An Embedded Mixed-Methods study highlights a lack of discussions on retention in clinical trial consultations.

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Abstract (180 words)

Objective

This study investigated trial consultations to identify whether and to what extent discussions of retention are present.

Study design and setting This embedded mixed-methods study design included a purposive sample of audio-recorded trial consultations obtained from four sites of a large multicentre UK based surgical RCT. Study participants included potential trial participants, trial Surgeons and Research Nurses.

Results: Forty-four participants were included in this study: Potential trial participants (n=37); trial Surgeons (n=4); and Research Nurses (n=3). Analysis revealed no discussion of retention across 79% of consultations. Of the remaining 21% where discussions of retention were present, only 3% (maximum) of the conversation related to retention. There was some evidence of good practice but on the whole the discussions contained inaccuracies about timing and delivery of questionnaires and the right to withdraw often highlighted without providing trial consequences.

Conclusion: This study is the first to explore trial consultations for discussions of retention. It suggests that there may be room for improvement within current practice. Further research is required to determine the generalizability of the findings reported to other clinical trials.

Key words: Clinical Trials, Retention, Communication, Informed consent

Introduction

Clinical trials are regarded as the cornerstone of evidence-based health care as if conducted rigorously they offer unbiased estimates of treatment effects. [1] Yet despite their importance, there are significant methodological challenges in ensuring trials are done well. Recruitment and retention have been identified as amongst the top priorities for research amongst UK trialists [2]. Whilst there is now a significant body of research asking various methodological questions about recruitment and using an array of methods to answer these questions, the same cannot be said for retention.

Retaining participants in clinical trials remains a significant challenge [3]. Recent work suggests that 50% of all trials have loss to follow up of more than 11% [4]. Missing data in trials is of concern as it has the potential to introduce bias and make the trial results unreliable or in some cases unusable in practice. Missing data is particularly problematic if the missingness is not at random. In other words, if there is differential loss to follow up in the control arm versus the intervention, or amongst people who are more unwell. If the missingness is at random it can still cause a problem. It has been proposed that less than 5% missing data is not problematic but more than 20% poses serious threats to validity – yet in some cases even less than 20% completion rates is a problem [4]. When data is missing, statistical analysis methods (such as complete case analysis or imputation) are used to address the problem. However it seems much more sensible to mitigate problems of missing data by designing effective approaches and strategies to maximise data collection. Without effective ways of reducing loss to follow up, trials currently include inflated sample sizes at baseline to allow for trial participants who will not be retained. Therefore, recruiting extra participants to account for low retention is a resource poor solution which costs more, takes longer, but ultimately potentially exposes additional patients to risks they needn't be exposed to or forgoes the opportunity to provide effective treatments.

A Cochrane review that aimed to identify interventions to improve retention in trials identified a range of studies using various approaches. Yet the only intervention with good evidence of benefit was monetary incentives to improve response to postal questionnaires [3]. It is of interest that most of the studies included in this review do not report patient involvement in the identification or development of the interventions under evaluation. This begs the question as to whether these retention interventions are fit for purpose. A recent synthesis of qualitative studies that explored participant reasons for trial drop out summarised that retention is influenced by a complex interplay between participants own internal influences (e.g. beliefs and preferences) and external pressures of the trial and their own lives [6]. This synthesis also

highlights the need to make participants more aware at the consenting stage of what can be expected by participating in the trial.

A recent study analysed the information potential trial participants are provided with when considering trial participation and focussed on information about retention [7]. Within the sample analysed, only 16% included statements about the value of retention yet 98% frequently reiterated the patients right to withdraw [7]. Investigations of written trial information certainly provide a great starting point to offer improvements. Given the suggestion that patients very much value the wider conversation that these documents seek to support when considering recruitment there has been a ground swell in recent years exploring trial consultations for key aspects of trial recruitment (e.g. balancing options, explaining randomisation etc) [8,9]. This analysis of consultations for discussions of recruitment has been ongoing in some trials for over 25 years and more recently has been developed into a key part of a complex intervention aimed to target recruitment to trial [10,11]. Using this approach of analysing discussions about trial participation between potential participant and clinical staff, our study aimed to explore whether and how discussions of retention are articulated during the initial conversations about trial participation.

Methods

This was a concurrent embedded mixed method study nested within an ongoing parent trial (ISRCTN55215960 and further information here:https://w3.abdn.ac.uk/hsru/C-GALL/Public/Public/index.cshtml).

Parent trial characteristics

The parent trial was a Phase III pragmatic effectiveness trial comparing surgery to medical management for gallstone disease with a proposed total sample size of 430. Patients were approached by a consultant surgeon and/or a research nurse in a UK secondary care setting about participating in the trial. In advance of the trial starting recruitment locally each site received a site set up meeting from the Trial Manager. During this training site staff involved in recruitment of potential trial participants were informed of the follow-up schedule (i.e. timing of postal questionnaires) sent to participants and reinforced the importance of discussing this with potential trial participants during informed consent. In addition to these initial meetings, sites received communication from the trial office through Newsletters and Investigator meetings which would target 'live' trial issues e.g. recruitment and retention. During the informed consent

process information was provided to every potential trial participant in a standardised Patient Information Leaflet (PIL) and supported through discussion with either/both a surgeon and research nurse. The written information within the PIL contained a statement that indicated postal questionnaires will be sent for completion. Potential trial participants could take as much time as they needed to make their decision. If a decision to participate was given, participants would be randomised to surgery or conservative management. Once randomised to the intervention, participants would be requested to complete and return postal questionnaires (which were sent centrally from the trial study office) at three, nine, 12 and 18-month intervals. Aggregate response rates across time points for questionnaire response varied from 57-80% at the time of conducting the study. The parent trial has standardised approaches administered centrally through the trial office that aim to improve the return of postal questionnaires. These are as follows. Postal questionnaire for the desired time point is issued and if no response at 3 weeks a reminder letter is issued. Following a further 3 weeks, if still no response a telephone call is implemented. If the call is unsuccessful then a final reminder is issued.

Recruitment and Sampling

The parent trial had already received ethical approval for the audio-recording of trial consultations as part of the ongoing qualitative evaluation embedded at the trial design stage**.** Several trial sites were recording informed consent consultations. Units for sampling were individual sites. A purposive sample of four (out of a total of 18, of which seven were eligible) sites with varying levels of retention (assessed by postal questionnaire response percentage at three and nine months) were sampled to provide a variety of discussions from sites with varying retention patterns. Variability was further generated within our sample - as the audio-recordings included were heterogenous in terms of site, surgeon, research nurses and duration of consultation; in a bid to promote increased generalisability of findings. However, maximum representation and diversity within consultation discussions were not possible due to the sample being convenience derived and time restrain limitations (as being conducted as a Masters degree project). To preserve anonymity, site names were anonymised and were labelled A, B, C, and D. Researchers aimed to analyse the 10 most recent (assuming that analysing most recent practices would be required if intending to implement a change based on findings) consultations where available; however, Site B had not yet reached 10 consultation recordings resulting in analysis of eight from that site.

Data Analysis

The major quantitative data for this embedded mixed methods study was provided by the parent RCT in the form of response rates (presented as %) for the return of postal questionnaires. This data provides information on retention across the trial as a whole and at an individual site level.

Audio-recordings of the consultations were transcribed verbatim and anonymised by redacting identifiable information. Data management and initial analytic coding were facilitated using Microsoft Excel. Analysis first took a deductive approach and entailed coding data transcripts into predefined categorical descriptions (such as 'presence of discussion of retention', discussion of questionnaires', 'discussion of withdrawal', etc) taking a constant comparative approach. The pre-defined codes were developed by all members of the research team based on research aims and informed by existing literature on information that may be important for retention [7]. Initial coding was conducted by PT with 25% check by KG with any discrepancies in agreement discussed with an arbiter (ED). Data was analysed inductively through a broad thematic process to identify overarching similar and divergent patterns across consultations. The development of the inductive themes was led by PT with input and discussion from the rest of the team to agree on the broad framework for analysis.

The qualitative data from the audio-recordings were further transformed into quantitative data using the Quanti-Qualitative Appointment Timing Approach (Q-QAT). Q-QAT quantified time spent on discussions of retention during the trial consultation [12]. Q-QAT data combining cross-case and within-case analysis was made across sites, trial surgeons (TSs) and research nurse (RNs) to observe changes in discussion patterns, information provision and retention rates as per previous descriptions [12]. Consideration of consultation duration (in minutes) was facilitated through descriptive statistics.

Results

Sample Characteristics

Thirty eight audio-recorded trial consultations from four sites were secured. Important to note that 1 participants trial consultation was split across 2 audio-recordings, therefore the 38 recordings represent discussion involving 37 potential trial participants. A total of 44 participants across the four sites were included in the consultations; three research nurses (RNs), four trial surgeons (TSs) and the 37 potential trial participants. Consultations varied across the four sites in terms of health professional present during the consultation, with three out of the four having both a trial surgeon

and research nurse present and one site having only a research nurse included in the audio-recording (see Table 1). Consultations lasted between three and 43 minutes (median 16 minutes). Figure 1 displays the median total duration of consultations (in minutes) by site, illustrating that conversations typically lasted for 20 to 25 minutes, with Site D shorter by approximately 13 minutes compared to other sites.

Time spent discussing retention

Of the 38 consultations, only 8 (11%) included any discussion about trial retention (see Table 1). From these eight consultations where retention was discussed, the proportion of time spent discussing retention ranged from 0.76% to 13.3% with a median of 3.8% across all consultations where retention was discussed (Table 1).

There was variation across the sites as to whether retention was discussed at all and if so how long it was discussed for (Figure 2 presents discussion of retention as a proportion of total consult time). Site A had no discussions of any aspect relating to trial retention present in the trial consultations. The other three sites all discussed retention to some extent across the sampled consultations. When considered as a proportion of total consultation time by site these retention discussions ranged from 0.27% to 2.95% of the total consultation time (Figure 2). The longest discussion about retention within a consultation, from across all sites, was 89 seconds and the shortest 20 seconds. Of the three sites that did discuss retention, some discussed it more frequently than others (see Table 1). Site B performed best with 62.5% of consultations analysed featuring discussions of retention, Site D had 20% of consultations presenting discussion of retention, and Site C with 10% of consultations discussing retention.

Content of discussions about retention

Broad analysis of the content of the consultations covering retention identified that 12.5% contained inaccuracies, 12.5% failed to detail the frequency of follow-up questionnaires to be completed, 25% were discussion prompted by participants, and 50% contained an imbalanced focused on patient's rights to withdraw.

When considering details of how retention was discussed across consultation included in this analysis, we identified examples of 'good' and 'could do better' practice. To first consider the 'could do better', these discussions largely focussed on process based information relating to the timing and purpose of questionnaires or on the participants right to withdraw.

Timing and purpose of questionnaires

Across all consultations where retention was discussed the timing and purpose of the questionnaires was mentioned. Some specified all time points (3, 9, 12, 18 months) and stated the mode of delivery (postal questionnaire) where as others provided incorrect information or were more vague about mode or indeed which participants would be followed up.

"So with the quality of life, I mentioned there was a baseline - and with those forms you'll get sent one 3 months, 9 , 12, and 18 ….." "They will be very similar to the baseline ones if you want to go into the study. And the study centre will send those out" Research Nurse Site B

'*Surgeon: Umm I mean you can always say uhh uhh that ah regardless of which treatment group you do - the study allocates to you , for example if it says observation then uh you will uh will require observation in about 3 months' time. Is that right?" (Doctor asking research nurse)*
Research Nurse: "Umm yeah, we just send you the questionnaire by email or by phone - so you will just answer them every couple of months. That's all we will do. There is nothing where you physically have to come or need to be examined or anything like that" Site C

"*Emm what we do is that we send you a questionnaire in the post. 3, 6, 9, 12, and 18 months. So it's every 3 months you get questions in the post. Kind of day to day thing about how your pain is and things and such. It does not involve another visit back for us. Emm, If you do get randomized to surgery – emm, it's a kind of a standard way to check for that. And then we also send you the questionnaires in the post as well.'* Surgeon Site D

Participant's right to withdraw

Within the limited conversations about retention there was time spent highlighting to participants that they had the right to withdraw from the trial at any time, that there decision was flexible but without providing any information on the consequences.

"*Like Mr X said, it is a randomized controlled study - so if somebody agrees to go into the study there is some baseline information that we do when they consent. So there is a consent process that I'd go through. Umm a consent form that you fill in. And you can withdraw your consent at any time. So if you fill in your consent from today, decided you wanted to do it - and then went home, thought about it - and thought, actually no this isn't right for me; you can withdraw at any time. Umm and again with the follow ups - so the follow up questionnaires you can always decide that when life gets busy and get in the way - if you decide actually, oh I've not got time to do these questionnaires, or*

too much other things going on - again you can choose to withdraw from the follow up as well. So if you decide to go into the study it is not set in stone. You can withdraw at any time alright?." Research Nurse Site B

There were some examples of 'good' practice within the consultations analysed. As previously highlighted informing participants of the timing and mode of delivery of the questionnaires was one. Another was sharing the questionnaires with participants during the consent discussion to give them an idea of what was expected of them.

"*With the follow-up, it's the same for both arms for the questionnaires. I will show you a copy so you know what is expected of you. This is the baseline. But it is the same for all of them. There is no massive essays. It's a tick box - and I don't know if you want to have a look through that. Umm it's all about the general health, following activities of daily living, discussing pain…"* Research Nurse Site B

Another example from the conversations during the consent process highlighted that completion and return of the questionnaires can also be considered as a proxy for continued consent to the trial.

'That's pretty good, perfect! And the questionnaire don't forget the questionnaires. In a way that is kind of confirming your on-going consent' Surgeon Site B

Participant prompted discussions

In addition to the examples of 'good' and 'could do better' practice identified within the consultations, there was also a sense that some of the conversations (2 out of the 8) relating to retention were prompted by potential trial participants. One potential trial participant was concerned about whether participating in the trial would affect pre-planned travel. With another asking abut what the expectations were across the course of the trial.

Impact of discussions of retention on consent to the trial

As these consultations are audio-recorded when the trial is introduced to the potential participant and a decision about participation is made, we investigated whether discussions of retention were associated with decisions to participate in the trial. The majority (n=22, 60%) of the participants included in the sample for this study declined participation in the main trial (Table 1), which is consistent with overall figures for recruitment to the trial over its duration. Of

the 15 participants who did consent to participate in the main trial, seven of these consultations (47%) included discussions of retention where as eight (53%) did not. However, if we consider the participation behavior of those participants for whom retention was discussed (a total of eight consultations), seven (87.5%) went on to consent to trial participation and only one (12.5%) declined. Unsurprisingly the majority of consultations fell into the category that did not consent to the main trial and did not discuss retention (n= 21, 55 %) with only one consultations across the 38 declining participation in trial where the consultation included a discussion of retention (see Table 1).

Impact of discussion on retention to return of postal questionnaires

To determine whether duration of retention discussions was linked to return of postal questionnaire we rank ordered the sites according to duration of retention discussions and compared this to their response rates for questionnaire return to explore potential association. Despite Site A having no discussion of retention in relation to total consult time (0%) (Figure 2), it had the greatest questionnaire response of 98% at three months and 81% at nine months (Table 2). Site B had the highest proportion of consultation time devoted to discussions about retention and was ranked second in terms of questionnaire response (80% at both the three and nine months). Whilst sites C and D discussed retention (albeit at a limited level), the questionnaire return rates were also poor at both time points. See Table 2 for site summary of consultations with discussions of retention and postal questionnaire return. There was no indication of an association between duration of discussions of retention and overall questionnaire response rates across sites. However, it is of interest to note that Site D, who had the lowest median consultation time, also performed the worst with regard to overall questionnaire response rates.

Discussion

Key Findings

We believe this to be the first embedded mixed method study to investigate clinical trial consultations for discussion of trial retention. Key findings revealed a lack of discussions of retention across the majority (79%) of consultations analysed. Furthermore, the findings suggests that almost half of the consenting participants were not provided with opportunities to discuss aspects of retention that may be important for their decision to participate. Of the 21% of consultations where discussions of retention were present, some contained inaccuracies, lacked critical details, required participant prompting and contained an unbalanced focus on participant's rights to

withdraw. All of this brings into question the adequacy of trial consultations in supporting informed choices about trial participation.

Our findings resonate with data from a recent study that analysed 50 patient information leaflets (PILs) for clinical trials across a cohort of publically funded UK based RCTs [7]. This analysis of PILs identified that retention is often poorly described within this written information with an unbalanced focus on the patients right to withdraw (present in 98% of the PILs analysed) without having to give a reason (90%) [7]. Contrastingly, only 16% of the PILs analysed included statements on the value and importance of retention [7]. This focus on the right to withdraw without providing information about the consequences of such behaviour for the trial mirrors the findings from our study with regard to the verbal information provided in the consultations. This echo chamber effect may not be that surprising if we consider that much of the international guidance relating to informed consent for clinical trials (from the Declaration of Helsinki) does not go further than specifying that trial participants 'must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.' [13]. This is also specified in the ICH GCP legislative guideline on informed consent for trials but it does also state that participants should be informed of the 'expected duration of their participation' – which does talk to aspects of retention [14]. Finally, the guidance on PILs produced from the UKs Health Research Authority highlights the importance of including information that covers what the participant will have to do and what it will mean to them to take part, but does not specify this is in relation to retention, in addition to these previous items [15]. All of these guidance documents are largely considering information provided to participant in written format. In line with this international and national guidance, the parent trial included in our study had minimal written information in relation to trial retention. Whilst this changed as a consequence of the findings of this study, it also allows inferences about discussions of retention and actual behaviour of participants to hold more weight. Therefore,expectation setting and discussions about consequences of poor retention perhaps need to be framed in a conversation. There may be promise in using a summary sheet of the key aspects for discussion (which would include retention and its importance) as a prompt to remind staff but also as a take-away reminder for the potential participant within the PIL.

A recent priority setting exercise with the trials community to identify research questions of importance for retention in trials has also identified the issue of what information should be communicated to potential trial participants to improve retention as a top 10 priority for future research [16]. Linked to this explicit priority on information needs, other priorities were identified

(by patients, trialists, clinicians) that also implicitly require information and conversation during the informed consent process e.g. 'how does a participant's ongoing experience of the trial affect retention?' and 'what motivates a participant's decision to complete a clinical trial'. Efforts to address these linked priorities could enable better expectation setting from the outset for potential trial participants about what they can expect from the trial and what the trial can expect from them across its duration.

We highlighted that there is a tendency for trial teams to highlight the right for participants to withdraw at any time without giving a reason but there was no matched information on the consequences of what that means for the trial. A requirement for including information about the consequences of not completing a trial, or possibly reframed as the potential benefits of completing all follow up activities would also link back to expectation setting. Evidence from the treatment and screening decision making literature supports the notion that to enable informed choices to be made, patients must be aware of all of the consequences relating to the decision they are considering [16]. In the context of a clinical trial, this would include information about participating or not and completing the trial or not. Preliminary evidence suggests that the inclusion of this type of information has a positive impact on reducing trial drop-out rates but more research is needed [17]. The acceptability of including this type of consequential information in PILs has been explored amongst a range of stakeholders [18]. It was shown that Ethics Committee Members felt this type of information could be perceived as potentially coercive however patients felt the information was well balanced and supported decision making [18]. Therefore, any adjustments to the retention information with a focus on consequences would need buy in from a range of stakeholders. Further analysis of trial consultations to explore whether the decision to participate (if expressed early in a consultation) then goes on to predict whether discussions of retention (and indeed other important aspects of trial participation) are discussed and the duration of these discussions. In other words, is non-consent also as informed as consent in these settings.

Our study focused on the verbal information provided in the initial trial consultation and showed that this was lacking with regard to retention. Whilst appropriate written information can act as a framework to support this conversation, training for staff involved in these discussions would also be key. Recent studies have highlighted the need to support and train staff involved in retention noting that the focus on recruitment can be detrimental to this endeavour [19]. There are now well established programmes to train health professionals to recruit to trials [20]. This training has been shown to be associated with an increase in health professionals' self-confidence in discussing RCTs

and an increase in recruitment to trials [20, 21]. However, to date, these training packages have largely focused their content on recruitment. Including key aspects of retention (e.g. potential research set backs caused by missing data and the significance of completing follow-up procedures) as a core component of this training would be a valuable addition. Careful consideration in relation to outcomes of importance for these training packages is also required. To date, outcomes have focussed on trainer related or trial specific outcomes [20]. Yet some assessment of how the process was for the potential trial participants should also be central if considering aspects of the informed consent process. Work in this area to determine a core outcome set for evaluating interventions to improve informed consent to trials is ongoing [22].

Strengths and Limitations

The main limitation of the study is that the analysis included a sample of conversations from one trial. Significant further work involving a larger sample size (aggregated across several trials from varying contexts) that is sufficiently powered to detect any difference would be required in order to determine causality. This study does not claim to present any causal inference, but rather is an initial exploration of whether and how retention is discussed in initial consultations about clinical trial participation.. In addition, no assessment of data saturation was made (largely due to the minimal data available within the discussions) and therefore analysis of a larger number of consultations would be required to promote generalisability.

It is of particular importance to note that all trial follow-up was captured through postal questionnaires which were administered through the trial study office and not a responsibility of the trial teams involved in the initial trial consultations. Therefore it could have modified the sense of responsibility with regard to follow up. In addition, it might be that recordings of the consultations may not have captured the entire trial conversations that occurred between potential participants and the site trial teams. Therefore, it is possible relevant data was missing from the data collected. However it is important to highlight that during the trial initiation training given to all sites it is specifically requested that audio recordings capture the entirety of the consultation.

Embedding a mixed-methods methodological evaluation within a clinical trial context maximises opportunities to identify (and resolve) problems with trial conduct. A significant strength of this piece of work is the real time capture of data during trial consultations to analyse discussions about retention, rather than relying on personal accounts of the process in interviews after the event. In addition, by investigating consultations from a multi-centre trial with various sites we were able to examine an array of generic and site-specific discussion inadequacies. Hence, such features may be likely to be transferable to other trials in other settings.

Conclusion

This research provides evidence of the lack of discussion about trial retention during consultations for a surgical RCT. It Ddraws further impetus to calls to focus on retention during recruitment and not just worry about it when it becomes a problem. Ways to tackle these deficits could include changes to the written and verbal information provided to participants during the initial consultation, training for staff to ensure key aspects are covered, discussions with regulatory and oversight bodies to ensure recommendations are deemed appropriate, and generating interventions that are centred in accounts from participants. Getting some of these solutions in place will allow trialists to design and deliver trials that retain the participants they work so hard to recruit.

What's New

Our study has revealed that trial staff may provide imbalanced information abut retention during the consultation process for potential participants. Thus, adjustments must be made to the current consultation style and supported with adequate written information. It should be noted that equal time should be spent discussing all key issues listed, alongside participants rights and responsibilities to ensure coercion is avoided. Previous studies have cited the need for recognition of the importance of retention (in addition to recruitment) from funding bodies and oversight

organisations, we would also echo this call [19]. Such a shift in expectations at the highest level, may provide clinicians the encouragement to adjust the on-going strain between upholding informed decision-making for participants and meeting target recruitment. Thus, a shift in priority could inspire a clinical trial culture concerned with maintaining consent (and the communication strategies to do so) as opposed to simply obtaining it.

Further research replicating this study across a range of trials is welcome and needed to ensure the findings presented here are replicable and transferable to other settings. In addition, exploring how best to communicate information relating to retention with participants should also be a recommendation going forward. Ultimately participant-centred retention interventions should be developed that are embedded in participants accounts and co-designed with those who are the end-users.

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Ethics approval and consent to participate

This study was approved through the parent trial from NHS North of Scotland Research Ethics Committee (16/NS/0053). Informed consent was obtained from all participants.

CRediT Author Table

	PT	ED	KG
Conceptualisation			■
Methodology	■		■
Formal Analysis	■		■
Investigation	■		
Data curation	■		
Writing – Original draft	■		■
Writing – Review and Editing		■	■
Visualisation	■		■
Supervision		■	■
Project Administration	■		

Declarations of interest

None

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