PwID). The International Trauma Questionnaire (ITQ) is a novel assessment instrument that is aligned to the ICD-11 diagnoses of Post-Traumatic Stress Disorder (PTSD) and Complex PTSD (CPTSD). The purpose of our preliminary study was to develop and evaluate an adapted version of the ITQ suitable for use by PwID confirming PTSD diagnosis at screening and allows for stratification of complexity of PTSD for participants as a part of Trauma-AID (ISRCTN: 35167485) - a randomised controlled trial of adapted Eye Movement Desensitisation and Reprocessing (EMDR) for PwID and PTSD.

Methods

The ITQ-ID follows the original ITQ, using wording and simplified scale developed in collaboration with PwID. The ITQ-ID was administered alongside a Trauma Information Form and the ID version of the Impact of Event Scale (IES-ID), to a total of 40 participants, who were current or recent clients of intellectual disability services in six English NHS Trusts. All were known to have been traumatised at some point in their lives, and some were currently undergoing therapy for PTSD. 37 participants completed the ITQ for a second time to assess test-retest reliability. Data were collected between May and August 2021. Because of the ongoing Covid-19 pandemic, three assessments were conducted over a remote video platform; the remainder were conducted face-to-face.

Results

We are awaiting the final validation results, available for presentation in October. However, interim results show the ITQ-ID may be superior to the IES-ID as a clinical instrument because it enables diagnosis and measurement of both PTSD and CPTSD. We will report further on comparisons between inpatient and community settings, internal and retest consistency, as well as component performance for concurrent validity with IES-ID.

Significance

The results are likely to support the use of the ITQ-ID for assessment of PTSD and CPTSD in PwID, in both clinical and research contexts. For Trauma-AID it will function as the definitive PTSD diagnostic instrument and individual results will be used to stratify randomisation and as confounder for treatment outcome. The investigators do not support changing the approved protocol to adopt the ITQ-ID as the primary outcome for the Trauma-AID study, but it remains an important secondary outcome.

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Understanding how Bayesian and Frequentist interim reports affect DMCs decision making for a group sequential design clinical trial.

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Introduction
Adaptive designs of clinical trials are becoming more common, however, there is relatively little information about how people make decisions at predefined interim analyses. Furthermore, it is unclear whether Bayesian methods are more intuitive and easier to interpret than frequentist methods, especially for those unfamiliar with trial design. Hence, we designed a small study to investigate how Data Monitoring Committees (DMCs) made decisions at planned interim analysis points.

Methods
Three hypothetical scenarios of a group sequential design comparing two treatments (intervention and control) were generated: i, stop for efficacy (intervention is better), ii, stop for futility (control is better) and iii, continue recruitment. Each scenario was used to create two interim analysis reports: one Bayesian and one frequentist. Six mock DMC meetings were set-up, with committee members recruited from the local medical school and clinical trials unit. Participants were allocated to DMC groups, with at least one statistician in each meeting. Each committee was presented with one Bayesian and one frequentist report, with the scenario chosen randomly. Participants were asked what decision they would report to the hypothetical Trial Steering Committee and recorded their understanding of each report and their agreement with the initial recommendation. After both reports were discussed, participants were asked which reported they preferred. Participant background information was also collected including: job role, knowledge of statistical methods, and experience of oversight committees. Ethical approval was obtained for the study prior to recruitment of participants.

Results
Recruited participants included statisticians, trial methodologists, clinical academics and administrative staff. Overall, there was no preference between the Bayesian and the frequentist reports. However, participants who reported previous DMC experience were less likely to prefer the Bayesian report over the frequentist. We found that DMCs were more willing to stop for futility than stop for efficacy. Whilst participants were briefed that both treatments were safe, we found that experienced trial statisticians also expressed that more information (i.e. the secondary outcomes) was needed.

Discussion
To our knowledge, this was the first study investigating the decision-making process for interim analyses of group sequential trials. Key learning points were that a high degree of confidence in the design was required for the DMC to stop for efficacy, and that committees desired a breadth of information to help support their decision making. We recommend that DMCs are carefully briefed on the study design and which data are available prior to any interim analysis points.

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Patient-researcher collaboration to guide the provision of information to support trial participants who stop taking part early

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Introduction
Keeping participants well informed about a trial and their involvement in it can benefit all participants. Participants who stop taking part before their participation was originally due to end may have specific information needs, particularly as stopping participation early can sometimes be a difficult experience. There is limited existing guidance for researchers about providing information to this participant group, and it is possible that sensitivities around participants' right to withdraw consent makes some researchers reluctant to provide it. Providing good quality information may improve participants' experiences taking part in research and maintain their willingness to participate in future. It may also ensure participants are informed about, and fully involved in, any decisions about their level of involvement in the trial. This may lead to more participants remaining involved but with reduced commitment (where possible within a trial's design), continuing to contribute outcome data in the process. This project aimed to produce a resource to help researchers provide clear, useful and timely information to trial participants who stop taking part early.

Methods
We conducted a comprehensive literature review to identify relevant existing evidence. We used the review's results to collate a list of information topics that might be relevant to participants who stop taking part early. Two groups of patient contributors were convened. A 'development group' took part (with representatives from other relevant stakeholder groups) in a series of structured meetings to produce draft guidance. A separate, larger 'review group' of patients provided feedback on the draft. The development group agreed a final version. We agreed all outputs through informal consensus after discussion and debate.

Results
The literature review identified 413 relevant reports. From these we assembled a list of 94 items that could be communicated to participants who stop taking part early. The patient contributors were diverse in their characteristics and experiences, and many had personal experiences of stopping research participation early. We successfully developed comprehensive guidance for researchers about how to provide useful information to this participant group in a sensitive way, with example participant-facing text where this could be helpful. We will present the results of the literature review and the main points of the final guidance.

Discussion
The final guidance is publicly available online, with some additional practical resources. We plan to undertake further piloting of the guidance and consider how the effects of providing good quality participant information could be more formally evaluated.

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A digital intervention for eczema self-care: paving the road from clinical trial to routine care

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Introduction

It has been demonstrated that it typically takes 17 years for research evidence to be used in practice. The Eczema Care Online study has generated an evidence-based online intervention for young people with eczema and parents of children with eczema. The effectiveness of the Eczema Care Online interventions has been tested in two randomised controlled trials.

Whilst digital health interventions such as Eczema Care Online might short-cut some of the implementation journey, with the potential for wide-reach and direct patient access, implementation planning is still required to ensure that it reaches the people who will benefit the most and is used by people in practice settings.

Against a context of a wealth of information about eczema already online, we integrated implementation planning alongside clinical trial delivery. Here we describe work carried out to ensure effective implementation of the Eczema Care Online interventions.

Methods/Approach

A multi-method approach centred around engaging stakeholders. The methods include:

1) Interviews with Eczema Care Online trial participants to understand their preferences for accessing and using the website.

2) Stakeholder workshops including secondary care staff, primary care staff, pharmacy staff, patient charities, individuals with eczema, and parents/carers of children with eczema to identify routes to implementation and refinement of how key messages are presented.

3) Content analysis of leading eczema information websites to understand how the intervention fits within the market and identify key collaborators and competitors.

All data have been processed through the lens of Normalization Process Theory to help us identify and address potential barriers to successful implementation.

Results

Stakeholder engagement and review of other eczema websites has resulted in an implementation plan that includes:

1) changes to the intervention required for successful implementation,

2) identifying routes to market,

3) developing a value proposition and understanding our unique selling points, and

4) key priorities for implementation.

Early implementation strategies will primarily focus on linking to the eczema community via patient charity partners and integration into primary care electronic records. We have also developed an infographic on how to use treatments which acts as a gateway into the intervention.

Discussion

This work provides us with a roadmap for implementation. Future work will involve liaising with charity partners, piloting the intervention in primary care settings, interviewing health professionals about the implementation of this intervention within their practice, and exploring adaptations required for implementing into a pharmacy setting.

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Associations between reactogenicity and immunogenicity following COVID-19 vaccinations in Com-COV and Com-COV2 trials

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Introduction
COVID-19 vaccinations protect by inducing immune system responses, however some people report solicited adverse reactions (hereby called reactogenicity) following vaccination. It is plausible that reactogenicity may be associated with immune responses, but it remains largely unknown for COVID-19 vaccines.
Previous research reported significantly higher humoral immune responses in men with severe adverse reactions (AR) after second vaccination of BNT162b2 (Pfizer/BioNTech) (hereby called BNT), compared to men with no/minor ARs, whilst the association was not found in women or for cellular responses in either sex. Other researchers concluded reactogenicity may not be associated with humoral immune responses following a single dose of ChAdOx1 nCoV-19 (AstraZeneca/Oxford) (hereby called ChAd) or BNT or two doses of BNT.
Different reactogenicity and immunogenicity profiles have been shown in Com-COV and Com-COV2 between heterologous and homologous schedules. In this exploratory analysis, we aimed to evaluate the association between reactogenicity and immunogenicity following of two doses of either heterologous or homologous COVID-19 vaccine schedules.

Methods
Both Com-COV and Com-COV2 are participant-blinded, randomised, non-inferiority trials evaluating safety, reactogenicity, and immunogenicity in heterologous and homologous schedules. Adults aged 50 or above with no or well controlled comorbidities and no confirmed previous SARS-CoV-2 infection were eligible. Com-COV participants were enrolled across eight UK sites to receive two doses of COVID-19 vaccines and randomised (1:1:1:1:1:1:1:1) to receive ChAd/ChAd, ChAd/BNT, BNT/BNT, or BNT/ChAd, at either 28-day or 84-day intervals. Com-COV2 recruited participants across nine UK sites who were previously immunised with a single dose of ChAd or BNT in the community. Participants were randomised (1:1:1) to receive a second dose 8–12 weeks after the first of either the same prime vaccine, or mRNA-1273 (Moderna), or NVX-CoV2373 (Novavax).
Reactogenicity was collected using self-reported diaries in the seven days following vaccination. Immunogenicity outcomes at 28 days post vaccination include serum SARS-CoV-2 anti-spike IgG concentrations, pseudotype virus neutralising antibodies, and cellular responses. We will fit multivariable linear regression models separately for each solicited AR to compare any event of severity grading 1 or more to no event, adjusting for study arm and covariates as fixed effects, separately for each trial. Additionally, we will fit interaction terms to evaluate sex-specific and schedule-specific associations.

Results and timelines
We will present geometric means, adjusted geometric mean ratios, 95% confidence intervals and p-values in autumn 2022.

Potential relevance and impact
Results will prompt hypothesis generation into biological explanations and assist in future vaccine development.

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Interventions to improve the publication and dissemination of trial evidence: A scoping review

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Introduction
Trial investigators have a responsibility to disseminate their findings. This is traditionally done by publishing in peer-reviewed journals. Whether the tested intervention is shown to have no effect, benefits or harms, and whether or not the findings are clinically important, the results should be made available. However, this does not always happen.
Clinical trial registries have helped reduce publication bias by increasing transparency regarding ongoing and completed trials. Investigators may have barriers to publishing due to funding, competing interests, and time. This scoping review aims to identify and describe interventions that target trial investigators to reduce publication bias.

Objective
To identify investigator-targeted interventions that have been tested regarding publishing trial results.

Methods
We conducted a scoping review. We searched PubMed and Scopus on 25 March 2022 using words related to interventions and "publication bias", "trial*", "publication*", "publish", etc., and without any language limitations. We used Rayyan - a web and mobile app for systematic reviews to screen in duplicate and independently. Data extraction was done using a pre-tested Excell spreadsheet.

Results
After de-duplication, we screened titles and abstracts for approximately 10,000 records and found 13 full texts to review, of which two studies published in 2016 and 2017 were eligible. One study investigated the effect of peer reviewers assessing the importance of the research question and the evaluation of that question before knowing the research outcomes. The other examined the effects of professional medical writing support for trial authors. Both studies reported that their interventions were effective because journals were more likely to publish submitted manuscripts from authors who received peer review feedback or writing support. The time taken to write the manuscripts was similar with or without the tested intervention, but the quality was better with the intervention.

Conclusion
From the initial results of the scoping review, the evidence regarding what works for supporting trial authors to publish their results remains scarce. Additional interventions may be helpful, such as prompting investigators by institutional ethics committees or trial registries after the estimated completion date of the trial. Additionally, interventions such as writing workshops, writing retreats, writing mentors, and using checklists like the Consolidated Standards of Reporting Trials or a combination may prove helpful. However, these would need to be tested.

P-273

Sharing results with participants (and community) in malaria related research: perspectives and experience from researchers

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Introduction
Results sharing with the participants or the communities after the completion of research is an essential element of ethical global health research. The main objective of this study was to explore the perspectives of malaria researchers on current practice and potential strategies and methods related to results sharing with study participants.

Materials and methods
This mixed-methods study used a sequential exploratory design with two phases: i) an initial qualitative phase to explore the topic and to inform the quantitative data collection, ii) a quantitative survey. Malaria researchers were identified through investigators' networks and were interviewed through Zoom using a semi-structured interview guide. All interviews were transcribed using Otter.ai, coded in QSR NVivo and underwent thematic synthesis.
The sampling frame for the quantitative survey was determined through clinical trials registries limited to malaria trials including both interventional and cluster randomized trials, completed and ongoing, including adults and children and all geographic areas and limited to phase 3 and 4 trials. Investigators were contacted via email and invited to participate. The quantitative survey also included open ended question that supplemented the qualitative analysis.

Results
Qualitative interviews were done with 12 participants. The final survey sampling frame included 221 participants, and the response rate was 20.4%. Disseminating results to participants after the trial was deemed critical for ethical malaria related research, with 38.1% indicating it is extremely important, while 45.2% thought is mostly important. Nonetheless, most of our respondents spontaneously referred disseminating results to the policymakers and wider stakeholders as important aspects of research to translate findings to policy, share among scientists, funders and wider groups. The practice of patient/community engagement were mostly focused on pre-trial and during the trial period for obvious instrumental goals of improving retention, coverage and adherence, but much less priority was given to the post-trial period. The main reason was the notion that the time lag between study participation and the availability of results was too long (42.4%). Other reasons included the assumption that the community is not interested (36.4%), and financial restraints (9.1%). The rich qualitative data revealed details accounts about operational, cultural, educational and economic aspects that pose barriers to results sharing.

Conclusions
Findings from this study offer insights on current practice, and barriers towards post-trial results sharing which can inform future strategies for post-trial result dissemination to participants.

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Assessing the reporting quality of early phase dose-finding trials: a methodological review

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Introduction
Incomplete reporting of the design, conduct and analysis of early phase dose-finding trials can hinder interpretability and reproducibility, and lead to erroneous conclusions on tolerability and efficacy. This methodological review investigates the reporting quality of published trials using broadly the CONSORT 2010 checklist with added items unique to early phase dose-finding trials.

Methods
MEDLINE via PubMed was searched for articles published in 2011-2020. Phase I or I/II trials, with planned interim dosing decisions (de/escalate, stay at the current level or an early stop), which aim to find a recommended dosing regimen(s) for further testing, were included. Data were extracted from 476 randomly selected trials, stratified by oncology (n = 238) and non-oncology (n = 238) settings.

Results
We noticed differences in describing dose-escalation components in oncology and non-oncology settings: definition of dose-limiting toxicity (DLT) or safety measures used to inform dose-decisions provided, if applicable (oncology/non-oncology: 84.3%/29.5%); DLT assessment period provided, if applicable (73.5%/35.4%); provided escalation and de-escalation criteria/rules (at least, partially) (84.0%/40.3%); definition of maximum tolerated dose or recommended dose(s), if applicable (72.1%/6.3%).
Only 1 (0.4%) cancer trial was randomised compared to 180 (75.6%) non-cancer trials. Notably, very few trials provided accessible protocols (6.3%), statistical analysis plan (3.8%) or lay summaries (1.5%).
Improvement in trial reporting over time is evident in some items, including participant flow and sample size justification.
The key items that are frequently not reported in both oncology and non-oncology settings include: planned/maximum sample size (oncology/non-oncology: 29.0%/44.1%), with justification (14.7%/24.8%); recruitment method (8.0%/21.4%); oversight committees (16.4%/37.8%), with roles and structure (7.1%/16.8%); who makes dose decisions (4.2%/16.4%); definition of analysis population: dose-determination (45.4%/46.6%), safety (47.9%/54.2%), key outcomes (42.2%/55.5%); rationale for starting dose (21.8%/17.6%); baseline demographic and clinical characteristics by each dose level (29.4%/62.2%); settings and locations where data were collected (36.1%/62.6%); participant flow diagram/table (35.7%/60.5%); losses/exclusions for each dose level (12.6%/35.7%).

Discussion
Important methodological features in design, conduct and analyses of early phase dose-finding trials are frequently omitted from published reports. Non-cancer trials appear better reported; as they are commonly

randomised, they may have adopted CONSORT 2010 guidance. This review supports the need for a robust consensus-driven guidance for dose-finding trial reporting, to allow their accurate evaluation and reduce research waste, and lays the foundation for developing a CONSORT Extension for early phase dose-finding trials (Yap, C. et al. Nat Med 28, 6-7 (2022)).

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Reporting Factorial Trials (RAFT): Development of Extensions to CONSORT 2010 and SPIRIT 2013 Statements

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Introduction
Factorial trials, in their simplest 2x2 form, are when two interventions (A and B) are tested in the same trial: participants are randomised to receive neither intervention, A alone, B alone or both A and B. These trials represent the potential for efficient evaluation in the context of no or limited interaction between the interventions. Factorial trials have specific design and analysis considerations in addition to standard items specified in Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) guidance, yet extensions do not exist for factorial trials. Such extensions are important to aid in critical appraisal and interpretation of these trials for grant reviewers, funding bodies, trial methodologists, editors, reviewers, and readers. The aim of the RAFT study, funded by MRC, was to improve the reporting of factorial trials by developing extensions of SPIRIT and CONSORT.

Methods
Development of the guidelines follows a four-step approach, which focuses on co-production, working with experts in the field of guideline development, factorial trials, ethics and funding board committee members and journal editors.
Literature review: identify a 'long-list' of reporting considerations specific to factorial trials.
Online Delphi survey: reduce the 'long-list' to a 'short-list' of considerations through a consensus process.
Consensus meeting: finalise the items to be included in the CONSORT and SPIRIT extensions.
Knowledge translation: synthesise results from stages 1-3 to develop a final checklist of SPIRIT and CONSORT extensions, guidance statements and an 'Explanation and Elaboration' paper.

Results Structure and Timelines
We have completed the literature review and are undertaking the Delphi study. The consensus meeting is scheduled for early September 2022. The finalised checklists are planned for development by the end of September 2022. The focus of the talk will be on the final checklists (plus explanation).

Potential Relevance and Impact
Development of these guidelines will support high-quality reporting of factorial trials, thereby enabling factorial trials to fulfil their potential in terms of offering an efficient way to evaluate healthcare interventions.

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Early Phase Clinical Trials Extension To Guidelines For The Content Of Statistical Analysis Plans

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Introduction

Early phase clinical trials aim to determine the safety and initial indicators of efficacy (phase I and II respectively) of interventions before subsequent phase III trials are conducted. The undertaking of later phase trials is often a lengthy and costly process predicated on accurate and robust conclusions from early phase trials. The design, conduct, and analysis of these early phase trials should be performed to the highest standards of rigour and quality, ensuring correct decisions are taken forward.

Detailed statistical analysis plans (SAPs) improve transparency, trial quality and robustness. Guidelines for the content of SAPs for randomised trials were published in 2017[1]. These acknowledged that despite some recommendations being transferable, specific consideration and guidance would be required for early phase trials.

Methods

Work on this extension included: a literature search (identifying peer-reviewed publications of applicable guidelines, example trial protocols and SAPs); a review of the EQUATOR repository; and an assessment of regulatory and funder requirements. Additionally, a survey of UK Clinical Research Collaboration registered Clinical Trials Units (CTUs) was undertaken (40/53 responded) to identify those conducting early phase trials (n=21) and establish current practice regarding SAP authoring and content.

Following these reviews, incorporating SAPs provided by CTUs, and considering the requirements of pharmaceutical and academic statisticians, regulators, and funders, the early phase trial extension to existing SAP guidelines were developed. These guidelines were discussed at a review meeting attended by international academic, regulatory, and pharmaceutical representatives, subsequently updated, piloted, and finalised.

Results

The early phase trial SAP guidelines have been published[2], building upon the structure of Gamble et. al[1]. Of the 55 originally proposed SAP guidance items, 30 remain unchanged, 25 have been amended, and a further 11 new items proposed. These alterations include items specific to early phase trials (e.g., design information and dose escalation decisions), and an update to the outcomes section regarding estimands following the adoption of ICH E9(R1)[3].

Discussion

Recommendations are provided for an extension to the existing SAP content guidance apposite for early phase trials. This work supports clinical trial statisticians, trialists and peer reviewers to facilitate an improvement in the quality of analysis, the reproducibility of methods and results, and the robustness of conclusions.

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Assessing the reporting quality of early phase dose-finding trial protocols in ClinicalTrials.gov: A methodological study

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Introduction
The paradigm of phase I trials has evolved in recent years. Innovative dose-finding designs have been increasingly implemented in clinical studies and protocols which combine phase I and II are becoming more popular in health research. However, the quality of early phase trial protocols is unknown due to a lack of reporting guidelines. This methodological study aims to address this gap by investigating the reporting quality of dose-finding trial protocols.

Methods
This cross-sectional study included early phase dose-finding trials with start dates 01/01/2017 – 31/12/2021 registered on ClinicalTrials.gov. The search was restricted to 1) full protocols in English language, 2) treating living humans, and 3) phase I or I/II trials that include a dose (de-)escalation component. No restrictions were applied to limit types of intervention or setting.
To evaluate the reporting quality, we created a checklist of items comprising: 1) the original 33-items from SPIRIT 2013 Statement and/or modified items tailored to dose-finding trials, and 2) additional items unique to dose-finding trials considered useful by the review team. Characteristics including sample size, multi-center/single-center, industry/non-industry, oncology/non-oncology and protocol year, were also collected.

Results structure and timelines
A total of 246 records were identified. The records were randomly ordered and assessed by two authors (GV and DP) independently for eligibility until an agreement was reached for 120 included protocols. At least 10% of the protocols will be independently reviewed by two authors to check for discrepancies or potentially spurious data.
To standardize the evaluation criteria, an initial roundtable discussion took place among all authors to discuss the first double-reviewed 8 protocols. A second roundtable will take place to evaluate the next 30 protocols. Data extraction and analysis will be completed by August and early September respectively. The primary endpoint for the analysis will estimate the overall proportion of adequately reported items along with a 95% confidence interval. The secondary endpoints include 1) proportion of protocols that report each item adequately, 2) factors associated with the quality of the protocol, and 3) descriptive analysis of commonly used statistical trial designs.

Potential relevance and impact
Incomplete or unclear information about the design, conduct and analysis in dose-finding protocols hinder interpretability, reproducibility and may lead to erroneous conclusions on safety and efficacy. This study will determine the reporting quality of early phase dose-finding protocols, identify the compliance with the available SPIRIT 2013 checklist and inform future guidelines for dose-finding trials.

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The development and piloting of the EQUITY and EQUITY-P quality appraisal checklists for publications reporting qualitative research in trials

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Introduction
To help ensure findings from qualitative research in trials (QRT) are effectively disseminated and implemented, complete and transparent reporting is crucial. Concerns about the visibility of QRT in reporting and poor reporting quality have been stated. QRT specific reporting guidelines can help to inform those reporting QRT about what is expected from them, improve reporting quality, and help decision makers assess the reliability and usefulness of findings. To support good reporting and quality assessment of QRT we developed and piloted two quality appraisal checklists: the Evaluating Qualitative Research In Trials and their Yields (EQUITY) and the Evaluating Qualitative Research In Trials and their Yields – Protocol (EQUITY-P) checklists.

Methods
Items from existing reporting appraisal tools for qualitative and mixed methods research were assessed and synthesised into common categories. Questions with items relevant to the linkage of qualitative research with the wider trial framework were then added. Items were tested and refined to produce the two final checklists: one for reported findings from the use of QRT (EQUITY) and one for published protocols of trials using qualitative research (EQUITY-P). The checklists were piloted on 121 QRT publications using the two checklists as appropriate.

Results
Items for information that should be reported on within the publications related to the research question(s), study design, data collection and analysis approaches and integration of qualitative research with the trial and other data sets. Additionally, the EQUITY checklist addressed the reporting of findings and their implications and the role of researchers. The EQUITY checklist comprised six sections with guiding questions and a total of 36 items. The EQUITY-P checklist comprised four sections with guiding questions and a total of 21 items. To help assess quality, items were dichotomised into yes (1 point) or no (0 points) for when criteria were/were not present. Responses were then summed to give a score between 0-36 for the EQUITY checklist and 0-21 for the EQUITY-P checklist. A cut off from 18 for the EQUITY and 10 for EQUITY-P checklists was used to indicate poor/good quality.

Reporting quality for publications was variable with a range of 4-35 (average of 20) for findings publications, and 4-18 (average of 11) for protocols. Most publications were of high quality (60% findings, 61% protocols). Quality over time was consistent (2011-2017).

Discussion
Using the EQUITY and EQUITY-P quality checklists can help ensure evidence from QRT is reported well and increase its usefulness for decision makers.

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Developing international consensus-driven SPIRIT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (DosE FIndiNg Extensions) study

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Introduction

Early phase dose-finding studies are a critical stage for the development of a new treatment, and directly influence whether compounds or interventions can be investigated in further trials and ultimately confirmed as safe and efficacious. There exists guidance for clinical trial protocol writing and reporting in the SPIRIT 2013 and CONSORT 2010 statements, respectively. However, neither the original guidance, nor their extensions, adequately cover the features of early phase dose-finding trials. The DEFINE study aims to enhance transparency, completeness, reproducibility and interpretation of early phase dose-finding trial protocols and their reporting, across all disease areas, and to build on the checklists outlined in the SPIRIT 2013 and CONSORT 2010 statements.

Methods

A methodological review of published early phase dose-finding trials was conducted to identify features and deficiencies in their reporting and to inform the initial generation of the candidate items. The early draft checklist was further enriched through review of the published and grey literature, real-world examples analysis, citation and reference searches and consultation with international experts, including regulators and journal editors. A modified Delphi process, involving worldwide, multidisciplinary, and cross-sector key stakeholders, is ongoing since 30 March 2022 to refine the checklists. An international consensus meeting in Autumn 2022 will finalise the full list of items to be included in both guidance extensions.

Results Structure and Timelines

The Delphi survey response rate was 206/244 (84%) in Round One bringing participants from 24 countries. Tailored to cover the specific features of early phase dose-finding trials, the Delphi survey included new or modified candidate items for SPIRIT (n=36) and CONSORT (n=43) extensions. Round Two of the Delphi survey is expected to complete in June 2022. Quantitative analysis and thematic analysis of participants' feedback from the Delphi survey will be presented.

Potential Relevance and Impact

By implementing a robust, comprehensive gold-standard methodological framework for guideline development, SPIRIT-DEFINE and CONSORT-DEFINE will allow investigators to address effectively the essential items that should be included in trial protocols and reporting, thus promoting transparency, completeness and reproducibility of methods. It will also provide a framework for peer review of dose-finding trial protocols and reports regarding the critical appraisal of the quality of the trial design and methods, and the risk of bias in the reported outcomes. The resulting improvements will ultimately contribute to reducing research attrition and improve patient care and safety.

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Implantable Cardioverter Defibrillator Lead Performance: An Individual Patient Data Meta-Analysis

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Introduction
Reliable post-approval surveillance of implantable cardioverter-defibrillator (ICD) lead performance remains a challenge. In the past, two ICD leads were recalled due to a high frequency of failures. In this systematic review and meta-analysis, we sought to provide a combined estimate of failure-free rate for recalled and contemporary non-recalled ICD leads by reconstructing individual patient data (IPD) from published Kaplan-Meier (KM) curves and to investigate whether estimates could be influenced by the characteristics of the study.

Methods/Approach
An electronic search was performed using the MEDLINE database (PubMed) from January 1, 1990, until November 30, 2021. Eligible criteria included observational studies aimed at assessing transvenous ICD leads in a general ICD population with or without cardiac resynchronization therapy function. To be included, studies needed to report the KM curve. The characteristics of the study and the definition of lead failure were collected from each study. Data coordinates were extracted manually from the selected KM curves. The primary outcome was failure-free estimates during study follow-up. Survival rates were estimated with the KM method and comparisons were tested with mixed effects proportional-hazard Cox models including study identifier as random effect.

Results
Our meta-analysis included 41,870 (63.1%) non-recalled and 24,493 (36.9%) recalled leads. The 8-year cumulative failure-free rate was 94.1% (CI, 93.6% - 94.6%) for non-recalled leads and 81.2% (80.3% - 82.0%) for recalled leads (hazard ratio [HR], 3.15 [2.85-3.47], p<0.001). Single-center trials estimated significantly lower failure-free rates in both the non-recalled (HR, 0.28 [0.15-0.51], p<0.001) and recalled (HR, 0.54 [0.33-0.88], p=0.014) group compared with multicenter trials. Similarly, estimates were significantly lower in small (i.e. extracted KM curve with less than 312 leads) versus large trials (HR non-recalled group, 0.54 [CI, 0.33-0.89], p=0.015; HR recalled group, 0.62 [CI, 0.43-0.89], p=0.009).

Discussio
In this meta-analysis including more than 66,000 leads, we provide pooled survival curves that may play a significant role in generating evidence-based standards for assessing clinically acceptable failure rates for transvenous ICD leads. Lead performance tended to be underestimated with single-center and small-sized studies; large multicenter trials remain the main tool to reliably conduct post-market surveillance of ICD leads.

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The STAR care pathway: from trial results to implementation into usual care

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Introduction
Over 100,000 total knee replacements (TKRs) are performed annually in the UK. The aim of surgery is to reduce pain and improve function. One in five patients will report chronic pain three months after surgery. The STAR Care Pathway is an intervention which was developed and evaluated in a pragmatic multi-centre randomised controlled trial. This personalised and multifaceted care pathway addresses the multiple factors that may contribute to chronic pain by providing screening, early postoperative assessment, referral for targeted treatment and follow-up over one year. The care pathway is delivered by specially trained clinicians.
The trial found that the STAR care pathway is a clinically important and cost-effective treatment for patients with chronic pain after total knee replacement. Participants who received the care pathway had fewer inpatient admissions after surgery, a reduced length of stay, less unpaid time off work, and improved pain at twelve months after treatment.

Methods/Approach
Trial findings were presented to managers at North Bristol NHS Trust. A business case was developed and funding was granted for an implementation pilot from January - March 2022. The care pathway was delivered following the protocol developed for the trial. Trial documentation was adapted for use in usual care using the COM-B model for behaviour change and evidence-based approaches to increase the return of postal questionnaires. Trial sites were contacted to understand their capacity to implement the intervention locally.

Results
Screening identified 26 patients who underwent TKRs from October – December 2021. Eight patients were excluded for clinical reasons. Screening questionnaires were sent to 18 patients. The response rate was 83%. All eligible patients attended the assessment clinic. The STAR Care Pathway is now permanently part of usual care North Bristol NHS Trust. Contact with trial centres indicated that many trained clinicians who had delivered the care pathway during the trial were no longer working at the Trust or had changed roles. This presented a barrier to implementation in those settings.

Discussion
The implementation pilot demonstrated that the STAR care pathway can be successfully delivered in usual care. Implementing the intervention at the trial co-ordinating centre may have been facilitated by the local presence of the research team and trained clinicians. Availability of trained clinicians can be a barrier to wider roll-out. An e-learning training package is under development with Health Education England which will enable wider national implementation of the STAR care pathway in the NHS.

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The impact of patient and public involvement in the dissemination of clinical trial results to participants

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Introduction
Patient and Public Involvement (PPI) is common during the set-up of a clinical study and often continues throughout recruitment, providing valuable feedback on study design and patient materials. Dissemination of results to participants is a key activity at the end of a study. Given the contributions that participants make to clinical studies, it is important that results are disseminated in a way that is meaningful and of interest. At the Bristol Trials Centre (BTC), several studies have requested PPI feedback on dissemination materials for study participants. We have conducted an internal scoping exercise to evaluate the contributions PPI groups can make to these documents.

Methods
BTC Trial Managers were sent a list of questions and asked to respond if they had experience of disseminating results to study participants. They were asked to summarise the format of their dissemination materials for participants, where and how they were shared, whether PPI provided any feedback on the materials and if so, to provide a summary of the key changes requested.
To summarise the feedback received from PPI groups the requested changes were categorised into the following themes: reprioritising content, addition/removal of content, formatting changes, clarifications/wording changes.

Results
Information was received about PPI input into 7 studies. Five of the respondents collected PPI feedback on dissemination materials and had notes available. These 5 studies covered various clinical specialties; ophthalmology, oncology, cardiac surgery and vaccinology. A results infographic or leaflet had been drafted for all five studies.
Suggestions for reprioritisation of content were noted for 3/5 studies, addition/removal of content for 5/5, formatting changes for 3/5 and clarification/wording changes for 3/5.
Examples of notable changes requested by the PPI groups will be described.

Discussion
This work demonstrates the value of consulting PPI groups when disseminating study results to participants and gives examples of patients prioritising outcomes differently to researchers. It also shows that PPI groups can contribute to the main content of dissemination materials in addition to formatting and wording clarifications. We therefore recommend including PPI groups at the end of a clinical study to ensure results are presented in a meaningful way to participants.
Unfortunately, feedback was obtained on the method used to circulate results to participants for only one study. This may be something to consider when consulting a PPI group at the set-up of a study as circulation methods can be constrained by the contact methods consented to

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Barriers and facilitators to the recruitment of disabled people to clinical trials: a scoping review

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Introduction
Underrepresentation of disabled groups in clinical trials results in an inadequate evidence base for their clinical care, which drives health inequalities. People with disabilities are considered one of the major underserved groups in medical research. People with disabilities should be able to engage in research activities to the same extent that is possible for the rest of the population. The first step to achieving this is the proportional representation in study populations.
This study aims to map the potential barriers and facilitators to the recruitment of disabled people in clinical trials in order to identify knowledge gaps and areas for further extensive research.

Methods
The Joanna Briggs Institute (JBI) Scoping review guidelines were followed to complete the current scoping review. MEDLINE and EMBASE databases were searched via Ovid. The literature search was guided by a combination of four key concepts from the research question: 1) Disabled Populations, 2) Patient Recruitment, 3) Barriers and Facilitators, and 4) Clinical Trials. Populations that were defined to have any kind of disability covered by the International Classification of Functioning, Disability and Health were included. Articles that didn't mention barriers or facilitators to clinical trial recruitment were excluded. Data on study characteristics and identified barriers and facilitators were extracted. Identified barriers and facilitators were then synthesised according to common themes.

Results
The review included 56 papers. The evidence on barriers and facilitators was sourced in large part from articles considering empirical evidence and from literature drawing on researcher perceptions and experiences. Carer and clinician perspectives were rarely represented in articles. A total of five emergent themes were determined across the barriers and facilitators identified in this study. These were: Risk vs benefit assessment, recruitment protocol design and management, balancing internal and external validity considerations, consent and ethics, and systemic factors.

Conclusions
Much work needs to be done to understand and accommodate needs specific to different disabled groups. Barriers are varied but include valid practical and ethical considerations, such as internal validity considerations and safety protocols. As well as mapping current barriers and facilitators, this review also delivers valuable lessons and direction for future inclusivity research. Gaps in the literature exist in understanding the role of carers and clinicians in clinical trial recruitment. Empirical evidence must be gathered to substantiate potential strategies to overcome barriers. Principles of co-design, person-centred consent and emancipatory ethics facilitated recruitment of disabled groups and should be prioritised.

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Walking The Walk - Embedding Patient and Public Involvement in the culture of the MRC CTU at UCL

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Introduction
In 2012 the MRC CTU at UCL adopted a policy that all our clinical studies should have patient and public involvement. To ensure that the involvement was relevant and useful rather than tokenistic, we have worked to embed high quality PPI in the culture of the Unit. This abstract describes our processes to achieve this, and includes the results of a recent survey of trial staff assessing our progress.

Approach
We have acted at strategic, programme and individual study levels. Strategic level activities include a PPI Group to oversee PPI across the Unit (made up of staff and patient representatives); the appointment of a PPI Coordinator within the unit, and incorporating patient representatives on our Protocol Review Committee, our Data Sharing Group, and our Quality Management Advisory Group (QMAG). Our PPI Standard Operating Procedure (SOP) specifies that each trial should have a PPI plan, documenting how PPI will be carried out at each stage of the study, which is appraised by the QMAG. The plan template was co-produced with our patient representatives. There is also a regular review of delivery of the plans, using a PPI annual review form. At a programme level, we seek patient and public input through existing community organisations, setting up PPI panels that cover multiple trials, and having patient representation on trial steering committees that cover multiple trials. Individual trials involve patients and the public through membership of formal committees, one-off discussion groups, standing advisory groups and participant involvement activities. There is a programme of capacity strengthening activities for Unit staff and patient/public contributors, including co-developed and co-delivered training, guidance and tools (some available https://www.mrcctu.ucl.ac.uk/patients-public/patient-public-involvement-resources/papers-guidance-templates/). We conducted a survey of MRCCTU at UCL trial teams to assess progress.

Results
Staff from 25/39 studies completed the survey. PPI training and the SOP improved understanding of PPI. 14/25 said the SOP had caused them to rethink/improve PPI for their trial. 14/25 trials had completed a PPI plan. It was viewed as very or somewhat helpful by 13/14 respondents. 10/20 respondents reported PPI had a lot of impact on the success and quality of the trial, 3/20 a little, 6/20 were unsure, and 1/20 reported no impact.

Conclusions
Embedding PPI in the culture of a clinical trials unit, through action at strategic, programmatic and study level, may improve the success and quality of trials. It also encourages application of good practice consistently across many studies.

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Patient and public involvement in maternal health and depression – ROSHNI-2 add-on study

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Introduction
Background
Patient and Public Involvement (PPI) nurtures a meaningful and active partnership between the public and researchers. PPI can ascertain which research topics are most significant to them, influence study design, and interpret and disseminate findings. Adoption of PPI in research has increased over time and can be advantageous. However, those usually involved do not always reflect the diversity of populations.
People from British South Asian (BSA) groups are under-represented as part of PPI in research. This study demonstrates the inclusion of BSA women in PPI activities. The ROSHNI-2 add-on study aims to increase our understanding of the pandemic-related impact on British South Asian (BSA) women, including Interpersonal Violence (IPV) in BSA communities.
***ROSHNI-2 is a national scale research study, designed to address the rise of British South Asian (BSA) women who experience Post-Natal Depression.

Aim: The PPI activities aimed to gain insight into the opinions of BSA women to develop a topic guide for the one-to-one interviews with previous ROSHNI-2 participants, health professionals and service providers on how we conduct the study and the viability of online one-to-one interviews.

Design
Setting: Four patient and public involvement groups in four sites across Bolton, Manchester, London and Lancashire.
Recruitment: PPI representation included British South Asian (BSA) mothers with lived experience of depression (previous ROSHNI-2 participants).
Methodology: Hybrid (face-to-face and virtual) group discussions (2 hours) to inform us of the study design, research topic and outcomes. Two Bi-lingual facilitators were allocated to each PPI group according to the language preferences.

Results
PPI groups consisted of 25 BSA (Bangladeshi, Indian, and Pakistani) women with lived experience of depression. PPI activity outcome included changes in the interview topic guide for women with lived experience and professionals' perspectives. Participants prioritized needs, discussed feedback drafts. Need for clear, valuing, non-stigmatizing language in interview were identified, particularly highlighting the sensitive nature of how COVID−19 pandemic affected BSA women differently.

Conclusion

PPI feedback helped shape, refine and confirm the research topic guide for the one-to-one interview and the contents and format of the online survey. PPI contributors had an overall positive attitude towards the study design and using online platforms for the data collection.

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Reporting patient and public involvement practice with children and young people in the design and conduct of paediatric health research

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Introduction
Active involvement of patients and the public in the design and delivery of health research, rather than as 'subjects' of research has been encouraged (if not required) for many years. However, defining how this is realised in practice, especially where children and young patients are concerned is limited, partly due to the low level of reporting of patient and public involvement (PPI) in general.
In April 2018 the National Institute for Health Research (NIHR) advised authors of research it funds to refer to the GRIPP2 Checklist to enhance the quality, transparency, and consistency of reporting PPI activities.
As a result of these developments within NIHR, this research (part of a PhD project) wanted to explore how CYP involvement in the design and conduct of clinical studies (in any type of intervention, comparison, or outcome) is reported. The aim was to examine in detail the reports that are completed by researchers to examine (a) the opportunities offered to CYP, including models and stages of involvement, (b) any reported impacts of involvement, and (c) reported challenges and facilitators.

Methods
- A search of the NIHR Journals Library was undertaken and identified 42 potential reports for analysis from a search of 545 reports
- Qualitative content analysis and Framework Analysis techniques are currently being used to analyse the data.
- A small group from the NIHR Paediatric Incubator was formed (led by the lead author) to iteratively test tools to assess the level of reporting of PPI with CYP. Further workshops with wider members of the Incubator have taken place to get a wider consensus on the tools, and a young person's workshop is currently being planned.

Timing of potential results
August 2022

Potential relevance and impact
Inadequate reporting of PPI creates a disjointed evidence base making it difficult to understand the different levels and roles patients and the public, (including CYP) have, resulting in a lack of understanding of what works best for them, in different contexts, and what impact their involvement has on the actual research itself and on those who get involved. This project has the potential to develop simple tools (informed by CYP) to support researchers on how to effectively report on PPI activities, which may also help plan PPI activities with CYP based on best practices.

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Methods to Improve Recruitment in Breast Cancer Treatment De-Escalation Trials: Examples from the ATNEC – Patient Experience Sub-Study (IRSCTN: 36585784)

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Background
Recruitment to de-escalation trials is challenging because of strong patient and clinician preferences and worry around 'under-treatment'. ATNEC is a phase III, randomised, multi-centre trial which assesses whether axillary treatment can be deescalated, post-surgery, in T1-3N1M0 breast cancer patients who have no residual nodal disease post-neoadjuvant chemotherapy. The patient experience sub-study (PES) is embedded within ATNEC to identify recruitment challenges and develop strategies to overcome them.

Aims
The PES aims to find out about participants' views on reduced axillary treatment and treatment de-escalation. It will help the research team to understand recruitment issues and develop effective and realistic strategies to ensure successful delivery of the trial.

Methods/Approach
A multi-faceted, recruitment intervention has been designed, with the following workstreams:
1. Semi-structured interviews/focus groups with researchers and participants
2. Audi-recording of consultations where researchers discuss the trial with potential participants
3. Assessment of screening logs

PES Findings to date (May 2022)

Workstream 1
13 trial participants have been interviewed and have talked openly about their personal cancer pathway and their own decision-making process regarding the trial. Initial analysis suggests that participation may be mainly altruistic:
Quote: 'I just thought well I've got nothing to lose by doing it….. You know things progress by people being on trials.'
HCPs from 5 trial sites have been interviewed and discussed the recruitment process. Sites appear to have individualised approaches which may later be reflected in recruitment rates.
Workstream 2
4 sites have commenced the audio-recording of initial patient consultations. First data expected by Summer 2022.
Workstream 3
Collection of screening data is ongoing.

Co-ordinating the workstreams:

The 3 workstreams will continue in parallel throughout the duration of the study, to shape the ongoing PES. Information gathered from participants and researchers will be used to support sites and enhance recruitment through knowledge exchange. 'Hints and tips' for screening, consenting and retention will also benefit from PPI involvement.

Patient and Public Involvement (PPI)

The ATNEC PPI team have been involved at every stage of the trial's development, involvement includes:

- Input into all patient-facing documents
- Production of a patient information video – Patient/Research Nurse consultation: link here
- Attendance at TMGs with set PPI agenda item
- Contribution to ATNEC reports
- Evaluation of the PES results

Conclusion

Strong PPI and site engagement is essential throughout the whole trial. Embedded PES enables knowledge exchange at all stages of the trial, not just at dissemination.

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A review of the impact of Public and Patient Involvement (PPI) in Cancer Clinical Trials

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Introduction
Warwick CTU cancer team performed a review of patient and public involvement (PPI) activities across the trial portfolio (2006-2022), together with an impact review. Trials included were a mixture of those which had completed recruitment, those with ongoing recruitment and those in set-up. The aim was to measure the level of PPI involvement and to gauge impact.

Methods
A review of the cancer team portfolio was carried out by listing the PPI activities and patient engagement. Each trial was assessed with the PPI activities measured against set-up times, recruitment and dissemination depending on the stage of the trial.

Results
PPI is essential at all stages of a clinical trial. Each trial had different experiences of PPI engagement. Older breast cancer trials (Mammo-50, OPTIMA, ARTemis and PERSEPHONE) all benefitted from early PPI engagement and PPI intervention at the grant application and Research Ethics Committee (REC) approval stage. In each trial patients assessed the trial design and proposed sub-studies with strong suggestions for improving the screening, consent and patient information. In the PERSEPHONE trial the REC mandated 5 consent forms for each part of the trial (Main trial, Quality-of-life, Tissue block collection, Fresh tissue collection and blood collection) which the patient advocate deemed 'a ridiculous waste of both research nurse and patient time' and influenced the REC to agree to reduce the number of consent forms to 2 (main-study and sub-studies). Other trials made use of the PPI advocate to produce clear and concise patient friendly materials as well as 'hints and tips' for the research nurses.
More recent trials (DP, ATNEC, REPAIR-MDS and PROPEL) have benefitted from innovative use of technology with UTUBE postings of patient consent videos and trial information. The use of Twitter, online surveys and websites has ensured that the trial information at set-up captures a range of PPI experience and reaches a wider audience. Haematology trials have expanded their PPI members to capture a range of people who can bring their patient experience to inform the trial.

Discussion
PPI engagement has expanded in recent years and has included innovative ways to capture patient experience and market the ongoing trials. Pre-set-up patient surveys provide a wealth of knowledge about the patient lived experience which has informed the trial processes in terms of timelines and assessments. PPI is encouraged and the level of engagement has increased over time to benefit the trial at every stage with demonstrated impact.

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Reporting of PPI and MCID in Phase III/IV Randomised Controlled Trials – a systematic review

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Introduction

Patient and public involvement (PPI) in clinical trial design contributes to ensuring the research objectives and outcome measures are relevant to patients. The minimal clinically important difference (MCID) in the primary outcome influences trial design and feasibility, and should be predicated on PPI. We aimed to determine current practice of MCID and PPI reporting in phase III/IV randomised controlled trial (RCT).

Methods/Approach

Following a search of Medline, Embase, and the Cochrane Central Register of Controlled Trials we included primary publications of phase III/IV RCTs, in English, inclusive of any medical specialty or type of intervention, that reported a health-related outcome. We excluded protocols and secondary publications of RCTs. We extracted RCT characteristics, the use of PPI, and use of the MCID.

Results

Between 1st July 2019 and 13th January 2020, 123 phase III/IV RCTs matched our eligibility criteria. 90% evaluated a medical rather than surgical intervention. Oncology accounted for 21% of all included RCTs. Only 2.4% (n=3) and 1.6% (n=2) RCTs described MCID and PPI respectively.

Discussion

PPI and the MCID are poorly reported, so it is uncertain how this contributed to trial design. Improvement in the reporting of these items would increase confidence that results are relevant and clinically significant to patients, and contribute to improving the overall trial design.

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Synthesising patient and public involvement and qualitative research to co-produce a neonatal surgical trial

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Background
Babies born with Oesophageal atresia (OA) are unable to swallow due to a gap in their oesophagus. After lifesaving surgical repair, a stricture (narrowing) can occur. Infants with OA routinely receive antacid medication to reduce the incidence of stricture, yet there is a lack of evidence to support this. The Treating Oesophageal Atresia to prevent STricture (TOAST) is a 7 -year randomised controlled trial to determine whether or not the routine use of antacid medication reduces the incidence of strictures. OA is a rare condition. New parents recruited to the trial would be managing their child's condition and administering the trial intervention in the context of online information and guidelines and that recommend use of antacid medication to manage reflux. At an early stage it was recognised that both patient and public involvement (PPI) and wider insight into the perspectives of parents of OA babies were crucial to establish trial feasibility.

Design
TOFS are the largest OA support charity in the UK. Their Trustee (JT) was part of the trial team and represented a Parent Advisory Group who regularly contributed to all aspects of the study. We conducted 18 semi structured interviews with parents of infants with OA. We reflect on how these contributions informed and facilitated the feasibility study to co-produce a clinical trial.

Results
PPI members' involvement in the development of the feasibility study protocol and research materials, including the interview topic guide, helped identify key issues and information to prioritise. Parents interviewed and PAG members both stated the proposed RCT would help answer an important question, yet highlighted potential barriers to trial success. They recommended that parents should be provided with treatment pathway for babies who have signs of reflux, which may also help to mitigate potential concerns of the TOFS Facebook group members. Importantly, both groups of parents provided insight to optimise trial design, including potential solutions to trial recruitment and retention concerns. These included suggested content for a mobile phone app and study information, recommendations about the best time to approach parents to discuss the trial, and important outcomes to measure.

Conclusion
Synthesising insight from both PPI and qualitative interview data ensured the successful conduct of a feasibility study and design of challenging trial in a way that is acceptable to families. Co-production with PPI members and parents will inform staff training to assist parent and clinician engagement and ultimately trial recruitment and retention.

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C3, the International CHORD-COUSIN Collaboration for Dermatology-Related Core Outcome Sets

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Introduction

Efforts to develop core outcome sets (COS) relevant to dermatology and skin care are increasing in number and scope. Core outcome sets in specific content areas such as dermatology can benefit from additional adaptations and support particular to the specialty.

Methods/Approach

A group of experienced COS developers in dermatology were convened to better understand challenges. Support of COS initiatives in dermatology was determined to require several elements: (1) a methods group to adapt COS methodology for dermatologic diseases and conditions; (2) facilitation of nascent COS initiatives with resources such as frequent meetings to monitor progress and methods consultants to provide advice; (3) encouragement of ethical participation by industry and regulatory stakeholders in COS development and dissemination; and (4) a dedicated international umbrella organization to support COS development in dermatology.

Timing of Potential Results

In 2021, C3, The CHORD-COUSIN Collaboration, an international umbrella organization for core outcome set development in dermatology, was created by combining the largely Europe-based CS-COUSIN (Cochrane Skin - Core Outcome Set Initiative) with the US-based CHORD (Consortium for Harmonizing Outcomes Research in Dermatology). C3 held its first scientific conference in January 2022, and at least 2 such conferences will be held each year. In addition to plenary talks and methods tutorials, C3 conferences included dedicated time and resources for individual dermatology COS groups to complete work and discuss specific methodology issues with other groups. The following core outcome set groups within dermatology have signed memoranda of understanding to be part of C3: LEAD (laser treatment in dermatology); CORALS (lichen sclerosus); HECOS (hand eczema); OUTPUTs (pressure ulcer); IMPROVED (cosmetic dermatology and surgery); COSCAM (capillary malformations); CONSIDER (incontinence-associated dermatitis); OVAMA (vascular malformations); OCOMEN (congenital melanocytic naevus); HOME (eczema); UPGRADE (pyoderma gangrenosum); HISTORIC (hidradenitis suppurativa); COMPPASS (pustular psoriasis); COAST (chemotherapy associated skin toxicities); ACORN (acne vulgaris); VOICE (vitiligo); REiNS (neurofibromatosis and schwannomatosis). C3 has a methods group which includes experts from its two constituent organizations

and representatives from individual COS groups. C3 has also developed rules for the ethical participation of industry in COS development and dissemination.

Potential Relevance and Impact

C3 has the potential to facilitate the development, dissemination and uptake of dermatology associated COS. C3 aspires to be a methodologically rigorous, ethically sound incubator for COS within dermatology and related clinical areas. C3 is a collegial environment that includes all stakeholders while providing particular, granular assistance to guidelines developers.

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Remote working in a pandemic on an urgent public health trial – challenge or benefit for patient and public involvement (PPI)?

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Introduction
Prophylactic Therapies in Care Homes (PROTECT-CH) was an urgent public health trial responding to the need to reduce the spread and severity of COVID-19 incorporating embedded PPI. In line with government pandemic guidelines, research activity was moved online. Remote working became the norm for many trial teams including collaborating with PPI partners. However, the fundamental processes, equipment and interactions needed to support this new, and in many instances, enforced way of working needs to be better understood to inform decisions on how to best work with PPI going forward. We reflect on our experience organising, planning and conducting a PPI group during the set-up of the PROTECT-CH trial.

Methods
The PPI group, consisting of 2 lay members and 5 trial team members, was formed at the start of the set-up phase and was in operation for 8 months until the decision was made that the trial was no longer feasible due to the changing epidemiology of COVID-19 in the UK (success of the vaccination programme).

Findings/Discussion
The PROTECT-CH PPI group was successfully convened online and contributed to the set-up of the trial. The intense engagement required to establish an urgent public health trial during the pandemic was enabled by online working. Due to the government enforced lockdowns, PPI members had more time to dedicate to the role and more impetus to engage in the project. At times the group were required to meet up to three times a week to cover ad hoc and urgent requests for engagement which would not have been possible with in-person meetings. In addition, online working required no travel time which was more convenient for those with caring responsibilities.
The size and composition of the group was also considered important for working online to be successful. A larger group would have been more challenging in terms of group dynamics and confidence to contribute. In addition, members were IT literate and had access to appropriate equipment and Wi-Fi but these varied ie laptop, iPad, which needed to be factored into how the group approached activities together to enable efficient working and rapid turnaround of tasks requested of the group. This would not have been possible if meeting face-to-face.
Researchers should consider the needs of their PPI members as well as those of the trial when planning and organising PPI groups. Alternative models of working should be explored and agreed with PPI to maximise engagement.

P-294

Understanding participation benefits to Patient and Public Involvement as an enabler to engagement in Clinical trials: Reflections from the STADIA Trial

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Introduction

To deliver and implement clinical and cost effective health care it is essential to engage patient and public collaborators. Understanding the influence of key impact factors such as age, gender, environment, socio-economic status and cultural or religious beliefs about a given intervention is crucial to enable its acceptability. However, the researcher-Patient and Public Involvement (PPI) relationship offers many further mutual benefits that are not always recognised by research teams. Better identifying and understanding these mutual benefits could assist not only with recruiting and retaining PPI partners to influence the research but may improve inclusion and diversity represented in PPI and trials. We reflect on our experience of PPI involvement in the STADIA Trial; a randomised controlled trial investigating a standardised diagnostic assessment for children and adolescents with emotional difficulties.

Methods

We carried out workshops with our PPI groups and consulted other PPI members (e.g. Trial Steering Committee PPI members, PPI Co-applicant) for their views and opinions about potential benefits of supporting a Clinical Trial.

Findings

Our PPI partners identified many benefits from participating in the STADIA Trial. Firstly, a sense of ownership and creative licence was developed through activities such as co-designing the trial brand, creating a group identity, and recruiting research staff. Secondly, in addition to providing significant and essential input to the design and content of trial materials this type of activity also enabled our PPI partners to develop leadership and project management skills, including skills transferable to other areas of life e.g. work, school, home. Thirdly, a level of personal development in terms of their own confidence in taking part in something new, which may have helped increase resilience. Listening to others' experiences of living with emotional disorders may also have created an opportunity for mutual support and to learn about and share coping mechanisms. Lastly, the training opportunities afforded by participating, such as experiencing novel IT systems and project processes, along with certificates of participation or achievement were generalisable for use in other settings e.g. for job CVs or school/college interviews.

Discussion

If we are to improve meaningful and diverse engagement in clinical trials, it is essential to understand the wider benefits of participation. A more indepth understanding of these benefits could facilitate a positive cycle of co-creation and development of true research partnership. Whether benefits of participation could be valuable in PPI recruitment and retention to improve inclusivity and diversity should be further explored.

P-295

Involving people living with dementia in the validation of analysis of qualitative interviews – the Journeying through Dementia Trial

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Introduction
The value of patient and public involvement in research is well documented. However, the involvement of people living with dementia in research is relatively new. Whilst PPI engagement empowers and values the voice of lived experience, there is also a need to understand how best to create meaningful opportunities in situations where engagement can be challenging. We reflect on our experience of organising and conducting co-researcher data validation workshops with people living with mild dementia and their carers as part of the Journeying through Dementia (JtD) trial.

Methods
Two half day validation co-researcher workshops were conducted with people living with dementia and their carers. Recruitment to the workshops was through the JtD trial Advisory Group of people living with dementia and volunteers from the Bradford Experts by Experience cohort. Impact of venue choice, travel, signage were all considered during workshop planning and preparation. Workshops involved discussions of their interpretations of anonymised qualitative interview data (quotations) extracted from interviews conducted with a sample of trial participants who had received the JtD intervention. Guidance was provided on the activity, for example to focus on language, tone and overall meaning of the quotation.
A total of 16 people living with dementia and their carers attended either one or both workshops. Twenty quotations (nine in workshop one, and 11 in workshop two) were reviewed and interpreted.

Results/Discussion
The workshops were delivered with a degree success. Overall carers were better able to engage than people living with dementia due to cognitive challenges. Along with practical issues such as venue choice, format of session and style and content of communication; more fundamental considerations included the type of activity chosen, how guidance was provided and expectation of engagement. All of these aspects were complicated by individuals' symptoms of dementia and ultimately their ability to maintain engagement in the workshop. Researcher concerns about overwhelming workshop participants with too much information meant that a range of approaches were needed to support and maintain that engagement. These included verbal and visual aids as well as planning of sessions to build up gradually to an activity to assess ongoing understanding. Although our co-researchers were able to engage with the activity offering valuable insight and observations to our analysis, those contemplating co-research with people living with dementia need to consider the planning and preparation of any activity, as well as the need to be adaptable to individual needs.

P-296

Patient and public involvement (PPI) in a study within a trial (SWAT) investigating electronic patient reported outcomes (ePRO) within clinical trials – the SPRUCE study.

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Introduction
Patient reported outcomes (PRO) provide a crucial insight into trial participants' experience of oncology treatments. In ICR-CTSU trials, these are currently completed by participants on paper. The SPRUCE SWAT investigates the impact of PRO questionnaire modality on the data received. To ensure the study is acceptable and appropriately patient-focused, we involved PPI partners in the development and oversight of SPRUCE.

Methods
A public survey was developed with PPI input, to assess public attitudes to electronic completion of healthcare questionnaires. We used advertisements in local papers to try and reach those without internet access as other avenues were limited due to the COVID-19 pandemic.

Virtual PPI focus groups were held to review the proposed SWAT design and obtain patient and public feedback on its relevance and acceptability to potential study participants.

Focus group members were invited to join the SPRUCE Patient and Public Oversight Committee, to provide PPI input throughout the study. Members were given a document providing more information regarding clinical trials, the SPRUCE study, and the committee itself. The first committee meeting gave PPI members the chance to test the ePRO database and give feedback on this and the patient-facing documents, for which we provided structured feedback forms. Members also provided feedback on the meeting itself.

Results
Out of 50 survey respondents, 13 completed the survey on paper, three of whom had no internet access. 76% of survey respondents indicated they would prefer to complete a PRO questionnaire electronically and 2% had no preference.
Eight survey respondents joined a focus group. All eight subsequently joined the Patient and Public Oversight Committee; each had access to the internet and would prefer to complete PRO questionnaires electronically.
Patient and public input resulted in changes to patient-facing study documentation, including wording of the patient information sheet and postal and email correspondence to participants.
Six committee members tested the online ePRO completion system using various personal devices, resulting in changes including the addition of a free text box for participants to leave comments.

Discussion
Despite challenges faced in accessing a diverse demographic of PPI input, including those with lower literacy levels, PPI input has improved the design and oversight of the SPRUCE study.

With the SPRUCE study open to recruitment, the Patient and Public Oversight Committee will continue to meet regularly to monitor the study's progress, with additional study updates between meetings to maintain good communication.

P-297

Co-design of a study to explore factors influencing patient participation in trials requiring travel to receive the experimental treatment (proton beam therapy).

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Introduction
It is unknown whether results of clinical trials evaluating state-of-the-art advanced radiotherapy technologies are generalisable to the target patient population as there may be additional barriers to recruitment. In addition to the usual considerations around cancer clinical trial participation, advanced technologies such as proton beam therapy (PBT) are only available at a small number of specialist sites meaning that travel and a stay away from home may be necessary for treatment. Such factors could influence a patient's decision to participate in a PBT trial and could mean that certain demographics are inadvertently excluded from the research. To inform future studies using advanced radiotherapy techniques such as PBT, we need to understand more about the patients who decline participation in PBT clinical trials and how they differ from those who accept.

Methods
We wanted to gain patient and public views on what factors might influence a patient's decision to take part in a clinical trial for new radiotherapy technologies such as PBT. We were also interested in patient and public views on the collection of personal data and preferences of data collection formats. A survey was co-designed with input from patient and public representatives including input into the introductory information for participants. 1:1 zoom calls were held between the researcher and three patient representatives. The survey was released as one of the first surveys on a new digital platform (Cancer Patients' Voice) designed to allow more people to contribute to research projects, and researchers to engage and involve underrepresented groups.

Result
Seven responses were collected; four respondents had taken part in a clinical trial. Additional factors not included in the initial survey, such as finance, were highlighted as being potentially influential on recruitment. Responses to the survey informed the design of a subsequent study within a trial (SWAT) to be run in partnership with the first PBT trial in the UK (TORPEdO) which compares PBT with standard radiotherapy in head and neck cancer. The SWAT includes a questionnaire that is available electronically and on paper due to survey respondents' preferences.

Discussion
If feasibility of recruitment to the SWAT is demonstrated within TORPEdO, we aim to roll it out to other UK PBT trials as they're opened to improve future trial design and recruitment, and retention of PBT trial participants. Results will give context to the generalisability of trial results and support ongoing efforts for inclusivity and equal opportunities in research.

P-298

Patient and Charity involvement in Trial Design, experiences from the PICCOS Umbrella Trial in Colorectal, Stomach and Ovarian cancers.

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Introduction
When setting up a new clinical trial, involvement of patients, their families and carers is good practice and often expected within funder guidelines. However, some trial designs are more complex, demand more from patients, and as such require additional input.

Methods/Approach
The PICCOS trial aims to treat peritoneal metastasis in colorectal, stomach and ovarian cancers using a new technique called PIPAC, where chemotherapy is aerosolized and administered via keyhole abdominal surgery. Challenges in development included; new surgical technique, limited UK availability, three tumour types, need to maintain systemic standard of care (SOC) chemotherapy, cross trust treatment and illness of patients. Wider patient involvement was therefore needed to ensure an acceptable and deliverable trial. Patient representatives (PR) from each tumour type were on the Trial Development Group (TDG). The PICCOS team also met relevant charities, with a specialist focus in the three cancer types, and set up a Patient Advisory Group (PAG), which first met during study development (pre-funding). Meetings were held online, included a presentation of the trial, structured question section, and open discussion.

Results
TDG PR fed into design, but encouraged wider consultation. They were key in developing a list of questions which formed the basis of discussions at the charity and PAG meetings.
The trial team were very encouraged by the enthusiasm and desire to help progress research expressed in the charity meeting.
The PAG discussed issues around patient travel to and from PIPAC sites, number of visits required, data sharing and access, potential toxicities, and differences between patients with different tumour types. Additionally highlighted was how to ensure patients felt comfortable in the change in care team when transferring from having chemotherapy at their local hospital, to PIPAC at a different center. It was felt treatment allocation disappointment and drop-out may be higher in the SOC arm vs PIPAC and as such it was recommended this be considered carefully when writing Patient Information. Patient reimbursement for travel was costed to the maximum allowed within the grant, but it was noted that this may fall short and could lead to inequality of access, so other options of support will be explored.

Conclusion
Early patient and carer involvement is important and useful, especially within complex intensive trials. Having PR on the TDG, charity input and a PAG prior to funding provided valuable insights and allowed some adjustment of processes and costs, which were well received by the funder.

P-299

Talking Trials: exploration of clinical trial perceptions amongst minority ethnic communities

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Introduction
Populations recruited into clinical trials need to include diverse participants of different ages, sexes, races, and ethnicities to ensure wide applicability. Existing data shows people from ethnic minorities are included in clinical trials at rates lower than we would expect given their share of the population. Working in partnership with the South Riverside Community Development Centre (SRCDC), a community organisation with expertise in engaging with ethnic minority groups, the aim of Talking Trials was to foster discussions around the under-representation of those from minority ethnic communities in clinical trials, and to identify and address concerns surrounding trial participation.

Methods
We conducted 3 co-production workshops with 13 co-researchers from minority ethnic backgrounds, to develop new insights into the issues of under-representation in trials. We discussed clinical trials, what they are and why they are important. We explored perceptions and understandings of clinical trials alongside engaging in participatory art activities to help overcome language barriers. The focus on co-production was a deliberate attempt to foster a network of individuals new to research to become involved as co-researchers and democratise research.

Results
Trusting partnership with SRCDC proved to be instrumental in forming a diverse co-researcher group. Co-production workshops were an effective tool to introduce our co-researchers to trials and health research. With little or no knowledge of clinical trials at the beginning of the process, our co-researchers settled into an intimate and cohesive group, freely sharing their initial fears and mistrust towards clinical trials. As conversations progressed, these attitudes clearly shifted as our co-researchers became open to participating in both clinical research and the research process itself. Artwork produced during the workshops was incorporated into an art exhibition. Quotes and creative pieces from the group were included to reflect the themes identified. Presenting the exhibition at the Riverside Festival enabled further engagement with a wider diverse community.

Discussion
Research benefits from including people from outside the research community in a process of shared learning. This inclusive and democratic co-production, enriched by the participatory art practices, provided a powerful means of enabling our co-researchers to create new insights and foster new relationships. Projects like Talking Trials can diversify the research process itself – for example, two of our co-researchers have commenced lay research partner roles on trial management groups. A lay advisory group is also being formed to enable ongoing, co-creation of health through active involvement in prioritising, shaping and communicating health research.

P-300

Proof of concept evaluation of an electronic payment card (Clincard) for reimbursement of Patient and Public Involvement (PPI) Contributors

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Introduction
Paying Patient and Public Involvement (PPI) Contributors through UK universities is recognised as inefficient, especially where cash payment is the preferred option. The payment timeline can be several weeks and can require substantial amounts of paperwork. Vouchers are common but restrict where PPI contributors can spend their payment.
The process of reimbursement should not itself be a barrier PPI. We set out to test an alternative to current PPI payment approaches.

Method
The University of Aberdeen partnered with Greenphire (a global clinical trial payment software company) to test whether digitisation of payments through Greenphire's reloadable ClinCard (MasterCard debit card) could:
1. expedite payment
2. improve satisfaction and "payment experience" among PPI Contributors
3. reduce payment process workload for finance, admin and research staff
In a 6-month pilot across five studies, participants will receive payments to their Clincard rather than receiving a shopping voucher. The following measures will be assessed:

PPI Contributor Measures:
Ease of card activation and use.
Satisfaction with the process of payment.
Customer Support (if used).

Finance Staff Measures:
Ease of Program Set-Up (staff access, payment configuration).
Workload efficiency of automated accounting reports.
Customer Support.
Ease of Disbursements and Management.

Admin and Research Staff Measures:
Ease of participant registration.
Ease of making payments.
Time saved via automated accounting reports.

Results
The evaluation began in March 2022. Participants (N=17) will receive an average of ~3 payments between March – August 2022, with each payment being around £25 depending on the study. Preliminary feedback indicates significant satisfaction among PPI Contributors and University of Aberdeen Finance staff, as well as

simple and rapid management of payments. Full data for the measures listed above will be available by ICTMC 2022.

Potential relevance and impact
Making payments to PPI contributors, especially cash payments, through UK universities can be difficult. If our pilot shows that Clincard works well for PPI contributors and University Finance staff, it offers University-based trialists an alternative way of efficiently reimbursing PPI contributors and may support the involvement of PPI contributors from more diverse backgrounds.

P-301

Creating an online PPIE group for perinatal research in a UKCRC-registered Clinical Trials Unit: experiences from Bump2Baby

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Introduction
Parents frequently juggle busy lives with childcare, family and work responsibilities, making it difficult to involve and engage them with maternal and newborn research. Bump2Baby Parents' Voices was set up in 2020 to enable meaningful patient and public involvement and engagement (PPIE) across a portfolio of studies being developed or running in by Nottingham Clinical Trials Unit (NCTU). Whilst PPIE was always included in NCTU's perinatal studies, it was not streamlined across the portfolio. The pandemic accelerated the set-up of a national, online group, using Facebook. Initial objectives were to grow the group and develop a community where parents could chat freely about topics, questions and concerns regarding maternity and newborn research.

Methods
A small multidisciplinary team met regularly whilst setting the group up. Branding and advertising materials were designed. A Facebook page and "closed" group were set-up. People wishing to join answered joining questions and agreed to group rules before being accepted. The group was advertised through national maternity and newborn groups and paid boosted posts on Facebook. Administrators drew up post schedules, including ongoing and upcoming projects and wider topics around research generally. Live sessions were run with clinicians, academics and lay co-investigators, via Zoom and "typed chat" posts. Data was collected on membership numbers, active membership and popular posts using the Facebook analytics.

Results
Membership has grown steadily to 215 members in May 2022. Most interaction with posts is 10-11am and 10pm. The most popular posts for comments are those which enable members to share personal stories, confirmed by a prize draw post asking members why they joined Bump2Baby with sharing and learning from lived experiences being a frequent response. Members stated they enjoyed learning about research relevant to their interests and that they wanted to help shape future research. Members have inputted into four funded studies and six NCTU studies in development. Input has been wide-ranging including acceptability of proposed study designs, when and how to seek consent, outcomes and data collection. It has also been used to facilitate wider discussions about research generally, share latest maternal and newborn health research and find parents for study-specific PPIE groups.

Discussion
Bump2Baby has streamlined PPIE in NCTU's perinatal research portfolio. Feedback from the group has been positive. Two-way interaction is important in the group, acknowledging we all learn from one another. Significant time, resource and planning is required to ensure posts appear regularly in members' Facebook feeds.

P-302

Patient organisations and the core outcome set revolution

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Introduction
This work links to the international Core Outcome Measures in Effectiveness Trials (COMET) Initiative. Core Outcome Sets (COS) can reduce research waste by promoting consistency in outcome reporting. They represent the minimum that should be measured and reported for a particular health condition. COS should be relevant to all research stakeholders, including patients and the public. Patient participation in COS development is considered crucial to ensure core outcomes are relevant to patients and other healthcare decision-makers. There has been a dramatic increase in patient participation over recent years.
Once developed, COS need to be used to reduce rather than increase research waste. Patient organisations are influential in policy decisions in healthcare, and many provide research funding for clinical studies and collaborate closely with the research community in their disease area. Our aim is to understand how COS developers can work best with patient organisations in developing COS and promoting their uptake. The project is being conducted with international COS developers and UK patient organisations. We seek to identify how patient organisations' influence could be better harnessed to enhance COS uptake, normalise their use and maximise collaborations between COS developers and patient organisations.

Method
We are seeking the opinions of COS developers to explore how they work with patient organisations in developing COS and promoting their use. Additionally, we are undertaking four interviews with key stakeholders from patient organisations. These interviews will help us to understand what they know about COS, what involvement their organisations have had to date in COS development and promoting their uptake, what other opportunities there are for promoting COS within patient organisations, and any challenges they perceive in these areas. During the interviews, we will also provide tailored information about COS. In subsequent follow-up interviews with stakeholders, we will explore what the patient organisations have done with their knowledge about COS from the initial interview.

Results structure and timeline
The results of this work will include an analysis of the COS developers' responses and summaries of key themes from our discussions with patient organisations.

Potential relevance and impact
Currently, there are challenges in ensuring COS uptake. There are opportunities for patient organisations to be involved in funding COS, supporting COS study design and delivery and promoting the uptake of COS once developed. Patient organisations have the potential to drive a COS revolution.

P-303

Using routine data for trials and parallel sample collection studies – the GBS3 – iGBS model

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Background

The GBS3 Trial (ISRCTN49639731) assesses whether universal testing of pregnant women for Group B Streptococcus colonisation reduces early-onset neonatal sepsis, compared to the current UK risk-factor based strategy. Approximately 320,000 pregnant women from 80 maternity units in England, Scotland and Wales are needed for this cluster randomised trial. GBS3 provides a platform for collection of umbilical cord blood samples for a parallel study, iGBS (NCT04735419), to determine a serocorrelate of protection for future GBS vaccine studies. GBS3 and iGBS have different sponsors but require similar descriptive data. We describe a model where data can be shared between studies to avoid parallel requests to routine data providers and unnecessary transfer of personal identifiable information.

Method

GBS3 has obtained the approval to use routinely collected health data without consent from the Confidentiality Advisory Group for England and Wales, and the Scottish equivalent. iGBS obtained a favourable ethics opinion for oral consent to collect cord blood. To define the GBS3 trial population and obtain descriptive data, e.g. ethnicity or gestational age at birth, GBS3 is requesting maternity datasets from NHS Digital for England and Scottish and Welsh equivalents. Mother and baby data can be linked via NHS number, date of birth and postcode. iGBS requires descriptive data of their population (a subset of the GBS3 population) which will also enable accrual data to be submitted for the Clinical Research Network portfolio. The GBS3 trial population is defined from maternity datasets through participating hospitals' codes where women gave birth within the trial time window. All data is directly sent by the data provider to a Trusted Research Environment (TRE) where is safely stored and remotely processed, linked and analysed by designated analysts. Maternity units will provide the GBS3 team with personal identifiers for women consenting for iGBS, who will be extracted from the maternity datasets within the TRE. Aggregate data will be tabulated for the iGBS sponsor. A data sharing agreement between the sponsors is in place.

Timing of potential results

The first data downloads will be undertaken in autumn 2022 and the success of the linkage will be assessed. Results from both studies are expected by August 2024.

Relevance and impact

Routine data is used in GBS3 to overcome some of the limitations of the traditional individual and manual approach, enabling a large study at lower cost. We have avoided duplication of the process for a parallel sample collection, reducing research waste.

P-305

Sharing individual participant data from clinical trials: experience over 4 years in Nottingham Clinical Trials Unit

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Background
The sharing of anonymised individual participant data with other researchers has been one of the focuses in the drive to reduce research waste. The onus of such data sharing falls largely to the host CTU and demands time and expert resource. The Nottingham Clinical Trials Unit (NCTU) developed a data sharing SOP in 2018, covering request and approval of data, anonymisation of data, quality checking, and data sharing agreements between the trial sponsor and requestor sponsor. We are currently conducting an evaluation of our processes using information collected over a four year period.

Methods
We will review metrics associated with data sharing requests. We will present summaries of the reasons data was requested, the source of each request, the decisions taken by the data sharing committee, summaries of the time each step of the data sharing process took, and whether there have been subsequent publications using these data. We will also present our current process alongside resource use at each step.

Results
Results will be presented at the conference highlighting the areas of strength and concern in our process. We will use these results to assess the risk of different strategies to make the data sharing process more efficient and also present our implementation plans.

Conclusion
This exercise will identify the strengths and weaknesses in our currently data sharing process and allow us to update our SOP to ensure data can be shared more efficiently.

P-306

Clinical Trial Staff Business Travel: an evaluation of pre-COVID carbon emissions from travel and projected impact of sustainability policies

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Introduction
The UKCRC-registered Edinburgh Clinical Trials Unit (ECTU) has a Clinical Trials Strategy that prioritises the design of clinical trials that are efficient, and economically, environmentally, and socially sustainable. We started a benchmarking exercise in 2022 to identify sources of carbon emissions across ECTU operations in line with the NIHR Carbon Reduction Guidelines. Because staff business travel is a significant driver of emissions, Edinburgh University's Sustainable Travel Policy was published in 2021 and advocates Climate Conscious Travel.

We aimed to:
- quantify carbon emissions generated by staff business travel in the 2 years preceding the first UK COVID-19 lockdown in March 2020
- calculate impact of the Sustainable Travel Policy restricting domestic UK flights

Methods
We extracted all business travel data generated by ECTU staff and affiliates for any purpose from a travel booking system operated by Key Travel and an internal electronic expenses system for the period January 2018 - March 2020. We calculated both direct and well-to-tank (WTT) carbon emissions as carbon dioxide equivalent in kg (kg CO2e), using UK Defra emission factors with radiative forcing (RF) values for air travel and 'unknown' fuel types for all overland travel.

Results
Over 27 months staff business travel charged to ECTU generated 34,346.44 kg CO2e:: meetings/consultancy (27,875.10 [81%]), site set-up (4,499.35 [13%]), conferences/training (1,769.68 [5%]) and other (202.29 [1%]). Emissions were generated by 33 staff members (total staff body of 65) and 15 affiliates. Affiliate travel, particularly by Chief Investigators, is often charged elsewhere so this is likely an underestimate. If ECTU staff had followed the Sustainable Travel Policy, emissions would have reduced to 16,057.14 kg CO2e (53% of total). If meetings and site set-up visits had been conducted remotely overall emissions would have been further reduced to 1,595.14 kg CO2e (5% of total).

Discussion
Avoiding domestic air travel would have more than halved ECTU's carbon emissions due to staff business travel before the COVID-19 pandemic. Further reductions could be made from sources that we did not quantify, such as staff commuting, trial participant travel and the transportation of trial supplies. The COVID-19 pandemic prevented almost all staff business travel, when activities successfully pivoted to a virtual format. We will monitor the extent to which staff business travel returns to pre-pandemic levels, and use these data to encourage behaviour change. Further work is needed to quantify carbon emissions from all aspects of clinical trials and develop interventions to reduce them

P-308

A systematic review of methodological approaches used by Cochrane reviews in gynaecology, and their component trials, to incorporate diversity in bothersome symptoms

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Introduction
When designing randomised controlled trials (RCTs), it is imperative that researchers choose outcomes which are appropriate and relevant to the population of interest. However, in gynaecology it is not one-size-fits-all, with patients with the same diagnoses experiencing differing symptoms. Where an intervention may have potential benefit for the underlying condition, how do researchers define eligibility and select outcomes in the likely scenario that potential participants may have no symptoms in common? It was anticipated that such strategies would include: restriction of eligibility to patients displaying a specific symptom; measurement of clinical outcomes of relevance only to a subgroup of participants. Both methods constitute examples of research inefficiency.
The aim of this systematic review was to identify inefficiencies in the design of recent RCTs, due to patients with the same gynaecological condition presenting with different symptoms.

Methods/Approach
We focused on Cochrane Reviews and their component trials in polycystic ovarian syndrome (PCOS) and endometriosis as exemplar conditions. We restricted to trials published since 2012 to consider 'current' approaches.
First, we defined categories of outcome for each condition, such as hirsutism, menstruation, anthropometry, and fertility. We noted trial characteristics including year of publication, sample size, nature of the intervention and the published risk of bias assessment. For each trial we then recorded the strategy applied and if reported, the number of potentially eligible participants excluded as a direct result of the chosen strategy, relative to the achieved sample size. Similarly, for each review we recorded the numbers of RCTs and participants excluded from consideration as a direct consequence of the applied strategy.

Results Structure and Timelines
There were 89 distinct PCOS trials, 70% (n=62) of which were included and 30% (n=27) excluded from 10 Cochrane reviews. Of the trials included, 60% (n=37) restricted their eligibility and measured clinical outcomes based on the symptoms and characteristics of the participants in the study. The second most common strategy was to measure and analyse one or more clinical outcomes that were not relevant to all participants (n=21, 34%). We will present results similarly for endometriosis and explore trial level characteristics associated with different approaches.

Potential Relevance and Impact
This project will present clearly the (in)consistency, range of practice and waste in current gynaecological research. The findings will lead on to inform investigation of novel trial designs such as basket design, in order to address the inefficiencies found using current practice and hence reduce research waste.

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A meta-research study of randomized controlled trials finds infrequent and delayed availability of protocols

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Introduction
Availability of randomized controlled trial (RCT) protocols is essential for the interpretation of trial results and research transparency.

Methods/Approach
In this study, we determined the availability of RCT protocols approved in Switzerland, Canada, Germany and the UK in 2012. For these RCTs, we searched PubMed, Google Scholar, Scopus, and trial registries for publicly available protocols and corresponding full-text results publications. We determined the proportion of RCTs with (1) with publicly available protocols, (2) publications citing the protocol, and (3) registries providing a link to the protocol. A multivariable logistic regression model explored factors associated with protocol availability.

Results
326 RCTs were included. 118 (36.2 %) made a protocol publicly available; 56 (47.6% 56/118) in form of peer-reviewed publications and 48 (40.7%, 48/118) provided as supplementary material. 90.9% (100/110) of the protocols were cited in the main publication and 55.9% (66/118) were linked in clinical trial registry. Large sample size (>500, OR, 5.90; 95% CI, 2.75-13.31) and investigator-sponsorship (OR, 1.99; 95% CI, 1.11-3.59) were associated with increased availability. Most protocols were made available shortly before the publication of the main results.

Discussion
RCT protocols should be made more readily available at an early stage of the trial.

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Interventions for improving the design and conduct of scientific research: A scoping review

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Introduction
Research waste is prevalent in many scientific fields despite a number of initiatives to improve research practices. These initiatives are often implemented without evaluating their effectiveness. It is therefore important to identify the interventions that have been evaluated, how they have been evaluated, and areas where further research is required.
A scoping review will be undertaken to assess what interventions, aimed at researchers, to improve research design and conduct have been evaluated. This review will consider when in the research pathway these interventions are implemented; what aspects of research design or conduct are being targeted; and who is implementing these interventions. One example of an intervention that has previously been tested is an incentive to encourage data sharing at publication.

Methods
A scoping review will be undertaken. Interventions aimed at researchers or research teams to improve the design or conduct of research will be eligible for inclusion. The review will not include interventions aimed at hypothetical research projects or any interventions implemented without evaluation.
The following sources will be searched: MEDLINE, EMBASE, ERIC, HMIC, EconLit, Social Policy and Practice, ProQuest theses, and MetaArXiv. Hand searching of references and citations of included studies will be undertaken. Searches will be limited to articles published in the last 10 years.
Data extraction will be completed using a data extraction template developed for this review. Each intervention will be assigned a type as per the behaviour change wheel framework.

Results Structure and Timelines
We will synthesise the results in tables, the following items will be tabulated and this will be done separately for aspects of influencing design and conduct.
- Type of Intervention as per behaviour change wheel framework
- Stage of research pathway
- Outcome

A narrative summary will be provided for each of the aims of the review. The protocol for this review has been published.

Timing of Potential results
The review will be completed by October 2022.

Potential Relevance and Impact
A large proportion of trials are identified as high risk of bias, which is costly to patients and funders. Many of the causes of the bias are easily rectified. Interventions that could be used to reduce bias in trial design before it occurs would allow us to reduce research waste. Thus a review of previously tested interventions will provide information on what interventions may be effective and what research gaps need further investigation.

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The most common clinical trial amendments, why they are submitted, and how they can be avoided (Amendments Assemble): mixed methods study on NHS Sponsored research

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Background
Amendments are changes made to a clinical trial after it has received regulatory approval. An amendment can take a significant amount of time and resource to develop, review and implement at participating sites. This can affect the efficient delivery of clinical trials and potentially contribute to research waste. This study aimed to establish what the most common amendments are, why they are submitted, and what, if anything, can be done to avoid them.

Methods
An explanatory sequential mixed methods design was employed. The first strand involved a content analysis on a sample of amendments, submitted in trials sponsored by a University Hospital NHS Trust between September 2009 and March 2020, to find the most common changes and reasons for amendments. The second strand involved thematically analysing semi-structured interviews with trial stakeholders to explore their views on the reasons underpinning the submission of amendments, and the potential for efficiencies that could prevent avoidable amendments.

Results
242 approved amendments were examined from 53 clinical research studies. The 'Addition of sites' was the most common amendment change, and the most common reason for amendments were 'To achieve the trial's recruitment target'. The root-causes for avoidable amendments identified by the 11 interviewees included: 'Rushing the initial application knowing an amendment will be needed later', 'Not involving all the right people to input' at the start of the trial, and 'Realising it's not feasible in practice when delivering the trial'. Missing regulatory checks following an onerous and error prone application process, were also identified as the cause of some amendments.

Conclusions
Trials need to be critically reviewed by various stakeholders, and have sufficient time allocated to planning and feasibility assessments to avoid some amendments. This may improve clinical trial efficiency, to benefit the trial participants, researchers, funders, sponsors, and regulatory bodies, and potentially bring new treatments to patients faster.

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Nudging clinical research transparency best practice on the ISRCTN registry

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Introduction
The ISRCTN registry now enables users to search for specific output types linked to trial records. Next, transparency best practice 'badges' will be applied to study records based on applicable recommendations for prospective registration, regular updating of the registry record and availability of protocols, statistical analysis plans (SAPs), results and raw data.

Methods/Approach
The hypothesis is that greater visibility of whether registry records are meeting requirements or recommendations for transparency will nudge trialists to update records according to best practice. The ISRCTN registry will also encourage trialists to update the record in a way that will improve the badges displayed.

Timing of Potential Results
The poster will include data on the baseline application of badges and the effect of the registry's actions to encourage best practice.

Potential Relevance & Impact
The eventual aim is that the presence/absence of badges can be visualised in a 'dashboard' view, which will provide sponsors, funders and other users with a tool to investigate and encourage adherence to transparency recommendations. If this approach encourages best practice, it could be applied to other trial registries.

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The Trials Methodological Research Agenda: A Priority Setting Exercise

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Introduction
Randomised clinical trials are studies that test the effects of interventions (treatments, medical devices or procedures) on human health. Trials methodology research seeks to improve how we design, conduct, analyse, report and interpret randomised trials. This helps ensure that practice and policy are informed by efficient, evidence informed trial processes. This project will identify and prioritise the Top 10 research questions on how we plan, do analyse and report randomised trials.

Methods
This study is an observational study including key stakeholders in trials. The process consists of three stages as follows:
(1) The first stage comprised an initial online survey consisting of open-ended questions to gain questions or comments from respondents about how we can improve how we plan, do, analyse and share the results of randomised clinical trials. Snowball sampling and social media were used to target a diverse range of stakeholders. Raw data was coded thematically by the research group, which will be used to develop a list of unambiguous questions that can be addressed by research and are understandable to all stakeholders.
(2) A second round survey will be distributed to stakeholders from the first round, and using snowballing sampling. In the second round, participants will be presented with the list of research questions and asked to select and rank their top ten priorities in order of importance, from 1 to ten.
(3) The final priority setting will take place in the form of a virtual workshop. This will allow participation from a wide group of stakeholders from different countries.

Results Structure and Timelines
The first survey yielded a total of 274 respondents providing 2409 questions and/or comments on trials methodology. The first round thematisation is complete and development of a list of research questions for the second round is underway. We expect to launch the second survey in July 2022, which will remain open until the end of August. The final priority workshop is expected to take place in October. Results from the first two stages and the top questions selected for the online workshop will be presented at the conference.

Potential Relevance and Impact
This research will develop overarching priorities for trials methods research. The broad scope includes all stages of clinical trials (design, conduct, analysis and reporting) and can inform the direction of future research on trial methods.

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Predictive models as counter-factual evidence in the estimation of treatments effects

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Introduction
There is an increasing demand to develop methodologies which may improve the efficiency of evaluating treatments. In oncology for example, there is a need to evaluate an increasing number of target therapies on decreasing patient populations. We investigate the possibility developing synthetic controls from parametric models as a means of measuring efficacy of experimental treatments.

Methods/Approach
Our method uses overall survival as the primary endpoint. We take validated parametric models which allow us to predict an individual's response to some 'control' treatment based on their clinical characteristics. We then develop a Likelihood which allows us to compare an observed outcome whilst on an alternative therapy against this 'control' prediction. This produces a hazard ratio which evaluates observed 'experimental' outcomes against counter-factual predicted 'control' outcomes. The approach can be extended to provide sub-population effects which may be useful in identifying potentially predictive patient characteristics. Estimation is performed using a Bayesian approach.

Results
We demonstrate the methodology firstly by comparing two treatments from separate randomised controlled trials in resectable pancreatic ductal adenocarcinoma. We show that a comparison of combined therapy (Gemcitabine plus Capecitabine- taken from the ESPAC-4 trial) against a monotherapy control (Gemcitabine – taken from ESPAC-3) gives a hazard ratio (HR) of 0.81 (0.58 - 1.09) compared against a HR of 0.79 (0.65 – 0.96) when the two treatments were compared directly in a randomised clinical trial. Efficacy estimates across patient sub-groups also show good levels of agreement. Further examples in HCC have compared observational data against validated parametric models and have been used to identify clear sub-group effects suggesting treatment efficacy may be dependent on patient characteristics. We have conducted simulation studies to show that these methods provide improved performance over propensity score analysis or multivariable regression when evaluating treatment effects across different settings.

Discussion
Parametric predictive models can be used to evaluate the efficacy of experimental treatments and can reduce/remove the need for contemporaneous controls in clinical research. They can be viewed as a type of synthetic control where counter-factual evidence is obtained at the patient level as opposed to the aggregate level. Their proper use in practice is dependent on the setting and they are susceptible to impact of bias due to unbalanced, unmeasured confounders as are other non-randomised methods of measuring efficacy. Their main benefit may be in increasing the efficiency of prospective clinical trials by reducing the number of control patients required.

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Getting Real about Synthetic Data

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Introduction
Why is it important to investigate and explore synthetic data and its potential uses? There is a real growing demand to be able to re-use data available in the health care / pharmaceutical sector whilst balancing the privacy and security of this data with the growing data protection legislation and regulations around the globe that have been established since the inception of the European GDPR (General Data Protection Regulation) in 2018. One way of assisting with this demand is to look at the emergence of Privacy Enhancing Technologies (PET). These technologies or techniques are designed to protect data through its lifecycle by adopting a variety of data minimisation techniques such as anonymisation / pseudonymisation / synthetic data production. The latter is becoming a rapidly evolving field with growing interest in its use by parties who wish to re-use and share data but face the challenges of jurisdiction and are faced with investigating new technical and organisational measures. Synthetic data production can potentially allow for much greater utility and sharing of data whilst also maintaining the protection and security of that data. Synthetic data is data that is artificially created / simulated rather than being generated by actual events and mirrors properties of an original dataset. It is a technique that is maturing rapidly so important to explore how it can be used to ease privacy constraints.

Methodology
With supporting viewpoints from across the pharmaceutical industry, seven use cases for synthetic data were explored for optimising data utility in order to improve data privacy and protection. In addition, discussion of various methodologies is highlighted which can be utilised to produce synthetic data together with the availability of utility measurements and parameters to ensure robust quality of generated synthetic data.

Results / Discussion
Outline of the seven use cases for using synthetic data together with outlining the merits, challenges and future direction of synthetic data within various industry and academic sectors and considerations of utilising and acceptance of this privacy enhancing technology (PET).

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The UK PRINCIPLE platform trial of early treatment for Covid-19; Operational challenges related to statistical complexity of adaptive platform trial design

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Introduction

The Covid-19 pandemic has highlighted the need for efficient trial designs that provide rapid evaluation of multiple interventions. Such novel trial designs include adaptive platform trials (APTs). Platform trials have been successful in several disease areas but thus far, are largely novel in primary care.

PRINCIPLE (Platform Randomised trial Interventions against Covid-19 in older people) is a UK-wide priority platform trial in primary care. Planning and implementing platform trials are complex, and apart from contributing to design and analysis, statisticians serve as critical mediators in implementation and in translating data into evidence. We will present key operational (non-methodological) challenges for statisticians and report actions/responses taken to navigate these challenges in the PRINCIPLE trial.

Methods/Approach

PRINCIPLE is a multi-centre, open-label, multi-arm prospective randomised controlled adaptive platform trial of interventions against Covid-19. The trial began recruitment on 2 April 2020. Since then the trial has recruited over 11,000 participants, evaluated seven treatments and reported five.

Using PRINCIPLE as an example, we present the following challenges faced by statisticians; i) complexity of the study design; ii) complex collaborations between different statistical expertise (Frequentists and Bayesians); iii) ensuring firewalls between unblinded and blinded statisticians (with respect to treatment comparisons) in the context of an open-label study, and; iv) the assembly of a DSMC with sufficient statistical and clinical expertise to oversee an APT.

Timing of Potential Results

Approaches to navigating these challenges included: i) large statistician resource involving a total of nine statisticians; ii) involving international APT statistician experts with clear distinct allocation of tasks based on expert knowledge; iii) blinded and unblinded statistical teams (with respect to treatment comparisons) implementing responsive adaptive randomisation and having clear communication plans between oversight groups; iii) DSMC membership covers expertise in APTs and planned analyses documented in statistical analysis plans and adaptive design report included and as appendix drafted by APT statisticians.

Potential Relevance and Impact

Awareness of potential challenges of these studies are important for teams planning or conducting APTs. Therefore we will share our experiences and the approach we took in dealing with these operational challenges in implementing and conducting a successful platform trial.

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Challenges of emulating a target trial for surgical management of full-skin thickness pressure ulcers using routine data

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Introduction
Emulating a "target trial" is the process of applying the design principles from randomised controlled trials (RCTs) to analyses of observational data. We emulated a target trial using routinely-collected health data to quantify the effectiveness of surgical reconstruction (SR) as treatment for a full-skin thickness pressure ulcer (SPU) (ISRCTN13292620).

Methods
We obtained an anonymised linked Hospital Episode Statistics and Office for National Statistics mortality dataset, including 291,326 patients with a diagnosis of SPU (ICD-10 codes L89.2, L89.3, L89.9 or L89.X) between 01/04/2011 and 30/09/2018. Using the PICO (Population=patients with SPU as primary diagnosis on admission; Intervention=SR; Comparison=non-surgical management; Outcomes=readmission with SPU) principle, we defined eligibility criteria, assignment to interventions and start and end of follow-up.

Results
A total of 1,634 patients were identified as eligible for inclusion in the target trial; 310 (19%) underwent surgical reconstruction. Dates of index admission with SPU were similar between those who underwent SR and those who did not; those who underwent SR were younger and had fewer comorbidities and were more likely to have had a cause of impaired mobility (injury or neurodegenerative disease) recorded. Analyses of the association between SR and time to readmission with SPU diagnosis within 12 months of the index SPU diagnosis are underway; we plan for analyses to be adjusted for the propensity for SR and for confounders identified from hospital admissions in the year before the index SPU admission. We encountered two specific challenges in this target trial emulation: (a) the comparator group may not be representative of the population eligible for the target trial since we had no information about patients who had a SPU but who did not have a hospital admission; (b) relevant outcomes such as wound healing time could not be defined from the dataset.

Discussion
We have encountered issues with capturing the eligible population and care pathway using these routine data sources, and identifying relevant outcomes. In all settings there remains a crucial need to understand the care pathway before trying to design the target trial emulation. Had we known this before proposing the emulation, the inadequacy of the dataset with respect to important outcomes would have been more apparent.

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Delays experienced in hyperacute stroke units post COVID in setting up new clinical trials: data from the TICH-3 Trial.

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Introduction
TICH-3 assesses whether tranexamic acid reduces death and dependency after hyperacute (within 4.5 hours of onset) spontaneous intracerebral haemorrhage (ICH). TICH-3 is a Phase III Pragmatic Randomised Controlled Trial embedded into the clinical pathway using initial verbal consent and simple randomisation. There are no additional clinical assessments and minimal data collection up to day-7 post randomisation. TICH-3 does not routinely collect all SAEs, only pre-specified safety events, reducing the burden on sites. Site set up post-COVID has demonstrated new challenges and we aim to explore the barriers to site set up in the post-pandemic era.

Method
In late 2019 an online form was circulated to UK hyperacute stroke units, including the 109 UK sites that were involved in TICH-2, to collate expressions of interest (EOI) for TICH-3. Contact with sites that expressed interest began July 2021 whilst ethical approval was ongoing. Full ethical approval was granted 18/11/2021. The sites that were responsive and completed eligibility screening were sent the local document package (LDP) and non-commercial agreement in December 2021 to begin local feasibility assessments. We reviewed the correspondence with sites and present the proportions of sites in various stages of site set up and the commonest causes of delays.

Results
EOIs were received from 83 UK sites, of which 71 (86%) were received pre-COVID-19 pandemic. Of the 83 sites: 4 (5%) have declined to participate in TICH-3 due to COVID-19 associated capacity issues and an overall lack of support for hyperacute activity; 4 (5%) have declined due to clinical workload and staff availability; 21 (25%) sites have not engaged since submitting the EOI. 54 sites (65%) were sent the local document package following eligibility screening and fulfilling site selection. Within 3 months of sites receiving the LDP: 0 (0%) sites were active for recruitment and 9 (11%) sites are active within 5 months. Of these 54: 3 (6%) lacked eligible Principal investigators and reported a lack of capacity leading to a 5-month delay; and 1 withdrew. 41 (77%) of the 54 sites are still in the site set up stage, 5 months since feasibility assessments began. Delays include no capacity to take on new studies, lack of capacity due to COVID-19, and pressure on NHS.

Potential Relevance and Impact
The data presented highlights the ongoing problems and delays experienced in trial initiation in hyperacute stroke units due to COVID-19, despite a streamlined trial methodology embedded in the clinical pathway.

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Delays experienced in hyperacute stroke units post COVID in setting up new clinical trials: data from the PhEAST Trial.

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Introduction
PhEAST aims to assess whether pharyngeal electrical stimulation (PES) is safe and effective at improving post-stroke dysphagia (PSD). PhEAST is an international prospective randomised open-label blinded-endpoint (PROBE) parallel group superiority phase IV effectiveness trial. Treatment is given over days 1-6 and assessments are made at baseline, days 14/90/180/365, and hospital death/discharge. Safety is assessed: SAEs over 0-9 days, procedure/device-related (S)AEs over days 0-14; and fatal SAEs over days 10-90 days. The engagement and set up of sites post-COVID has demonstrated new challenges and we explore barriers to this.

Method
In the summer of 2020 a form was circulated to UK stroke units, to collate expressions of interest (EOI) for PhEAST and these were listed in the NIHR grant application. Contact with these sites began November 2021 in parallel with ethics approval (granted 7/1/22, Scotland 9/2/22). Responsive sites were sent the local document package (LDP) and non-commercial agreement January-May 2022. We report the commonest causes of delays.

Results
Initially, EOIs were received from 56 UK sites in August 2020. Of these, reasons for declining were: 3 (5%) due to COVID-19 associated capacity issues; 11 (20%) clinical workload/staff availability; 3 sites (5%) other feasible reasons. 10 (18%) sites submitting EoI did not engage further. 15 (27%) sites were sent the LLP after fulfilling site selection criteria. Within 3 months: 0 (0%) sites were active for recruitment and 1 (2%) site is active within 5 months. Of these 15: 3 (5%) are unable to start set-up at present due to delays in R&D set-up post COVID-19. 11 (20%) of the 15 sites are still in the site set-up stage, 5 months since feasibility assessments began. Delays include no capacity to take on new studies, lack of capacity due to COVID-19, and pressure on NHS. Updated data will be presented at the time of the conference.

Potential Relevance and Impact
The data presented highlights the ongoing problems and delays experienced in trial initiation in hyperacute stroke units post-COVID

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Delivering an adaptive trial in orthopaedic surgery: lessons learnt from START:REACTS

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Introduction
The Sub-acromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery (START:REACTS) trial had two main objectives: I) to evaluate the efficacy of a novel surgical device used in the treatment of irreparable rotator cuff tears and II) to implement and assess the use of a novel efficient adaptive design. Adaptive designs are relatively rare in the orthopaedic surgery specialty and there is a pressing need for methods to rapidly evaluate surgical techniques and devices.

Methods
START:REACTS (ISRCTN17825590) recruited participants from June 2018 to July 2020, when it was stopped at the first planned interim analysis. Final primary outcome data were obtained in July 2021 and results were made public in April 2022.
A package of statistical simulations was used to define a set of candidate stopping boundaries. Clinical feedback on a range of scenarios was obtained from a group of surgeons at an orthopaedic conference before selecting the final boundaries. Key design features (such as binding stopping rules) were discussed and agreed by both the study data monitoring committee (DMC) and trial steering committee (TSC). Patient representatives were part of the TSC and trial management group, allowing both for insight into study design and to facilitate rapid feedback for any issues arising.
Once the design was agreed, the exact stopping parameters for the study were fixed and held independently by the study statisticians and reviewed by the DMC. The DMC were briefed on the interim analysis process and were given draft “adaptive charters” to illustrate the supporting data for the decision-making procedure at the two planned interim analyses.

Results
The trial stopped for futility at the first interim analysis, with results now in the public domain. Stopping the study at the first interim analysis reduced time to dissemination of results by at least 11 months, this may have been much longer due to the pandemic. Clinical and PPI support allowed an unplanned change in the primary outcome collection from in person to via post to be rapidly implemented to mitigate the effects of the covid-19 pandemic.

Discussion
We have demonstrated that it is feasible to conduct an adaptive group-sequential RCT in an orthopaedic surgery setting. Such trials can provide important answers to the clinical community in less time and at reduced cost. They may reduce the exposure of patients to potential harms both in the trial itself and across wider clinical practice.

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Incorporating clinicians elicited informative prior distributions into a planned Bayesian analysis

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Introduction
Bayesian analyses with informative prior distributions are very valuable for trials that have restricted population (e.g., rare disease, highly specialised subgroup etc.). Broadly there are two approaches to developing informative prior distributions for model parameters in a Bayesian analysis, either a mathematical data-driven approach or a behavioural approach. Based on the recommendation by Dallow et al. (1) we used a behavioural approach for a non-inferiority trial and the challenge was to incorporate the elicited priors in the planned analysis model.

Methods/Approach
The aim of the TREAT trial is to determine whether mepolizumab is as efficacious as omalizumab at reducing asthma attacks in children and adolescents with severe therapy-resistant asthma. A Poisson regression model is planned to compare the 52-week exacerbation rate between the arms adjusting for minimisation variables. We conducted a prior elicitation workshop using the Sheffield Elicitation Framework (SHELF)(2) with the roulette method. We aimed to specify informative priors for two model parameters (log mean of exacerbation rate in control arm and between-arm change in log exacerbation rate). To facilitate clinical interpretation, we chose to elicit clinicians' opinion for transformation of these (the mean exacerbation rate in control arm and the relative treatment change in percentage). We sought solutions to fitting the elicited distributions to the planned analysis model. was achieved using the flexible rjags package. (3)

Results
Eight experts participated in the 2-day workshop. A Training Document and Evidence Dossier were shared with the delegates prior to the meeting. A Gamma (6.36,4.5) and Normal (-5.05, 12) distributions were selected as priors for the mean exacerbation rate in control arm and the relative treatment change respectively. Solution to incorporating the elicited transformed distributions into our final model to obtain posterior distributions for parameters of interests was found using rjags (3)

Discussion
Elicitation is a recommended way to develop informative prior distributions, but it can sometimes be challenging to elicit opinions for the model parameters directly. Another approach is to use clinically relevant transformation of parameters and use of rjags enables a flexible tool to incorporate the resulting prior distributions into the model.

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Use of Electronic Data Capture in acute clinical settings: experiences from two recent studies.

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Introduction

Electronic data capture (EDC) presents a possible mechanism to make clinical trials more efficient. By entering the data directly into the database, EDC can be more time effective than standard, paper-based data capturing process requiring subsequent electronic entry and verification. Whilst this approach has been quite widely used for scheduled questionnaire and in-person appointments, there is less known about the feasibility of use in acute settings. In this case study we report the lessons learnt from two recent studies where EDC was completed within acute NHS settings during the COVID-19 pandemic.

Approach

EDC systems were developed in REDCap Cloud (RCC) and accessed using standard issue/brands specified by participating NHS Trust, and local infection control and privacy policies had to be followed. Study one was the BREATHE trial, a cluster randomised controlled feasibility trial in acute-on-chronic breathlessness patients, based within the Yorkshire Ambulance Service (ISRCTN80330546). Paramedics accessed RCC and completed consent and data entry on their Toughbooks® when attending eligible emergency call-outs. Study two was the multicentre observational FASTer study conducted across three NHS emergency departments (ED) in East Yorkshire and North Lincolnshire. Participants identified in the ED were approached by a research assistant and completed consent and several questionnaires directly onto an iPad®.

Results

The pandemic severely impacted BREATHE with only 13 participants recruited. There were no issues with completing e-consent and for recruited patients data completeness was 100% for the intended primary outcome. Focus groups with paramedics suggested that accessing the study database was problematic at times with reasons including inability to log in due to passwords expiring or being forgotten, poor internet access and time constraints. In contrast, FASTer recruited over 1021 participants in 8 weeks and 997 (98%) participants had sufficient data completed to enable inclusion in the primary analyses. The researchers were embedded within the ED and utilised the hospital WIFI and as a result access to the system was less sporadic.

Discussion

It is possible to use EDC in an acute setting with good data completeness. However, consideration should be given to the setting, likely frequency of recruitment and internet access when considering the use of paper CRFs or EDC. Contingency plans need to be in place in the event of access issues. Early engagement is needed with participating NHS Trusts about data governance, tablet specification and internet access, and with clinical and research staff about the practicalities of using EDC in acute settings.

P-324

Methodological challenges in a large cluster RCT using routine data sources and suggested solutions: lessons learned from the GBS-3 trial

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Introduction
Common methodological challenges in the design, conduct and analysis of cluster randomised controlled trials (cRCTs) are well documented and if not properly considered may introduce biases including identification and recruitment bias, baseline imbalance, loss of clusters, and incorrect design and analysis. Other challenges exist but are not well documented, some heightened by the effect of COVID-19. This presentation will highlight some of the unanticipated challenges which we have encountered in implementing the GBS3 trial and how we have dealt with them.
GBS3 is an ongoing cRCT assessing whether routine testing of women for Group B Streptococcus colonisation (using Enriched Culture Medium (ECM) or rapid test) either in late pregnancy or during labour reduces the occurrence of early-onset neonatal sepsis, compared to the current risk factor-based strategy. We plan to recruit up to 80 sites (obstetric unit with/without an alongside midwifery unit) with approximately 320,000 women. Outcomes will be obtained from routinely collected health data (RCHD).

Challenges and proposed solutions
We provide an overview of the challenges we have encountered, their implications and how we have dealt with them. First, there were longer waiting times for intervention implementation due to logistical challenges and the effect of COVID-19. The time between randomisation and opening sites to data collection was longer than anticipated especially for rapid test sites. Hence, data from the control sites would be collected at an earlier calendar time compared with those from the intervention sites, leading to distortion of between-groups comparison by secular trends. As we are using RCHD, we have proposed to extend the data collection period for risk-factor sites to ensure data used for the comparison of the two strategies is contemporaneous. Other challenges included potential post-randomisation changes to cluster composition due to merging of NHS trusts and potential dilution of the treatment effect in the ITT analysis (intended place of birth) occasioned by change of intended location of childbirth for women who had been offered the ECM.

Conclusion and relevance
Despite careful planning to minimise the common methodological issues, we still faced other unanticipated challenges. We share these to create awareness for other researchers designing and implementing large cRCTs. Our proposed solutions were possible due to the use of RCHD, but careful consideration need to be taken when directly collecting individual patient-level data.

P-325

Mission Impossible! Retaining old randomised clinical trial data: the ISIS-2 Legacy Database experience

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Introduction
ISIS-2 (Second International Study of Infarct Survival) was a clinical trial that investigated whether streptokinase (used to dissolve clots in blocked arteries) and aspirin (a blood thinner) helped prevent death in people having a heart attack. The trial found that patients taking streptokinase and/or aspirin were more likely to survive than those taking the placebo. These results transformed clinical practice worldwide and are still relevant today. Initial results were published in 1988, with follow-up results published in 1998, which showed that benefits lasted for at least 10 years.
Participants were recruited in hospitals from 1985-1987 (in the UK and 15 other countries). In the UK further information was collected via electronic health records (EHR) from Central Registries e.g. the Office for National Statistics (ONS). EHR data collection continued until 1997.
Researchers at Oxford want to preserve the original database which produced these important findings and to keep the data for future research potentially using EHR data linkage, but this presents several challenges:
-Original consent no longer valid
-Impractical to contact surviving participants to reconsent
-Database includes identifiable data
-NHS Digital now responsible for data originally provided by ONS
-How to retain data while meeting current legal requirements

Methods
-Consultation with a Patient and Public Involvement (PPI) panel
-Privacy Notice provided on study website
-Application to Confidentiality Advisory Group (CAG) for Section 251 support (to allow data retention without explicit consent).
-Application to a Research Ethics Committee (REC) for a Research Database
-Data Sharing Agreement (DSA) with NHS Digital

Discussion
The PPI panel were strongly in favour of retaining data providing appropriate protections are in place and any future research is done in-line with the original protocol.
At the time of writing, submissions have been made to both CAG & REC. Their decisions are due in late June 2022. A NHS Digital DSA amendment will be submitted after this.
Attempting to retain this old database has proved challenging. Issues encountered include:
-Establishing who's responsible for pre-1997 ONS mortality data
-Unclear which CAG & REC pathways apply
-Different organisations having varying definitions of 'identifiable data'
-Staff and funding needed to do the applications and administration
-Overall length of approvals process (1.5 to 2-years)

Conclusion

Retaining an old database for future research can be done and has the potential to contribute meaningfully to current research, maximising the value of the data. However, the process is complex, time consuming and requires considerable resources.

P-326

Methodological considerations for unblinding participants during double-blinded randomised controlled trials: Why, when, and how.

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Introduction

Double-blinded trials seek to keep participants, clinicians, and investigators blinded throughout the trial. Emergency unblinding may occur, where medically necessary. No standard practice exists for informing participants of treatment allocations following trial involvement. Participants are typically only unblinded, if at all, when the trial concludes and results are available, leading to variable delays between unblinding and trial involvement.

We discuss rationale, methodological considerations, and approach used to unblind participants as they end trial participation in our double-blind trial.

Methods

ATLANTIS is a randomised, multi-centre, parallel-group, double-blind, placebo-controlled trial of low-dose amitriptyline as a second-line treatment for people with irritable bowel syndrome in primary care. 463 participants were randomised to receive 6-months of treatment, some with the option to continue treatment for an additional 6-months. Participants provided outcomes at 3, 6, and 12-months. All researchers involved in recruitment, treatment delivery, and follow-up were blinded to treatment allocation.

Patient and public involvement highlighted that potential participants valued the option to be told their treatment allocation when they completed trial involvement. Amitriptyline is a readily available drug and, although un-licenced for this indication, is available to be prescribed by GPs. Timely unblinding allowed participants to make informed and supported decisions on continuing or initiating amitriptyline after trial participation.

Unblinding participants before trial end could threaten trial integrity, especially the overall blind, but potentially could improve recruitment and patient experience. We carefully considered our approach for:

- Maintaining blinded trial team, investigators, research nurses
- Measuring outcomes, ascertainment bias
- Participant choice, information provision, follow-on support
- Unblinding of GPs, future potential recruitment bias
- Participant treatment discontinuation, trial withdrawals
- Chronic disease requiring ongoing treatment post-trial

We implemented a bespoke semi-automated system to unblind participants and GP, when requested. A trial specific evidence-based leaflet was provided alongside treatment allocation. It included contact details

for an independent researcher, authorised to be unblinded should participants wish to discuss their allocation.

Results Structure and Timelines (s)
Recruitment is complete and follow-up ongoing.
A preliminary, blinded summary of the number of participants requesting treatment allocation, and post-unblinding events will be presented. Participant interviews will explore participant's experience of unblinding in a nested qualitative sub-study.

Potential Relevance and Impact
Withholding participants' treatment allocation until trial results are available may have clinical and ethical implications. We demonstrate our approach to unblinding participants, protecting the overall blind, without compromising trial integrity or validity to maximize benefits to participants.

P-327

Using machine learning to maintain and improve the ORRCA resource: Lessons learnt and future considerations.

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Background

Several resources have been developed to support methodological research, such as the COMET, DIRUM and ORRCA databases. The Online Resource for Research in Clinical triAls (ORRCA) was launched in 2016 to respond to the challenges of identifying relevant research on recruitment and retention of clinical trial participants. Large scale literature reviews were used to create the two databases which are now maintained annually by volunteers. However, this is challenging given the exponential growth of literature. One approach to addressing this challenge is the use of machine learning algorithms to minimise the burden of article screening and data extraction.

Methods

We present a case report on the use of a machine learning methods to support maintenance of the ORRCA resource. As part of a PhD studentship, a machine learning algorithm was developed and tested for use within the recruitment database. Abstracts previously screened by the ORRCA team were grouped by publication year and coded as 'not eligible' at abstract review, 'potentially eligible' (excluded at full text review) and 'included'. These datasets were then used to train and test an algorithm. Following validation, the algorithm was used to rank the relevance of abstracts published between 2018 and 2019. The top 45% were then screened by volunteers for inclusion in the next database update. Similar methods are being used to explore if the algorithm can improve the search functionality in the ORRCA website and reduce the manual data extraction currently required for categorisation into the search filters.

Results

We will report on the use of machine learning from a project management perspective, including a brief, non-technical overview of the algorithm development methods and the subsequent impact on updating ORRCA. We will share challenges and opportunities identified: time savings; resource implications and the scope of the algorithm. Evaluation will include analysis of the ranking scores of articles included in the latest database update. We will also present the search terms used within the ORRCA database between 01/09/2016 and 31/08/2022 and feedback from patient and public contributors to give context to the value of machine learning methods alongside alternative approaches to reducing the burden of database updates.

Relevance

Machine learning methods have great potential to support updates of resources that regularly screen published literature. However, there are important practical considerations that needed to be addressed in order for successful implementation and to realise the time saving benefits over the longer term.

P-328

Lessons Learned - Managing Trials of Advanced Therapy Medicinal Products

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Introduction
Early phase trials of advanced therapy medicinal products (ATMPs) are expensive, time consuming and complex to initiate and deliver. They require expertise and support from multiple departments, services and organisations to deliver projects according to strict go/no go milestones agreed with study funders. The knowledge and know how obtained when working on the trial is often lost once the trial has ended and the multi-disciplinary team is disbanded. As the number of advanced therapies in development is rapidly increasing, we decided to explore the impact of introducing a 'Lessons Learned' meeting for all stakeholders involved in an ATMP trial supported by the GSTT/KCL Biomedical Research Centre.

Methods/Approach
Stakeholders of the trial will be mapped and invited to attend a meeting to discuss the challenges and barriers faced during the set-up, delivery and close out of the trial. They will be encouraged to openly discuss what worked well and what they would like to change from their experience of the contributing to the trial.

Timing of Potential Results
The trial under review has now closed and the Lessons Learned meeting has been conducted. Results will be summarised and disseminated by July 2022.

Potential Relevance and Impact
We will present a summary of the issues raised, exploring areas that can result in changes to process or procedure. We will establish a guideline for delivering a 'Lessons Learned' meeting, and conclude with a list of recommendations for trial teams of advanced therapies to consider implementing.

P-329

Improving the methodological quality of nephrology trials through embedded methodological research: Our experience in the Nightlife study.

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Introduction

Nephrology trials have historically been low in number and of poor quality, having limited impact on patient care. The NightLife study (ISRCTN87042063) is a randomised controlled trial assessing the effectiveness and cost-effectiveness of thrice weekly, extended, in-centre nocturnal haemodialysis versus standard care using a mixed methods approach. We are addressing key methodological uncertainties through a programme of embedded methodological research which will inform the trial conduct/analyses.

Approach

A programme of both quantitative and qualitative methodological research is embedded into the trial. The quantitative methods research will (i) conduct a systematic review of how nephrology trials deal with death/transplant in their analyses of the Kidney Disease Quality of Life Instrument (KDQOL) and (i) perform a simulation study to compare methods for analysing the KDQoL in the presence of informative drop-out. These studies will inform the analysis plan for the primary outcome of the NightLife study. We are also conducting statistical mapping between the KDQOL and EQ-5D-5L so that the KDQOL can be used in economic evaluations. In terms of the qualitative methods research we are using a QuinteT Recruitment Intervention (QRI) to understand recruitment issues with the aim of implementing changes to optimise recruitment as the trial is underway. We are assessing the use of virtual photovoice to capture patient experience. We have also planned a Study within a Trial (SWAT) to evaluate participants' perspectives and preferences on clinical trial results dissemination.

Results Structure and Timelines

Our findings will be implemented within the trial as it progresses and disseminated so that others can learn from our results. To date we have highlighted the poor handling of informative missing data in the analysis of the KDQoL in completed nephrology trials, with the majority of studies excluding those who have died/had a transplant from their analyses. The QRI is revealing the challenges of recruiting patients with chronic conditions, where the treatment arms are very different. Virtual photovoice has allowed unintrusive access to lived experiences of dialysis. The trial will complete 10/2024.

Potential Relevance and Impact

Our results will improve the conduct and analyses of the NightLife study, which will optimise the trial's ability to improve clinical care for haemodialysis patients. The results also have the potential to improve the quality of nephrology trials more widely. This work highlights the importance of embedded methodological research and its potential; we would urge funders to encourage applicants to incorporate such research within their grant applications.

P-330

Implementation of a questionnaire administration & reminder system via multiple methods according to patient choice

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Introduction
Patient reported outcome measures (PROMS) collected via participant completed questionnaires (QoLs) provide valuable outcome data and have different considerations to other study data collection processes. DOMINO-DFU includes optional QoLs at Baseline, 4, 8, 12, 24 and 52 weeks. 3 administration methods are available; paper, email or text message (SMS). Our aim was to provide multiple methods of questionnaire administration and give participants the option to choose their preferred method.

Methods
Contact preferences were collected by research teams at baseline. Administration of electronic questionnaires were set up using a REDCap database and purpose-built application. Email and SMS messages containing a weblink to the questionnaires were automatically triggered at follow-up timepoints. Reminders were automatically triggered if a questionnaire was not returned within a prespecified timeframe.
Postal questionnaire letters were generated using a configurable report (built by Clinical Trials Research Unit (CTRU) Information Systems) and posted by CTRU staff. Reminder letters were sent if a questionnaire had not been received at CTRU within a prespecified timeframe.
Questionnaire administration was monitored via an excel spreadsheet for all methods.
All messages and letters were ethically approved prior to use. Changes were made to the postal administration following feedback from participants that reminders were being sent for already completed questionnaires. Alterations were made to the electronic system following complications which resulted in message duplication for some participants.

Results
We have implemented a questionnaire administration system based on participant choice. Difficulties with each method were identified and resolved. Procedures were updated based on our experience to inform future projects.

Discussion
Set up of multiple methods for questionnaire administration is complex and resource intensive. There are additional complications to consider for reminders when follow up visits are ≤4weeks apart, particularly when postal systems incur delays. Retrospective registration narrows the timeframe even more and can impact QoLs due at week 4. This, among other issues, resulted in a complex electronic questionnaire administration system, causing issues with implementation, testing, and maintenance once live. Delivering electronic questionnaires is a useful data collection tool, however the complexities of an automated system need considering alongside study requirements. A non-automated manual system can be effective and overall, less resource intensive.
There are many perceived benefits to electronic questionnaires (sustainability, efficiency, convenience) whilst paper-based questionnaires remain an important option to ensure inclusivity for all. Further research

to look at the uptake of each method (including patient characteristics) and impact on compliance is planned.

P-331

Follow-up dependent outcomes in pragmatic cluster randomized clinical trials: experience from the TIMCI study

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Introduction
Despite global progress achieved for child mortality reduction in low- and middle-income countries, there is a lack of robust research evidence to inform policies for improving the detection and management of severely ill children at primary care level. Pragmatic randomized controlled trials (RCTs) can guide decision-making, but pose inherent methodological and practical challenges with impact on validity and generalizability. This abstract presents the experience from the Tools for Integrated Management of Childhood Illness (TIMCI) project in Tanzania.

Methods/Approach
The TIMCI project aims to reduce morbidity and mortality in sick children under five attending primary care facilities while supporting the rational and efficient use of diagnostics and medicines by providers. As part of the impact evaluation, a pragmatic three-arm 1:1:1 parallel group, superiority, cluster RCT will compare health outcomes in children attending facilities assigned to pulse oximetry embedded into an electronic clinical decision support algorithm, pulse oximetry alone or routine care. The co-primary outcomes are proportion of children with severe complication by Day 7 and proportion of children referred and hospitalized within 24 hours of consultation (as proxy for appropriate referral). Outcomes were planned to be assessed on Day 7 by phone due to the scale of the trial (anticipating 110,880 children over 12 months). A six-week pilot was conducted with the intent of optimizing and stabilizing the intervention packages and the research processes before the start of the RCT.

Timing of Potential Results
Review of pilot data revealed challenges for obtaining outcomes at Day 7, with more than 50% of children lost to follow-up. After implementing a set of mitigation strategies, including options for physical follow-up, the RCT opened for recruitment in March 2022. As the success of strategies to improve the primary outcomes assessment was still unknown, a protocol amendment added an interim analysis (July 2022) to measure the impact of the introduced procedures on follow-up rates. The results will guide decision-making as to whether the design in its current form will allow the study to achieve its objectives, modifications to the primary outcomes are required or different analytical approaches need to be considered.

Potential relevance & impact
The challenge in assessing health outcomes in the context of this large-scale trial combined to a comparatively rare event, raised questions regarding the appropriateness of these measures and the use of standard methods for their evaluation. The TIMCI experience may provide practical considerations on designing and analyzing pragmatic RCTs.

P-332

Assessing the impact of COVID-19 to an ongoing clinical trial objective - A case study

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Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) has presented unprecedented challenges to the ongoing oncology clinical trials with various deviations from protocol treatments and follow-up assessments across different treatment groups in a trial. Sensitivity analyses are needed to assess these deviations to the planned primary estimand. PARTNER is an open label, randomised, 3-stage Phase II/III study to evaluate the safety and efficacy of the addition of olaparib to platinum-based neoadjuvant chemotherapy in breast cancer patients with triple negative (TNBC) and/or BRCA positive. The primary endpoint is pathological complete response (pCR) at surgery following 7 cycles of chemotherapy. The first TNBC patient was recruited in September 2016 while the last in December 2021, a total 538 patients recruited. The overload of the health care facilities had a high impact on the patients who were still on treatment (16.9%), particularly early on during the pandemic, and recruited during the pandemic (20.4%). Those who had finished treatment before the pandemic (45.2%) or recruited after the pandemic (17.5%) were mostly unaffected. To investigate the possible impact on the primary endpoint, a simulation study was performed to estimate the bias, variance and MSE.

Methods

The simulation was designed to match the settings from the PARTNER study. Three different scenarios of COVID-19 impact on treatment effect were considered. The pCR rates were assumed to (1) remain intact over the period; (2) decrease in 1% and 5%; (3) decrease in 5% and 10% in both arms, for patients recruited during pandemic and still on treatment at the pandemic outbreak. Another set of scenarios with an extra reduction in treatment arm with 5% was also explored.

Results

The results provide some evidence that a supplementary estimand with a precise description should be added in the final statistical analyses plan for the trial affected by COVID-19 pandemic.

Potential Relevance & Impact

The results will provide evidence to inform the choice of estimand strategy selection and analysis methods in ongoing clinical trials during the pandemic. This could also allow trialists to select methods with appropriate considerations with respect to the resulting bias.

P-333

Site Set-Up in a pandemic - efficiencies to help with reset: experience from the HEAL-COVID trial

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Introduction
Clinical trial site set-up is time consuming and represents a significant workload within CTUs and at sites. During the pandemic efficiencies were enabled for trials awarded UPH status. Post Covid efficiencies to help with research reset are needed. We review the strategies implemented for HEAL-COVID that aimed to help expedite site openings and reduce site burden and consider their translation to the post pandemic research environment.

Method/Approach
Communication was key with regular meetings with the trial team, site Principal Investigators (PIs) and the Clinical Research Network (CRN). Site training was streamlined as much as possible, with training videos available to view from the trial website removing the need for individual site initiation visits. Site staff completed online training forms that automatically linked to their site training/delegation log. Only PIs were required to provide GCP certificates, all other site staff were only required to complete study specific training for their role. Trial documentation was made available to view or download from the trial website, helping to minimise paper documentation. The administrative burden on sites was reduced as much as possible, for example by removing the requirement to add local headers to participant information sheets, with only a contact details of the site being added to the front page. The contractual agreement process was also streamlined; the site agreements were pre-signed by Sponsor, edit protected and changes were non-negotiable helping to substantially reduce the sign off process and timeline for execution.

Results
These strategies enabled over 70 sites to open to recruitment within 3 months from study greenlight, with 105 open to date.

Discussion
The fast track process for approvals and UPH status inevitably helped accelerate site initiations. However, the prioritisation of UPH trials was removed during the trial and the set-up processes continued to be effective.
Some of the approaches employed such as using pre-signed contracts and holding regular meetings with the CRN may be difficult to implement outside of the pandemic and their scalability needs to be considered. Many of the strategies employed in the HEAL-COVID trial such as the centralised approach for providing documentation and role specific training that linked to site delegation logs could be applied to other studies and has the potential to help improve site set up time and reduce burden at sites.

P-334

HOPE-ing for success: changes to the HOPE-e feasibility study due to COVID-19

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Introduction

HOPE-e is a NIHR-funded randomised placebo-controlled study to investigate the feasibility of using hormone replacement therapy (HRT) in post-menopausal women with hand osteoarthritis. The study closed to recruitment for 6 months due to the COVID-19 pandemic. Prior to re-opening, several adaptations were made to minimise the risk of exposure of participants and staff to COVID-19 and to enable the study to re-open to recruitment.

Methods

When planning changes to the study, patient safety, study viability and local capacity were all considered. There were no concerns raised by the Sponsor when gaining approval for the amendment. Five main changes to the study were implemented which included splitting the screening visit so that some procedures were carried out remotely, making the baseline/randomisation visit remote and building in flexibility for the follow-up visits to be remote or face-to-face.

Results

Making these changes had largely positive outcomes for participants with no loss to follow-up and 92% of participants reported having a good experience of taking part. The changes introduced resulted in less face-to-face screening visits as ineligible patients were identified prior to this (2/29 patients). The randomisation rate increased from 0.5 to 4 (randomisations/month) following the adaptations. The flexibility of more remote visits and the use of a courier was liked by participants, particularly those who lived further from sites or worked, allowing more people to consider taking part and was one factor in the increase of the recruitment rate. Implementing these changes allowed the study to re-open and meet its recruitment target.

Discussion

Although remote visits did not enable all procedures to be carried out, loss of data did not impact the primary study objectives or outcomes. In fact, the majority of the 'Covid-related' adaptations were beneficial to the study and would be used again in future studies.

P-335

Not just lab coats and stethoscopes: behind the scenes effort in the delivery of large phase 1-3 clinical trials during a pandemic – Adaptive approach

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Introduction
Trials are first and foremost conducted to answer key scientific questions and getting the science right is critical. But once the protocol is approved and the science is determined, trial failure or success determined by good communication and having a structured, adaptive, pragmatic, risk based approach to the management of the trial. This reality was clearly emphasised during the recent pandemic where established and new systems were pushed to the limit to ensure rapid delivery of a vaccine.

Methods
All Projects share the following basic principles
1. Set a clear objective aimed to bring about change (Project Scope)
2. Consider the tasks which need to be completed to a prespecified standard (Project Deliverables and Critical Success Factors)
3. Determining resources needed to achieve the objective (Resource Planning)
4. Timeline for delivery (Project Schedule)

Clinical trials on the whole follow the above principles but the multifactorial input in trial delivery (e.g. slow recruitment, delay in drug availability, safety pauses) can result in needing to adapt our expectations and timelines. We used a variety of systems to allow for real time assessment of trial progression alongside a system of resource reallocation to allow for timely delivery of our trials.

Results
Using the COVID-19 vaccine trials as a case study we will present details of some of the systems used to track critical tasks and how we worked as a team to enable reallocation of resources in a rapid effective manner.

Conclusion
Rapid delivery of clinical trials requires an adaptive risk based approach where context is the key in decision making.

P-336

Process Evaluation of a COVID-19 Trial – the PROTECT-CH Experience.

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Introduction
Despite an established literature on the RCT method, the publication of RCT protocols and reporting guidelines such as CONSORT, large parts of the RCT process remain hidden – driven by individual actions and organisational commitment.
From design to delivery connections are formed, decisions are made, and challenges negotiated. Understanding these less structured (and less regulated) moments of trial methodology may support more efficient trial set-up and delivery.
Here we reflect upon the set-up phase of the Prophylactic Therapies in Care Homes (PROTECT-CH) trial. This is an NIHR funded study intended to collect data in more than 300 care homes during the Covid-19 pandemic. Whilst the changing epidemiology of Covid-19 in the UK (due to vaccination take-up) made the trial unfeasible, PROTECT-CH rapidly established a platform trial design and an infrastructure to support research in care homes.

What lessons can be learned from this experience?

Methods
This is an iterative process evaluation of the set-up phase of a large, platform trial testing prophylactic measures in UK care homes.
Methods include a documentary review of PROTECT-CH working groups (remit, minutes, and outputs), an online survey of working group members, and qualitative interviews with key stakeholders.

Results
24 working groups were identified in a hub and spoke model. Representatives of 20 of these groups completed an online survey about group function and activity. 24 key stakeholders, including grant holders, methodologists, clinicians, public contributors, and sponsor, participated in a semi-structured interview.
The evaluation identified that 91 individuals representing 25 organisations were involved in the set-up process. These represented a mix of academic, clinical, PPI, and methodological contributors, and represented a national network of collaborators and stakeholders.
Key challenges included:
1) Working collaboratively in an effective and efficient manner in time-pressured circumstance.
2) Establishing systems, processes, and infrastructure with a research naïve community (care homes).
3) Establishing trial design with key factors (data availability, finalised treatments) uncertain.
Key successes included:
1) Rapidly establishing an experienced multidisciplinary team to develop PROTECT-CH.
2) Establishing trial protocols and mechanism for collecting routine data.
3) Establishing dedicated training materials and reporting templates for care home research.

Discussion

PROTECT-CH has highlighted the challenges of establishing rapidly a large RCT during the Covid-19 pandemic. It has, however, demonstrated some of the systems and organisation that make this possible and has produced resources that others might find valuable in the future.

P-337

COV-BOOST: one vaccine trial answering multiple sequential policy questions during pandemic

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Background

Protection against SARS-CoV-2 infection waned after initial COVID-19 vaccine two-dose schedules. Periodic or seasonal boost dosing has been considered by policy makers, initially to prevent infection but subsequently (with new viral variants) to protect the most vulnerable.

Methods

The COV-BOOST trial (ISRCTN: 73765130) is a multicentre, randomised, controlled, phase 2 trial of seven full dose and three half dose COVID-19 vaccines used as a third booster dose. The trial was designed at the start of the UK second dose vaccination campaign in May 2021. The 18 study sites were split into three site groups (A, B, and C). Within each site group, the participants were randomised to three or four experimental vaccines, or a control vaccine (MenACWY), with equal probability. The aim was to investigate the reactogenicity and immunogenicity of different vaccines that may have been available to use as a 3rd dose in the UK population following initial two doses of ChAdOx1 nCov-19 (Oxford–AstraZeneca; hereafter referred to as ChAd) or BNT162b2 (Pfizer–BioNtech, hearafter referred to as BNT).

Results

Between June 1 and June 30, 2021, 3498 people were screened. 2878 participants met eligibility criteria and received a COVID-19 vaccine or control. Among all the vaccines arms in both populations who received ChAd/ChAd and BNT/BNT as their initial doses, mRNA vaccines induced the highest humoral and cellular responses at day 28. Based on the COV-BOOST results, the UK Joint Committee on Vaccination and Immunisation recommended mRNA vaccines (BNT and half dose mRNA-1273) as the third primary dose in September 2021. Following the change in the UK vaccination policy, two sub-studies were designed to answer further questions on the booster interval and to assess fourth doses of mRNA vaccines. Participants in the control (meningococcal vaccine) arms were randomised to receive one of three mRNA vaccines with a longer interval. Those in the original 3rd dose BNT arms were randomised to receive BNT or half mRNA-1273 as a fourth dose. In the fourth dose sub-study, both BNT and half mRNA-1273 as fourth doses significantly induced immune responses. Peak responses after the fourth dose were similar to, and possibly higher than, peak responses after the third dose. These findings supported the UK fourth dose vaccination campaign in vulnerable population in February 2022. The results from the interval sub-study will be reported by July 2022.

Conclusions

COV-BOOST demonstrates that carefully planned vaccine trials can answer multiple sequential policy research questions during a pandemic.

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Impact of COVID-19 on a large ongoing multi-arm multi-stage (MAMS) multicentre cancer clinical trial (PLATFORM): Lessons learnt from the pandemic

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Background
The PLATFORM study is a large phase 2 randomised multi-arm multi-stage (MAMS) multicentre adaptive trial to evaluate the efficacy of maintenance therapies following completion of standard first-line chemotherapy in patients with HER-2 positive and HER-2 negative oesophagogastric adenocarcinomas. The primary endpoint (progression-free survival) will be compared between the standard treatment arm (A1 or B1) against each of the maintenance therapy arms.

Objective
The COVID-19 pandemic has interfered with the conduct of cancer clinical trials causing significant changes to some study activities. Therefore, impact of these COVID related (COVID-RD) implications and protocol deviations should be explored.

Methods
Failed randomisations, withdrawals and protocol deviations between 23/2/2015 and 20/4/2022 were extracted from the study database and classified as COVID-RD if the term COVID-19, Corona (or any variation) was present. Computerised Tomography (CT) scans for all patients and timepoints were also extracted. All potential COVID-RD implications were summarised by year using appropriate summary statistics.

Results
Recruitment to the PLATFORM study halted due to COVID-19 on 19/3/2020 and reopened on 19/11/2020. Out of 46 sites, 12 suffered delays with reopening due to COVID-RD issues, 4 of which are yet to reopen. Additionally, there were 19 reported COVID-RD failed randomisations. There were only 2 reported COVID-RD withdrawals. 248 protocol deviations have been reported since the start of the study in 2015, and 121 (49%) of these were recorded in 2020-2021 and COVID-RD. The majority 87% (105/121) of reported COVID-RD deviations were a missed physical assessment, although this was often replaced by a telephone consultancy. Despite only 6 missed or delayed CT scans recorded as COVID-RD deviations, 38 CT scans from 18 patients were missed in 2020 alone as CT scan completeness dropped to 85% of 248 scheduled scans amongst 90 patients, compared to completeness rates of >94% in 2015 -2019. Differentiating retrospectively between true protocol deviations such as unoffered scans and missing follow-up data due to no-shows was a challenge in this study; data which we would have benefitted from capturing in real time.

Conclusions
As in many clinical trials, PLATFORM suffered a considerable drop in recruitment during the COVID-19 pandemic. Preliminary data show a substantial increase in deviation reporting, although the majority of

these do not result in loss of endpoint data. Future evaluation will clarify the true rate of unreported missed CT scan deviations and whether COVID-RD might have impact on the primary endpoint.

P-340

Retention to paediatric randomized controlled trials during the COVID-19 pandemic: a qualitative study

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Introduction

Retention to paediatric randomized controlled trials (RCTs) is a novel research area. No qualitative studies using interviews or focus groups have investigated factors which effect retention across multiple trials within different disease areas and settings. The aim of this qualitative study was to investigate follow-up and retention for those involved in paediatric RCTs and how it can be improved. These results focus on the effect of the COVID-19 pandemic on retention to trials, and follow-up.

Methods

I conducted a qualitative study based on in-depth semi-structured interviews with clinical trialists who had experiences of working on paediatric RCTs. Trialists were purposefully sampled across different disease areas and settings in the UK. 20 interviews were audio-recorded and analysed thematically.

Results

Six themes were generated from these data. These were the impact of lockdown measures, adapting, or not adapting, follow-up methods, impact of remote data collection methods, effect of pandemic on condition, and the positive effect of the pandemic.

The impact of lockdown measures was differential depending on how restrictive the measures were, and whether participants, or their caregivers, were being asked to complete follow-up. Trials that did not adapt their data collection methods found that follow-up was challenging. However, those trials that did change their data collection methods found that they did not always maintain pre-pandemic follow-up rates. The condition under investigation in the trial may have also been affected by the pandemic, and this influenced participant's willingness to remain involved in the trial. The pandemic also helped change the views of some participants who previously preferred completing outcome measures on paper.

Discussion

Retention to paediatric RCTs has been affected both positively and negatively by the COVID-19 pandemic. Future work is needed to translate learnings from RCTs during the pandemic such reducing burden in competing outcomes measures, challenge of relying on data usually collected in-person and using online methods of data capture for participants.

P-341

Adopt to adapt: Efforts to Keep the RAMPART Trial of Adjuvant Immunotherapy in Renal Cancer on Track in the COVID-19 Era

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Introduction
The RAMPART trial is an international, UCL-led, multi-arm multi-stage (MAMS) platform trial investigating the use of immune checkpoint inhibitors after nephrectomy in patients with renal cell carcinoma. It was initiated with a control (active monitoring) and two research arms (durvalumab monotherapy and durvalumab with tremelimumab) and has been open to recruitment since July 2018. Due to the COVID-19 pandemic, recruitment and treatment delivery was suspended for four months in the Spring/Summer of 2020 and accrual has only recovered in 2022.

Methods/Approach
The RAMPART team provided clear communication to sites on how to manage priorities during the temporary suspension and relaunch of the trial. The protocol was amended to ensure the safe treatment of patients and to offer flexibility to conduct consent and certain assessments remotely. Sites were asked to focus on the submission of high priority data to permit continued oversight of patient safety and allow primary outcome data to be collected. Data completeness has been carefully monitored and targeted data chases have been conducted to maximise data integrity. We have explored the extent to which the pandemic will prolong recruitment and follow-up, and the timelines for our primary analyses. To maximise options for patients and to aid accrual, we examined the impact of re-randomisation of control arm patients within the protocol, an approach that has been employed in other trials within the CTU in other disease areas.

Results Structure & Timelines
This section will contain an update on compliance, recruitment, sites open and timelines for analysis. In order to be able to present these adequately and robustly, we will use data up to September 2022.

Potential Relevance & Impact
The pandemic era has been challenging for clinical trials. Adaptations can be made to prioritise patient safety, to allow activity to continue where there is capacity and to ensure trial integrity is maintained.

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Rapidly designed data capture in a rapidly evolving global pandemic, lessons to be learnt

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Rapidly designed data capture in a rapidly evolving global pandemic, lessons to be learnt

The design of a well-thought, comprehensive, yet nimble and focused Case Report Form (CRF) can greatly affect a study success. CRF designing requires enormous planning and attention to minute detail. Neither conditions were facilitated by the emergence of a global pandemic in 2020 requiring a hastily set up clinical trial investigating potential life-saving treatments.

The clinically-driven, rapidly-designed, resulting CRF met several challenges in its implementation that greatly affected the speed, accuracy and reporting of the clinical trial. All aspects of data collection, management, quality control and ultimate analysis were severely hampered by the following avoidable pitfalls in CRF design:

- Usage of a composite primary endpoint whose determination required cross-validation of several sources
- Duplication of data sources
- Collection of elaborate and/or unimportant clinical data
- Usage of clinically novel or clinically uncommon outcomes
- Poor connectivity of related parts of the CRF and lack of a clear hierarchical structure differentiating crucial data points vs potentially useful clinical information
- Persistent confusion of terms (i.e. “discharge” and “study termination”)
- Usage of daily patient status questions regarding safety vs detailed safety reporting
- Lack of foresight in understanding the disease follow-up (discharge from hospital & long term outcomes)
- Poor implementation of a “discharge” visit option
- Poorly designed “Termination of treatment form”
- Misuse of the End of Study form
- Lack of tools to quickly identify crucial missing data in real time

Given the adaptive design of the trial and the rapidly evolving pandemic, additional challenges were met in having to reactively adapt the CRF to accommodate new arms of the study. The added uncertainty of a hugely variable and unpredictable rate of recruitment made the retrospective quality control of the data very demanding and ultimately inefficient.

We will present a series of examples of improvements and mitigations, where greater input from experienced statisticians and/or data managers at design stage could have improved the CRF, streamlined the data acquisition and ultimately relieved pressures on the clinical staff conducting the trial under very challenging circumstances.

We argue that the challenges presented by a global pandemic demanded a nimbler and more focused data acquisition process and such lessons would be beneficial for clinical trials at large.

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Setting up a breast cancer surgical de-escalation study in the UK during the COVID-19 pandemic – lessons from the ATNEC Breast Cancer Study (IRSCTN: 36585784)

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Background
ATNEC is a phase III, randomised trial with embedded radiotherapy QA (RTQA). ATNEC opened to recruitment in Dec-2020, in the midst of the COVID-19 pandemic. The trial assesses whether axillary treatment can be deescalated, post-surgery, in T1-3N1M0 breast cancer patients who have no residual nodal disease post-neoadjuvant chemotherapy.

Methods
Site Set-Up -
Site initiation meetings (SIVs) were performed virtually using Microsoft Teams, which had several benefits:
- easier to schedule - important given limited NHS resource,
- facilitated attendance of the wider team,
- presentations were recorded,
- permitted CI to attend each session, allowing issues to be troubleshooted.

48 sites are open to recruitment; median time from SIV to opening was 30 days. An average of 3 sites per month have been activated since ATNEC opened.
Regular virtual site catch-up meetings allow easy access to trial team and resolve any issues.
RTQA Streamlining
COVID-19 limited the capacity of radiotherapy departments to engage with RTQA requirements. In response, the RTQA process was streamlined:
- Clinicians who had participated in the RCR 'Breast Outlining Course' could be streamlined for outlining requirements.
- Implementation of prospective reviews of the nodal/internal mammary chain plans for each site's first randomised patient.
- Streamlining planning QA through previous RTTQA trial participation

The median time from first contact to RTQA approval for streamlined centres was 65 days vs. 101.5 days for non-streamlined centres, illustrating the benefit of streamlining measures.

Screening Data
Recruitment to de-escalation trials is challenging. ATNEC collects screening data to monitor acceptance rates and reasons why patients decline the trial to identify ways to improve recruitment. Screening data until 30-Apr-2022 shows that 69% of eligible patients were approached (183/265) and, of those approached, 47% were consented (86/183). For the 68 patients who declined, the most common reasons were; preference for axillary treatment (34%), preference for no axillary treatment (12%), no reason documented (22%) and ineligibility (18%).

Node marking
ATNEC held virtual node marking training workshops. The sessions provided site education and publicity for the trial.
Collaboration agreements were set-up with industry partners to provide node markers for free for trial participants, to encourage uptake of the trial.

Conclusion
Set-up of ATNEC during the pandemic required adaptation of the study to limit burden to sites by ensuring it was pragmatic and aligned with existing patient pathways. The use of virtual tools for site training and engagement was crucial, in the absence of face-to-face meetings.

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Retrieved waste blood sample use in GenOMICC at Barts Health during COVID-19 maintained quality and reduced risk when compared with fresh blood draws nationally

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Introduction

In order to allow all patients with severe COVID-19 to have access to the GenOMICC study across Barts Health sites (including the Barts Nightingale hospital at Excel Centre) we needed to collect blood samples using research teams with limited specialist knowledge.

Methods

To protect research staff, we realised that most of the blood samples from routine intensive care on our five sites were left over when the autoanalyzer had taken it's "mosquito's sip" of the blood taken from the patient. This was routinely stored, refrigerated, for around a week or so (to allow for laboratory re-analysis or other requests from the clinical team).

The "legal eagles" group from our Patient Powerhouse obtained two senior human rights legal opinions, within 48 hours. Both lawyers suggested that it was reasonable to store waste blood after routine analysis of blood taken for clinical care, until such time as the patient, or their relative was able to give consent for the use of the sample, or if not, to allow for routine discard of the sample.

Results

Of the 389 samples collected at Barts Health, most were from discarded waste blood samples (114 refrigerated, 216 frozen) the rest were 51 fresh blood draws.

Allowing for samples still in process, of the discard samples, 4 samples failed (2 at whole genome sequencing (WGS) and 2 at bioinformatics stage). To date 303 successful WGS have resulted from DNA extracted from discarded waste blood samples (overall pass 98.7%).

This success rate of sequencing of DNA from waste blood samples was almost identical to that of those samples taken fresh from the non-Barts sites- 167 fails out of 12,818 fresh samples (overall pass 98.7%,).

Discussion

Preliminary data from the GenOMICC study suggests that the quality and success rate of genome sequencing from discarded blood, exclusively at Barts Health, was not inferior to that of blood taken de-novo by the sites in the remainder of the trial.

The future of personalised healthcare will increasingly involve generic consent for use of samples and records etc for research. In summary there appears to be no difference in quality, and it would be useful to now test this hypothesis more formally. This forced innovation driven by the pandemic may prove useful in the future.

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COVID-19 impact on blood sample collection and follow-up in TRACC (Tracking mutations in cell free tumour DNA to predict Relapse in eArly Colorectal Cancer) study.

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Objective
COVID-19 pandemic has interfered with the conduct of cancer clinical trials having a huge impact on some study activities. Therefore, investigation on the impact of data collection, analysis, and interpretation of results is required.
The TRACC Trial was setup by Royal Marsden to assess whether detection of ctDNA predicts for relapse in patients with colorectal cancer that have undergone surgery with curative intent. Here we present a preliminary exploration of impact of COVID-19 in TRACC on sample collection and potential effects on primary endpoint (detectable ctDNA at the first postoperative visit & disease free survival)

Methods
Data on blood collection and time to relapse were investigated, by year of surgery. Information related to missing blood collection up to 1/12/2021 were extracted and classified as due to COVID if the term COVID-19, Corona (or any variation) was present.

Results
Of 1,081 patients registered into TRACC, 772 patients had surgery prior 01/10/2021. Between the start of the trial (December 2016) to 1/12/2021, 1,267 blood samples were recorded as not taken with the majority (78%) happening since the pandemic outbreak, of these 63% were reported as due to COVID-19.
Comparisons between pre-pandemic (2018) and post pandemic (2020) saw blood collection compliance in the first year following surgery of around 86% and 42% respectively, with only 48% of patients having post-operative blood sample in 2020 (with 79% of reported missing samples due to COVID-19) compared to 96% in 2018.

The pandemic also affected follow up visits, potentially delaying relapse diagnosis with impact on survival estimates. Preliminary analysis shows that late follow up visits (post 1 year following surgery) may have been mildly affected, with time from last contact to relapse being slightly higher in those who had surgery prior to COVID-19.
Patients who had surgery in 2018 have shown a median lead time from last contact to relapse equal to 2.8(IQR: 1.0-5.4), whereas in 2020 was 2.6(IQR:1.2-4.0).

Conclusions
A substantial increase in number of missing visits was reported during COVID-19 pandemic. Preliminary TRACC data shows the impact on the primary endpoint might vary depending on year patients undertook surgery.
Patients recruited at start of the pandemic (2020) will mainly be affected with post operatively bloods not being available, whereas delays experienced in follow up visits and relapse diagnosis might affect patients

recruited before the pandemic outbreak. Future analysis (in progress) will clarify the extent of impact of COVID on the primary analysis.

P-346

Not just lab coats and stethoscopes: behind the scenes effort in the delivery of large phase 1-3 clinical trials during a pandemic – Site management

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Introduction
Large late phase trials need to be delivered across multiple sites which in normal times can be a logistical nightmare, but during a pandemic when you cannot physically visit your sites all the usual issues can be amplified. Quality trial delivery requires good communication, ensuring trial teams are aware of the expectation on them, feel up to date on any changes, feel involved and feel listened to. Success of a trial is dependent on establishing a collaborative relationship with your sites, ensuring ownership of the project is inclusive not exclusive.

Methods
Communication with sites can be done in many ways, through personal contact, newsletters, weekly meetings or simple emails. There is a choice of bespoke software to support this activity, but many academic units rely on readily available generic software. We used a mixture of all of the above using email, TEAMs and WhatsApp.

Results
A variety of communication strategies were required for effective site management. No single system alone was adequate as communication varied depending on the nature of the information to be shared, the preferences of the individual and the stage within the trial. Using the recent COVID trials as a case study we will present the advantages and disadvantages of the different methods used.

Conclusion
A good relationship with site and Sponsor is key to delivery of trials to time and target, with high quality data collection. Clear communication with sites, ensuring the teams feel valued and fully informed is critical to this relationship. Our experiences delivering the COVID vaccine trials have demonstrated that using readily available well-known systems in a mix and match adaptive basis proves most the most effective approach

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Not just lab coats and stethoscopes: behind the scenes effort in the delivery of large phase 1-3 clinical trials during a pandemic – Staffing

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Introduction
Managing clinical trials of whatever size and complexity requires groups of individuals with a broad skill set. Trial failure or success can be determined by the quality of the associated documents and processes that are put in place to support the study team. Having clear guidance and ensuring understanding as to when processes are fixed or where there is flexibility is important in developing an autonomous work force. This reality was clearly emphasised during the recent pandemic where the speed at which delivery was required was only possible by ensuring we had a team of well-trained supported individuals.

Methods
Setting up processes and structures to support a rapid response to the COVID-19 pandemic required review of past successes and failures and a good understanding of clinical trial delivery. The delivery of the trials involved training across 19 sites of large teams of research experienced, but often vaccine trial naïve staff. The processes put in place needed to carefully balance ensuring sites and staff were confident enough to drive day to day decision making, whilst feeling supported should they need to escalate issues.

Results
Documentation design had to be adaptable allowing it to accommodate multiple rapid amendments. Consistency in design and presentation was important so teams became familiar with formats and could easily find new information. Determining the content and limiting who needed to read which documents was critical in ensuring a robust, but not burdensome training programme. Finally ensuring that there was access to ad hoc support from key authorised individuals for escalation of key matters and rapid responses ensured clearing of bottlenecks often before they had become a major issue.

Conclusion
Although much of the techniques used during the delivery of the COVID-19 vaccine trials was not new it gave us a unique opportunity to refine these processes and documentation across the full life cycle of the development pipeline. Ensuring training documents and supporting plans covered the full breadth of trial delivery and management ensured standardisation across our sites, high quality delivery of our trials, and the establishment of a well-trained workforce who are well placed to support future trial delivery.

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Preventing COVID-19 in care homes: challenges experienced in the PROTECT-CH and BEET-Winter trials

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Care home (CH) residents experienced considerable morbidity and mortality from COVID-19. Nitric oxide (NO), niclosamide and ciclesonide possess anti-SARS-CoV-2 activity in vitro, and the first two have broad antimicrobial activity, at least in vitro. We report experience from two CH-based COVID-19-prevention cluster-randomised controlled trials.

PROTECT-CH was a phase III open-label platform trial commissioned by NIHR and was requested to test 42 days of inhaled niclosamide and ciclesonide in a post-exposure prophylaxis design in 750 CHs/25,000 residents. It received urgent public health (UPH)-badging and MHRA/research ethics approvals. A website/database were implemented, and 300 CHs wished to participate. Delays were caused by drug and other contracting issues, trial insurance, training and recruitment issues mostly due to the lack of research infrastructure around CH. The trial closed in December 2021 because CH COVID-19 case rates fell dramatically thereby rendering the trial unfeasible.

BEET-Winter was a placebo-controlled feasibility trial testing dietary nitrate supplementation given for 60 days in a pre-exposure prophylaxis design in 30 CHs. UPH-badging was rejected, and ethics approval took two months. Just 6 CHs eventually participated with 49 residents recruited in early 2021. 76% residents received >50% of nitrate-containing juice and those randomised to nitrate had higher urinary [nitrate] levels, 50 [157] v 18 [40] mg/L, difference 25 [0, 90]. Data paucity precluded other treatment group comparisons. There were no cases of COVID-19.

Performing these CH trials during the COVID-19 pandemic was extremely challenging, primarily due to central delays, low CH interest whilst immersed in the first two waves of infection, limited research experience in CHs, pharmacovigilance requiring GP involvement, and contracting and insurance issues. A long-term CH research network is urgently required. NHS-based clinical research within NIHR structures has been widely successfully during the pandemic and ongoing refocusing of NIHR to include care research offers many opportunities.

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The Highs and Lows of COVID-19 clinical trials

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Data from ClinicalTrial.gov illustrates the explosion of clinical trial research that has taken place over the last 2 years. In April 2020, just over 500 clinical trials related to investigating COVID-19 were registered globally and within less than a year this had increased to over 4,000 studies. To date (May 2022), this has doubled to just under 8,000 studies. Of these, 2,519 (32%) have been completed and 1,322 (17%) have been terminated, suspended, or withdrawn. The latter displays a relatively large number of research waste, illustrating the challenges that trials have faced in terms of conduct during the COVID period.

This study outlines the challenges and lessons learned from a large COVID-19 adaptive clinical trial- RECOVERY RS, in terms of set-up, conduct, analysis, completion and dissemination. It then relates the experiences to a wider context of how clinical trial research has been conducted during the pandemic and what lessons we can take forward, should we be faced with a future pandemic.

In brief, speed was of the essence when setting up RECOVERY RS. But this meant that balance was needed between quality/scientific rigour and speed. The trial was deliberately kept very simple to ensure its deliver. However, obtaining data from NHS Digital was not timely, despite the urgency and priority imposed by NHS England. This had implications on our statistical boundaries and the results we presented at each of our interim analyses for the Data Monitoring Committee. Due to the different waves of COVID-19 and the introduction of the vaccine/booster, predicting future recruitment projections was difficult: in the 2nd wave, it was reported that mortality had declined by 20%- having implications on our primary outcome. The delivery of the study had an impact on the vast clinical trial unit resource and staff, which compromised on delivery of non-covid trials.

On reflection- the clinical trial model remains the gold standard, despite the fact initially, at the start of COVID-19, non-randomised observational studies were heavily endorsed: FDA issued an emergency use of convalescent plasma based on >35,000 study in Aug 2020 and then 5 months later RECOVERY contradicted these results, showing no benefit. Furthermore, prevention is better than cure – only 11% of trials focused on prevention and none looked at assessing social distancing or lockdown measures. The excessive duplication of efforts and lack of collaboration urges for a broad national/international infrastructure for pandemic trials.

P-350

The LEARN study: using participant experience to improve trial design for neurodegenerative diseases.

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Introduction
A significant number of advanced medicinal therapeutic products (ATMPS) for the treatment of neurodegenerative diseases are moving to clinical trials. The nature of ATMPs (cell, gene and protein products) and the challenge of circumventing the blood brain barrier mean that many require direct cranial administration. Combined with the ongoing and often complex management of neurodegenerative disease, the requirement for direct central nervous system administration and complex multi-component assessments results in a number of unique challenges pertinent to ATMP evaluation in neurodegenerative disease. Understanding the patient journey during AMTP investigations is important for both mitigating against these challenges and to aid recruitment and retention in clinical trials as candidate ATMPs move forward into Phase III studies.

In this study we set out to understand the experiences of participants from a trial in which people with Parkinson's disease received infusions of a growth factor (GDNF) via permanently implanted intra-cranial drug delivery catheters.

Methods
We conducted semi-structured interviews with GDNF trial participants, their family members/ care partners and trial delivery staff using topic guides informed by our participant consultation group. We also attempted to interview people who had discussed taking part in the trial but declined participation. Interviews were conducted on-line alone or in dyads, depending on the preference of the participant and were observed by a second non-participatory researcher. Interviews were transcribed verbatim and analysed thematically using NVivo software.

Results
The experiences of participants in the GDNF trial were largely positive, expressing strong feelings of collegiality and working towards the greater good. Specific issues surrounding the nature and timing of assessments and post operative care were identified. These related to the importance participants put on additional support in attending study visits being beneficial to their overall experience. A common thread relating to negative experiences lay with the difficulties participants faced once the trial had ended, which included learning about the negative outcome of the trial and the sudden lack of interaction following an intensive study period.

Discussion
Listening to the voice of lived experience from novel complex trials is vital to inform the design of efficient, patient-centred studies to maximise recruitment and retention. Simple modifications to trial conduct can significantly enhance the participant experience and advocates for the inclusion of broad and diverse patient experience in the development of future ATMP studies.

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Site-reported benefits and challenges of implementing a platform study of molecular screening and therapeutics in Australia. A survey of clinical leads at treatment centres

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Introduction
The Molecular Screening and Therapeutics (MoST) program is a platform study designed to efficiently assess the activity of genomic-driven cancer treatments, implementing a diverse range of phase 2, single-arm trials for patients with rare and advanced cancer.
The platform trial was initially undertaken at a single centre within each of the 8 states and territories in Australia. The platform now offers 12 concurrently recruiting trials across over 20 centres nationwide. We seek to understand the operational needs and barriers for delivering this master protocol at study centres.

Methods/Approach
The University of Sydney surveyed study principal investigators (PI) at each participating centre to evaluate the opportunities and challenges of operationalising the program in this qualitative study. First a small tactical group of 2 - 3 PIs brainstormed ideas with the program co-chairs and codesigned questions and themes to take to a broader group of site PIs. Feedback was collected in the group setting, with follow up by email for additional comments. The SWOT (Strengths, Weaknesses, Opportunities, and Threats) matrix was used to understand the position and perspectives of the diverse group of organisations in relation to project planning.

Results
The working group identified several strengths of the program, including provisioning of genomically selected trials to patients otherwise not available on standard indications of drug therapies, offering large panel genomic sequencing to patients, and upskilling of site staff in adopting a protocol of complex study design.

Resource allocation was a common threat experienced during program implementation. In particular, staff allocation was challenging as the pipeline of clinical trials expanded. Furthermore, changing the perspective on viewing the entire platform trial as a cohesive program, rather than discrete investigator-initiated studies was difficult, although fundamental to leveraging the efficiency offered from the innovative trial design. All sites reported that COVID-19 pandemic resulted in significant delays in opening new studies due to reallocation of healthcare resources.
To mitigate resource constraints at larger referral centres, potential solutions include expansion of the program to a broader group of centres, including smaller, rural centres. Centrally-coordinated and strategic distribution of genomic-selected trials may allow wider access to the program and ensure sustainability.

Discussion

While advantages of genomic-based platform trial are recognised, strategies to overcome challenges experienced at participating sites are needed in managing operational constraints imposed by existing trial review processes, as well as resource limitations in staffing and infrastructure.

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Usefulness of the pragmatic-explanatory continuum indicator summary (PRECIS) tool in low- and middle-income countries

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Introduction
The aim is; i) to systematically review the literature on the use of the pragmatic-explanatory continuum indicator summary (PRECIS) tool and its subsequent iterations in low- and middle-income countries (LMICs), and ii) to qualitatively evaluate the usefulness of PRECIS-2 for assessing pragmatic and explanatory features of the Mega Randomized Registry Trial Comparing Conservative vs Liberal OXygenation Targets (Mega-ROX) trial at Ziauddin Hospital in Pakistan. The objective is to identify opportunities to refine PRECIS to optimize utility in LMIC settings based on strengths, weaknesses and applicability of the tool identified from published literature and perspectives of researchers, patients and families.

Methods/Approach
Systematic review (i): The search will be conducted in PubMed from inception to identify original peer-reviewed research that cites any of the original PRECIS publications or mentions PRECIS, and applies the tool to research conducted in a LMIC. Two authors will independently screen records and extract data on the purpose, method, results and experiences of using PRECIS. Challenges and successes of applying PRECIS will be qualitatively analyzed using the constant comparative method, and data will be summarized using descriptive statistics and narrative synthesis.

Qualitative evaluation (ii): Study activities include two-round online PRECIS-2 rating processes with six researchers preceded by observed group discussions, and semi-structured interviews with the researchers, two patients and families. Data recorded on observation guides and interview records transcribed verbatim will be coded in an inductive manner and analyzed thematically with NVivo (released March 2020) qualitative data analysis software.

Timing of Potential Results
The systematic review results will be supplemented by lessons learned through the qualitative evaluation, which is the first part of a larger mixed-methods study being conducted in a total of six sites in Nepal and Pakistan evaluating Mega-ROX and two other trials using PRECIS-2. Results from the wider study are not expected to be ready for presentation, but we aim to share our experience of employing PRECIS-2 for the evaluation of Mega-ROX in Pakistan.

Potential Relevance & Impact
Development, modifications and validation of PRECIS has almost exclusively been based on input from trialists located in high-income countries. Differences in social, ethical, cultural and contextual realities in which LMIC trials are conducted could conceivably influence the applicability of the tool, and thus published experiences identified through the review and reported use of PRECIS in low-resource settings such as Pakistan will provide valuable lessons for further refinement and application of the tool globally.

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Consequences of population drift over time in large scale platform trials: lessons from the COVID-19 Pandemic

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Introduction (covering aims/objectives/settings)
Platform trials and adaptive designs have garnered increasing interest in recent years as an efficient way to investigate multiple putative interventions in a single framework. During the Covid-19 pandemic they provided a setting to evaluate several potential treatments at a time when effective interventions were desperately needed. One of the statistical challenges in platform trials is population drift. This can occur through different mechanisms such as changes in inclusion criteria of participants enrolled into the study. The impact of population drift is a topic of ongoing research. Here we present an example of how population drift might influence our interpretation of the results using the PRINCIPLE (Platform Randomised trial Interventions against Covid-19 in older people) trial.

Methods/Approach (making clear the approach e.g. applications and implementation, mixed methods, opinion, qualitative, quantitative, review, simulation, survey, SWATs).
The PRINCIPLE trial is a national priority platform of repurposed interventions for Covid-19. The trial has two co-primary endpoints; self reported recovery and hospitalisation/death.
Various changes occurred over the course of the PRINCIPLE trial. Some of these have included changes in the target population due to varying inclusion criteria alongside new interventions. The trial was also conducted within a backdrop of various policy changes, for example: introduction and easing of lockdown, introduction of mass testing and the vaccination programme. We describe how these changes have influenced the overall event rate and the effect of treatment. We discuss how time drift was accounted for in the PRINCIPLE trial and what questions might remain.

Results Structure and Timelines (what form would the results takes)
In the PRINCIPLE trial time drift was modelled to account for the impact of population drift. In addition a sensitivity analysis modelled the treatment effect in the concurrently randomised control population. We will discuss how the changing patient population has influenced the underlying event rate, the treatment effect and what lessons can be learned for the analysis of future platform trials.

Potential Relevance and Impact (why might the results be important or interesting)
The PRINCIPLE trial provides a rich example of complex real world trial data in which to explore the effect of changing population over time. With increased interest in platform trials as an efficient way of exploring multiple interventions, it is of vital importance to minimise bias when there is temporal variation in the patient population. Future work hopes to build on this topic using the example of PRINCIPLE.

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