CONSIDERATIONS AND METHODS FOR PLACEBO CONTROLS IN SURGICAL TRIALS

STATE OF THE ART REVIEW AND ASPIRE GUIDANCE

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ABSTRACT

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of surgical interventions. The aim of this paper is to provide a summary of current knowledge on placebo controls in surgical trials.

A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting. This review outlines what a placebo-surgical control entails and our understanding of the placebo phenomenon in the context of surgery. It considers when placebo-surgical controls are acceptable (and when they are desirable) in terms of ethical arguments and regulatory requirements, how a placebo-surgical control should be designed, how to identify and mitigate risk for participants in placebo surgical trials, how such trials should be conducted and interpreted.

Use of placebo control is justified in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale. Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that results of a trial would be associated with high risk of bias, particularly due to the placebo effect. Feasibility work is recommended to optimise RCT design and conduct. This review forms an outline for best practice and provides guidance, in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist, for those considering the use of a placebo-control in a surgical randomised controlled trial.

INTRODUCTION & BACKGROUND

Compelling evidence of efficacy and safety should underpin all routine clinical therapies, ideally based on data from randomised controlled trials (RCT), and surgical therapies are no exception. Whilst an RCT comparing surgical treatment to ***no*** surgical treatment provides evidence of overall efficacy, it fails to account for certain biases, especially placebo. These potential biases are

particularly high for surgical interventions, where placebo effects have been shown to have substantial magnitude and duration, often amplified by the particular context of surgical care [1,2]. A surgical placebo control can be used to minimise bias but its use can be controversial as it poses potential risk to the patient with reduced potential benefit and presents ethical, design and trial conduct challenges.

Previous reviews have been conducted of placebo-controlled surgical trials [2-4] including their use, issues of recruitment and feasibility, and impact on outcome and serious adverse events [5,6]. These reviews have not, however, explicitly considered issues of trial design such as definition and content of placebo, when it is appropriate to use (or not use) a placebo control in a surgical trial, what factors should guide the choice of a placebo design and how that choice influences intervention standardisation. Some information on the ethical implications of surgical placebo trials is available [7-12].

This review aims to provide state of the art knowledge on all aspects of placebo controls in evaluation of surgery. The insights are primarily based on the outputs of a workshop funded by the UK's National Institute of Health Research and Medical Research Council which brought together an international team of interdisciplinary experts with a strong track record of research in this field. The workshop included a systematic update of salient literature, in depth discussion of case studies and exposition of direct experience and best practice. The work culminated in the production of practical guidance for researchers; the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist. We have restricted our focus to studies of adults with capacity to consent to participate in surgical research.

WHAT IS A "PLACEBO" IN THE CONTEXT OF SURGICAL TRIALS

Understanding the placebo phenomenon

Placebo effect knowledge is dominated by two main psychological theories, both of which apply to surgery. These are broadly labelled: 1) "conditioning", a learning theory in which placebo effects are underpinned by associative learning with the placebo paired with an active treatment to trigger a physiological response; and 2) "response expectancy", where the placebo effects are underpinned by the patient's conscious or unconscious expectation that the placebo will have a particular effect [13]. Colloca and Miller integrated the learning and response expectancy theories to suggest that patient expectations are the central psychological mechanism that mediate placebo effects [14]. According to this model, the brain decodes the psychosocial context, formulating (conscious or unconscious) expectations about outcome that then trigger placebo responses. In turn these expectations are shaped by learning mechanisms around three types of "signs" (signs are things that convey specific meanings to individuals) in the psychosocial context [15]: 1) **indices** which generate expectations through sensory or memory-based associations for individuals; in essence a conditioned response [16]; 2) **symbols**, which generate expectations through culturally-specific conventions including language, ritual and doctor-patient communication [17]; and 3) **icons** which generate expectations through perceived similarities with the object, in short, expectations through social learning mechanisms [18].

The manner in which patients are informed about the placebo control also shapes patients' expectations. Any imbalance in the tone and quantity of information given about the benefits of the index procedure compared to that given for the placebo control can be stark and can influence outcome [19].

Further work has characterised how different domains of the psychosocial context of healthcare are at play in clinical trials and may influence the response to a surgical placebo. These key domains include the treatment characteristics; the healthcare setting; clinician characteristics; patient characteristics; and the patient-clinician interaction. Examples of the ways that they may influence the placebo response is presented in Table 1. [20,21] With regard to the placebo response in general, it should also be noted that there is some suggestion of genetic susceptibility to placebo with biomarkers indicating at least a moderate influence of genes on placebo response[22]. Furthermore, a largely unexplored aspect of placebo is the geographic and cultural differences in patients that could influence a response. Both such factors would apply to surgical placebos similarly to that of pharmaceutical placebo but would also apply equally across groups in a randomised design.

Definition of a surgical placebo

In this paper, surgery is defined as an invasive procedure using any access to the body (incision, natural orifice or percutaneous), includes use of instrumentation and operator skill [23]. One important distinction to highlight is between the concept of placebo for evaluation purposes, as in an experimental placebo control (as described in this paper), and the notion of purposely using placebo for benefit or treatment.

A clear definition of experimental placebo is lacking for surgical trials and classical definitions can introduce conceptual confusion rather than clarity. The blurred lines for *surgical* placebo are epitomised by the various descriptions in the literature. These vary from "a surgical intervention with theoretically little benefit"[5] to "sham" surgery (entirely simulated surgery or small superficial incision only)[24] to a "placebo surgical intervention", a procedure in which presumed "active" components of the procedure or the critical surgical element have been removed [25]. In the latter, the "placebo surgical intervention" consists of routine delivery of most of the operation, but with exclusion of the presumptive "active component". However, identification of, and conceptual clarity in defining the "critical surgical element" in surgery can be far from straightforward.

Rather than using the all-encompassing and generic "placebo control" to describe any form of placebo content, greater clarity can be achieved by describing the placebo control in terms of its *fidelity* or proximity to the complete surgical procedure [26]. Varying levels of fidelity are possible from *low fidelity*, in which there is little similarity to the complete surgical intervention (i.e. skin incisions only, thus resembling what surgeons would have traditionally described as a "sham" treatment) all the way to treatment with a complete set of surgical attributes, viz. *maximum fidelity* (i.e. the surgical procedure under evaluation). In between these extremes a *high fidelity* placebo may have identical surgical content and attributes to the complete surgical procedure but solely without the presumed active or critical component. A *medium fidelity* placebo may have fewer surgical components and less resemble the complete surgical procedure (Table 2).

For example when evaluating the efficacy of arthroscopic subacromial decompression of the shoulder various choices for the placebo control exist. *Maximum fidelity* is the complete decompression surgery; a *high fidelity* placebo may be identical surgery but without removal of bone only; a *medium fidelity* placebo may be very similar surgery but without removal of bone/soft tissue and lacking some other operative procedures i.e. just the insertion of an arthroscope; and a *low fidelity* treatment being surgical skin incisions only. Similarly, in a study of endoscopic radiofrequency ablation in patients with dysplastic Barrett's esophagus the normal or maximum fidelity intervention involved ablation using a catheter. Patients randomised to the placebo intervention group underwent a lower fidelity procedure involving upper endoscopy, esophageal intubation and measurement of esophageal inner diameter only.[27]

It should be noted that this working framework is dependent on the theoretical premises of the operation and postulation of a "critical surgical element". This is not always possible, especially with surgeries that create effect by a multi-modal or dependent set of procedures.

WHEN ARE PLACEBO-SURGICAL CONTROLS ACCEPTABLE?

Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that the results of an open trial would be associated with high risk of bias.

Ethical considerations are fundamental to the decision as to whether one can use a surgical placebo control. Patients participating in a placebo controlled surgical trial are exposed to the risks of a surgical intervention that lacks the presumptive causally effective element (i.e. the critical surgical element). Participants are, therefore, potentially being exposed to some of the risks of surgery with less of the perceived benefits. Ethical standards suggest, however, that exposing research participants to such risks is allowed provided equipoise exists among the study arms, study harms have been minimised and are acceptable to the participant [28,29].

The use of a placebo control in a surgical RCT is consistent with the ethical principle of beneficence provided the benefits and harms posed are reasonable and risks are offset by the social value of the study [7]. One way to determine whether the benefits and harms of a trial are acceptable is to perform component analysis [30]. In component analysis, a trial's therapeutic procedures must be considered separately from its nontherapeutic procedures. However, in surgical placebos this separation is not straightforward as a placebo intervention lacking the critical surgical element may nonetheless induce physiological changes in the patient. Thus, we distinguish between the placebo control that includes warranted therapeutic procedures, in which the prospect of direct patient benefit is supported by evidence, and nontherapeutic procedures, in which no such warrant exists and the procedure is conducted for scientific purposes.

The analysis of benefits and harms in placebo controlled surgical trials is further complicated by the fact that the placebo control includes both warranted therapeutic and nontherapeutic procedures. To address this, a two-step ethical analysis is required. First, one must consider whether the use of any placebo control is justified i.e. whether equipoise holds in the face of a placebo control. Equipoise is defined as "a state of disagreement or uncertainty in the informed, expert medical community about the relative clinical merits of the intervention arms in a trial" [31]. Disagreement or uncertainty should be understood in terms of the state of evidence rather than unsubstantiated opinion. If equipoise exists, then it does not matter to the surgeon which trial arm the participant is placed into; given the state of knowledge at the beginning of the trial, both arms are deemed to be broadly consistent with competent surgical care [30]. A placebo control is permissible to evaluate a novel surgical procedure in a condition for which there is no proven, effective surgical intervention. Additionally, the case for placebo control design for surgery becomes stronger when the evidence base supporting a procedure in common use is poor, such as for vertebroplasty [32]. Although the surgical procedure is commonly used, equipoise exists because of the lack of supporting evidence.[32] Thus, in both cases, the use of a placebo control is consistent with equipoise because there is sufficient uncertainty over whether surgery offers any advantage over non surgical management alone.

If placebo is justified, then the appropriate level of fidelity to the surgical intervention must then be considered. To make this determination, two standards are relevant [30]. First, the harms posed by the intervention must be minimized. Second, the risks posed by the placebo intervention must be

outweighed by the value of the knowledge generated. The first standard asks us to consider whether the risks are necessary; the second standard asks us to consider whether the risks are proportionate to scientific value. Research ethics committees commonly struggle with the assessment of scientific value, and use of the "value-validity framework" is recommended. [33] The assessment of scientific value requires that (1) the research question is clinically important, (2) the hypothesis is justified by the current state of evidence, and (3) the study is well situated in a research portolio. [33]

Lastly, the issue of patient consent is foremost in any discussion of placebo surgical trials. Surgical trials with a placebo control are inherently complex studies and conveying clearly to prospective participants what is at stake is a challenge. There is a threat from so-called therapeutic misconception, whereby research participants systematically misunderstand research elements, such as randomization or placebos as being designed to benefit them directly [34]. Full disclosure is therefore imperative to ensure the patient is aware that they may receive a surgical intervention omitting the presumptive critical surgical element. Informed consent must clearly identify which procedures hold the evidence-based prospect of direct benefit (where such evidence exists) and which are primarily performed to further science only. Inter alia, it is important that surgical placebos are not described in therapeutic terms, such as "treatment" or "active" procedures, when there is no clinical indication for the placebo procedure. However, communication to the patient is also required on the well-founded doubts about the efficacy of the 'real' procedure, most often the reason for conducting the trial in the first place.

As placebo surgical trials provide a potentially nontherapeutic intervention additional protections may be indicated. It is important to ensure adequate patient comprehension of the likely (lack of) benefit from placebo allocation to reduce therapeutic misconception.

A variety of techniques have been shown to enhance comprehension in informed consent for research, including enhanced consent forms (i.e. simplified forms developed by an interdisciplinary team involving end-users) and additional discussion time [35]. There is preliminary evidence that the modality (verbal, written, audio-visual) and who (e.g., the treating surgeon or an independent researcher) presents the information may also make a difference to potential trial participants in placebo surgical trials [36]. Formal testing of participant understanding of key elements of consent, especially relevant to the potential participation in a placebo arm, may serve to enhance comprehension and document understanding [35].

There are many arguments around the balance of the cost and financial impact to design, conduct, report and disseminate the findings of a placebo surgery controlled randomized trial versus the continued performance of the surgery in question without high level evidence. This is an ethical subject in itself, however, without such a study, ineffective surgery may continue with costs and resource consumption, crowding out more effective treatments, and with risk to patients for little or no benefit.

How have placebo surgical trials been used?

We undertook a systematic review to update the latest published literature on surgical placebo rationale and methods. The methods are shown in Text Box 1 and more details provided in Supp App 1. The review updated and extended a previously reported systematic review [3] until December 2017. Data were extracted for trial characteristics and methodological areas of interest, including: i) Rationale for use of placebo interventions; ii) Patient information; iii) Intervention standardisation and fidelity; iv) Delivery of co-interventions and anaesthesia; v) Trials offering treatment

interventions to patients allocated to placebo; vi) How risk is minimised because of the invasive placebo. The findings of the review have been written up for publication separately[37] but a brief summary of findings is given below.

Fifty articles were added giving a new total of 96 placebo-surgical RCTs. Most were for gastrointestinal indications (n=40, 42%) evaluating minimally-invasive luminal endoscopic interventions (n=44, 46%). Over two thirds randomised fewer than 100 patients (n=65, 68%) and approximately a third were conducted at a single site (n=31, 32%).

The most common reason given for using placebo interventions was to quantify placebo effects (in response to perceived limitations of previous non-placebo-controlled trials and known/expected placebo effects associated with the surgical procedure under evaluation). Information provided to patients was variable. A small number of trials reported minimal information about standardisation and fidelity of interventions. Two thirds matched anaesthesia protocols between treatment and placebo groups and nearly half of trials offered treatment to placebo patients on conclusion of the trial.

Reporting of the placebo surgery was limited and variable. This suggests there is a need for clearer and more consistent reporting of rationales for placebo use, patient information provision, standardisation and fidelity of interventions, and the use of co-interventions.

How should a placebo-surgical intervention be designed?

An in-depth understanding of the presumed critical surgical element is essential for placebo trial design. Assessment of any potential risks to patients and strategies to ensure the placebo effectively mimics the treatment is also required. As part of the project, we developed a framework to optimise the design and delivery of placebo-surgical interventions in RCTs. The DITTO (Deconstruct, Identify, Take out, Think risk, Optimise) framework was developed from the systematic review of published literature and built on a previously published typology [38] which facilitates the deconstruction of any invasive intervention. Full details of the framework are published separately [39]. In brief, the DITTO framework suggests five stages are required in the formulation of a placebo-surgical intervention (Table 3). Stage 3 of DITTO, involving identification of the critical surgical element, is exampled by an RCT evaluating the use of endobronchial valves in patients with chronic obstructive pulmonary disease. The full fidelity treatment intervention involved endobronchial valves placed bronchoscopically to occlude all segmental bronchi of the target lobe. Patients randomised to the placebo group underwent diagnostic bronchoscopy only without valve placement as this was deemed the critical surgical element of the procedure. [40]

Who is the placebo-surgical trial being designed to inform?

When designing a placebo-surgical trial, it is important to identify at the outset who the trial is attempting to inform. This will influence the overall design of the study including decisions as to whether a third, no-treatment arm should also be included and which outcomes to include.

Policymakers divide into two broad groups – those who issue guidance about how interventions should be used in health care, and those who commission services and pay for them (or reimburse patients in an insurance based model). In most health systems the people who make decisions about service provision strive to maximise the health returns they get for their health care investment. They may value information about the placebo effect of an intervention differently to clinicians and/or patients.

Often guideline producers want to understand how a health gain is generated, and often feel uneasy when a gain is mainly generated through a non-specific placebo mechanism rather than the anticipated anatomical, physiological and psychological processes that the intervention's logic model may suggest. For interventions which may have a significant placebo effect a guideline producer would like to see robust studies which explore that effect (such as a three arm study comparing active intervention, placebo, and usual care – discussed below). This enables them to explore any placebo effect which may inform the guidelines produced, will help inform a payer's decision whether to reimburse a treatment, and suggest further research to explore or modify the intervention [41,42]

Should a placebo-surgical trial have a no intervention arm?

There are four broad possible categories of groups (arms) in a surgical placebo trial: 1) the index surgical intervention being studied, 2) a placebo control (with varying levels of fidelity from simulated surgery/minimal skin incisions to near full fidelity); 3) non-operative care and 4) a no intervention group. The value of a no-intervention arm should always be considered.

Non-operative care has the advantage of reflecting the real-life alternatives (surgery versus a different type of treatment). The disadvantage is that it does not allow testing of any direct or placebo effect of non-critical aspects of the procedure, including patient expectations and concomitant treatments. It provides evidence for most appropriate treatment rather than fundamental efficacy.

A no intervention arm has the advantage of measuring the natural history of the condition without any treatment. It is useful to show how beneficial *any* surgery can be compared with doing nothing at all. A change in outcome may still be observed in a no intervention arm for various reasons (such as a Hawthorne effect and regression to the mean), which will also contribute to the observed effect in all groups. Nevertheless, the absence, or presence of only a modest, difference in the observed effect between surgery and no intervention would cast serious doubt on the value of the surgery regardless of the mechanism. Similar to a non-surgical control, the no intervention group cannot take account of any placebo effect due to surgery and cannot provide any information about the proposed mechanism for benefit. Whether or not the straightforward refutation of the mechanism for the effects of surgery (using a two armed comparison, placebo v normal surgery) is sufficient to conclude on surgical benefit overall remains a matter of debate.

It is argued here that a placebo trial including a no treatment comparison may be scientifically superior but considering the resource requirement, may not always be possible or justified. Two arm surgical trials can also be very useful and informative. A decision on the number and type of arms should reflect the research question and be considered in terms of sample size and analysis, ethics and trial feasibility. A study with the focus on mechanism and an assumed subsequent efficacy can positively utilise a two arm approach. A study wanting to additionally explore the value of surgery overall, regardless of mechanism, is better served by a three arm study with a no treatment control. This is despite the potential for so called "resentful demoralisation" in patients having an unarticulated or hidden preference for surgery.

Finally, in terms of trial conduct, the potential for crossover is most certainly greater in a three arm study with a no treatment control. The threat and implications of this must be weighed against the advantages stated above. A feasibility study assessing both options may be sensible before embarking on a definitive design.

IDENTIFYING AND MITIGATING RISK IN PLACEBO SURGICAL TRIALS

The ethics literature on the use of placebo-surgical controls stresses the need for any potential risk from use of a placebo to be mitigated. The evidence on risk is mixed. The review by Wartolowska *et al*. showed that placebo-surg0ical controlled trials did not appear to carry any greater risk than any other treatment or control group. However, most of the placebo RCTs in that review only evaluated endoscopic or minimal access interventions. A review from the Study Center of the German Surgical Society also found that placebo-controlled serious adverse events were similar between true intervention and placebo groups and raised a concern that trials of more invasive placebo interventions might entail significant risks for study participants [4]. This issue is highlighted by trials such as the ORBITA study in interventional cardiology. The placebo group were in this case found to have a greater number of adverse events than the normal treatment leading to difficulties and contention in interpretation.[43]

Assessing risks of a placebo-surgical control, especially in relation to fidelity, is complex and difficult to quantify. Inert treatments such as low or minimum fidelity surgery may seem to have less risk than a surgical procedure with higher fidelity (in which more tissues may be involved), but this simple model may not hold. For example, those undergoing a placebo-surgical procedure, despite a priori higher risk, may still experience apparent benefit (although not achieved through any known [or theoretically causal] mechanism). Similarly, the apparent “safety” of a minimum fidelity procedure, in which there is little tissue damage, is tempered by the risk of anaesthetic complications. It should be remembered that the risk of any anaesthetic complication or surgical site infection after incision will apply to all groups undergoing surgery and similar anaesthesia (including those in the placebo arm). Discussion should include the situation when a surgical treatment's risks in a "low/minimal fidelity" placebo surgery group can potentially outweigh the benefits of the study findings to society. This can be difficult to reconcile. It is not clear how much risk is “too much” and when a placebo surgery control group trial is "not worth it". It remains a complex area and will depend on individual procedure risk plus routine surgical risk (anaesthetic etc.) with consideration of the perceived capacity to benefit from the specific surgery in question.

Previous literature has suggested various strategies for risk mitigation including:

- Restriction of eligible patients to those with a low clinical risk profile (e.g. restriction to ASA grades 1&2)
- Reducing the invasiveness of the surgical placebo (this forms part of the balance between fidelity and risk alluded to above)
- Review of the form of anaesthesia used for the placebo-procedure
- Use of only highly experienced surgeons
- Enhanced monitoring with oversight committees

It is important, therefore, that all means of risk mitigation are explicitly outlined before undertaking a placebo control surgical trial. Where the overall risk of any placebo-surgical control is deemed to be unacceptably high (despite all possible risk mitigation strategies) a placebo-controlled design should not be used. However, without a sufficiently robust trial the surgery may continue unabated with all patients continuing to be subjected to all risks related to the procedure. In this situation, the more risky the procedure, the more urgent the need for a sufficiently robust (placebo-surgical) trial.

TRIAL CONDUCT ISSUES FOR PLACEBO- SURGICAL TRIALS

There are a number of key considerations which must be accounted for in the trial conduct phase.

Nomenclature for patients

The nomenclature for patients in placebo-surgical trials is important and patient representatives are uneasy with descriptors such as "deception" and "sham" for surgical evaluation [44]. Whilst such terms may often be seen in a scientific or trial design context, they are less acceptable to patients due to their negative connotations and should be avoided. Reporting guidelines under TIDieR (Template for Intervention Description and Replication) are currently being updated for placebo control (Personal communication, J Howick).

Informed consent

As identified earlier, as placebo-surgical trials pose an unusually high degree of nontherapeutic risk ensuring enhanced information for informed consent is important. It is proposed that consenting material would include, but not be limited to:

- A full description of the placebo-surgical procedure;
- A statement that whilst benefit may accrue through undergoing a placebo-surgical procedure, that there is no known mechanism by which the placebo surgery should result in direct benefit for the index complaint;
- Recognition that the use of the placebo-surgical procedure is for research purposes;
- The need to avoid language in the consent process that may unwittingly promote any therapeutic misconception;
- Possible risks or discomforts linked to both index and the placebo-surgical procedure

The proposed level of fidelity of the placebo control can be helpful in deciding what information should be communicated to potential placebo surgical trial participants. The concept helps avoid therapeutic misconception in trials of this type. Any information should also clearly describe the standard index surgical procedure for the condition should they not participate in the trial and outline the known benefits and risks of this standard surgery.

Recruitment

Maximising recruitment for a placebo control surgical trial is an important concern. A previous systematic review found that slow recruitment, due to difficulties finding eligible patients who agree to participate, was the major barrier to successful trial completion [5]. The wider literature has also noted that individuals can hold inherent beliefs and preferences about surgery as an intervention per se, which may consequently affect their willingness to participate in a placebo-surgical trial although this can be measured and accommodated for [45]. Randomisation, however, ensures that any such confounder (and indeed any other unknown confounder) is balanced across intervention arms.

There are many reasons for poor recruitment to placebo surgical trials but the testing of treatments that are already widely accepted, available and affordable, despite an absence of high certainty evidence supporting their use, is often cited. In such a case, it has been postulated that both surgeons and patients may be reluctant to accept a 50% chance of placebo (for a two arm trial), particularly when placebo involves invasive surgery. This could be partially mitigated by inclusion of a third arm non-surgical treatment although this would increase trial complexity and cost.

Strategies are being developed to improve recruitment for surgical placebo trials. Recruitment communication planning is crucial. This involves identifying and engaging all relevant stakeholders, identifying where people seek treatment and information, developing and testing tailored messages and creative materials, selecting appropriate delivery channels and messengers, and monitoring and evaluating process and performance. Donovan *et al.* [46] have developed the Quintet Recruitment

Intervention for optimising recruitment and informed consent into trials based upon identification of the motivators and barriers for trial participation. Increasingly, business models and modern marketing theory and techniques have also been used to inform strategies for recruitment [47-49]. The idea is to achieve public buy-in by highlighting prestige and legitimacy, both signalling worthiness of the placebo design. Empirical work has shown that when well informed, patients can be willing to take part in placebo-surgical trials and highlight many positive reasons for doing so[44]

Although it is known that the preferences of patients and health professionals, including surgeons, can have a decisive influence upon trial recruitment [50] many questions remain unanswered [51]. These include whether transmission of preference can be mitigated if consent is obtained by trained and ideally neutral recruiters; whether well-informed patients are more or less likely to accept randomisation; and whether or not surgeons should be allowed to restrict randomisation to eligible patients only when personally uncertain as to which intervention would be the best option for an individual patient [50]. Patient engagement is also critical to the future value and success of placebo controlled surgical trials. In particular, patient representatives can help with identifiable issues such as the 'unblinding' stage and how patients know both when and how they can access this information.

One of the strategies observed in the recent review was to offer participants randomised to the placebo control group the 'active' intervention once the primary endpoint for that individual has been assessed. Whilst this approach appears ethical and is commonly used, it essentially exposes the patient to more risk (i.e. the risks associated with the placebo surgery and then from an unproven intervention). For this reason, (and unless clinician autonomy appropriately overrides trial convention) the offering of the definitive treatment should likely be reserved until after a final analysis.

The issue of quality control also arises for the surgical procedure. If information on mechanism is required (and it mostly is from these studies) then the surgery should have a definite minimum quality and be performed by experienced surgeons. The "can it work" question tends to trump the "does it work" question and this mandates the use of highly competent surgeons. Evaluation of surgical quality of all surgeries performed in such studies may be needed for validation.

Involvement and engagement of other key stakeholders

The public needs to be better educated about surgical evidence and, despite several strong initiatives to improve the situation, there remains a lack of high quality evidence for surgical procedures. Engagement and acceptance from the public that these trials are required is essential. Previous research has highlighted the importance of identifying and engaging key stakeholders beyond the inclusion of the surgeon (e.g. patients, anaesthetists, operating theatre teams, ward nurses. health service managers, and policy-makers) from the outset [6]. For example, anaesthetists are key clinical stakeholders and are crucial in decisions as to how risk can be minimised in the placebo-surgical intervention. The peri-operative period is where the greatest risk to patients lies in placebo trials and therefore the area where the greatest focus comes from clinical, ethical, regulatory and other risk management stakeholders.

INTERPRETATION AND TRANSLATION INTO CHANGE OF POLICY AND PRACTICE

In over half of the placebo controlled trials of surgery so far reported in the peer reviewed literature the results have shown no benefit of the definitive procedure over the placebo control [3]. In many others the placebo effect remains strong but sits alongside a small but genuine treatment effect from the procedure. The presence of some effect from the index procedure is, perhaps, not surprising bearing in mind the ethical and academic justifications required for the use of a surgical placebo

control. Justifications must include some reasonable preliminary evidence that part or all of the treatment effect of the surgical procedure under investigation might be due the placebo effect.

The investigators responsible for undertaking and reporting such trials must, therefore, anticipate that the results of the trial will be disruptive to accepted clinical care pathways and guidelines. Investigators should also expect, and be prepared for, push-back and resistance from clinicians and patients whose beliefs and convictions are being challenged by the results. Such trials will also generate interest from other stakeholders including payers (state and insurance based), press and the media. There may be an argument to call for an increase in the use of placebo controls for RCTs in surgery to elucidate mechanisms and eliminate redundant procedures.

Experience with placebo controlled trials of knee arthroscopy suggest there can be a significant lag between evidence becoming available to a significant change in practice. In the case of knee arthroscopy for osteoarthritis the original publication was in 2002 yet it has taken 15 years for the findings to be partially adopted [24]. Similar resistance from the clinical community has been encountered with trials of vertebroplasty for osteoporosis [52] and, more recently, subacromial decompression for shoulder pain [25]. Consistent features of the resistance are, firstly, a belief by members of the surgical community that the patients recruited to the trial do not represent the usual population undergoing the procedure and, secondly, an assertion that the surgeons involved in the trial were not sufficiently expert in the procedure. In other words, the trial results "do not apply to me and my practice". An illustrative example of this was the response from 15 combined Surgical Associations of a single country to the CSAW placebo-controlled trial for subacromial decompression surgery [25] which stated that "contrary to previous reports, the CSAW trial does not provide any new insights" and "for [this institution's] Health System there are no consequences from the CSAW study". In contrast, the National Health Service in the UK, short of de-implementing subacromial decompression, moved to categorise the procedure where it can only be provided if pre-conditions are met.

In anticipation of these issues, it is important to plan for the implementation and impact of findings with full engagement of all the relevant stakeholders, from the outset including key leaders in patient groups, professional associations and clinical communities involved in routinely delivering the treatment under investigation. If the results are likely to have global implications then an international approach to evaluation should be adopted. Insights from implementation science are also particularly relevant in this regard, with a range of theory-informed and evidence-based strategies available to help address expected barriers to behaviour change [53].

Once the results are known, then the implications for shared decision-making and clinical practice should be explored. Advice for patients should include information about the likely benefits of both the definitive and alternative treatments.

KEY MESSAGES

Our review has described how placebo controls may justifiably be used in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale for the study. A surgical placebo control is not appropriate for all evaluations of surgery. They may be best reserved for operations associated with lower surgical complication risk, potentially low efficacy, unjustified usage, and where a significant placebo response is expected. Against a complex set of ethical issues, it is particularly important that these trials have the greatest possible chance to answer the primary research question in a robust manner (high internal validity) with high generalizability for the relevant clinical community (high external validity). New surgical procedures of unknown value should also be

evaluated and may benefit from placebo control investigation. It is important, however, that they are designed appropriately and that any risks associated with the placebo-surgical control procedure are mitigated. Considering levels of fidelity to the index surgical procedure provides a useful lens through which to conceptualise the construction of a surgical placebo together with associated benefits and risks. A practical checklist (ASPIRE – **A**pplying **S**urgical **P**lacebo **I**n **R**andomised **E**valuations checklist), which summarises the learning points from the review and represents a minimum standard which researchers should attain and demonstrate when designing a placebo-surgical trial, is presented in Figure 1.

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CONTRIBUTIONS

All authors, except JB, JS and MF attended the workshop and contributed to the development and content of the manuscript. All authors (including JB, JS and MF) reviewed, contributed specific expertise and edited the manuscript prior to submission.

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Table 1: Influences of different domains of the psychosocial context of healthcare on the placebo response

Contextual domain	Example relevant to placebo-surgery
Treatment characteristics	A placebo-surgical control that is highly similar in its characteristics to the "real" procedure may influence participants' response to the placebo procedure
Healthcare setting	Having a placebo-surgical procedure conducted in an operating theatre, with all the enhanced procedures that entails, might affect participants' response to the placebo
Clinician characteristics	Participants' placebo response may be influenced by the perceived high status of the practitioner (the surgeon) performing the placebo procedure
Patient characteristics	A patient's previous experience of undergoing surgery and how it affected them might influence their response to a surgical placebo
Patient-clinician interaction	Where the surgeon has detailed and extensive interaction with the patient, this may influence their level of response to the surgical placebo

713 **Table 2: Levels of fidelity to the complete surgical intervention for placebo surgical trial design.**

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Fidelity		Descriptor
The index procedure		Complete surgical intervention as specified for evaluation in an RCT
PLACEBO	**High** fidelity	Near complete attributes of the index procedure
	Medium fidelity	Intermediate attributes of the index procedure
	Low fidelity	Few attributes of the index procedure
No surgery control		No attributes of the index procedure.

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717 **Table 3: Stages of the DITTO framework**

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DITTO Stage	Description
Stage 1	**Deconstruct the treatment intervention, including the co-interventions.** The updated typology is used to deconstruct the treatment intervention resulting in a comprehensive list of treatment components and steps, including co-interventions.
Stage 2	**Identify the critical surgical element;** The critical surgical element (which could be one or more components or steps) in the surgical intervention is established and thus which treatment components/steps are included or not in the placebo intervention.
Stage 3	**Take out the critical surgical element:** The critical element is omitted from the proposed placebo intervention.
Stage 4	**Think risk and feasibility** Once the critical surgical element has been omitted it is important to take account of potential risk to patients, feasibility and the role of the placebo intervention within the RCT (e.g. as a control intervention to elucidate treatment mechanism). This may result in further components or steps being omitted from the placebo intervention.
Stage 5	**Optimise placebo:** The use of placebo optimisation strategies are to be considered throughout the design process (e.g. sensory masking).

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721 Text box 1. Methods used in the systematic review of placebo-controlled trials of surgery[37]

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Systematic review methods

Eligibility criteria

Articles reporting RCTs (including long-term follow ups and protocols) comparing an invasive procedure with a placebo procedure in living humans were included. Pilot RCTs retrieved by the review update search were included as a source of potentially useful information about methods. Interventional procedures that change the anatomy and requires a skin incision or the use of endoscopic techniques were included. 'Placebo' referred to a surgical placebo, a sham surgery, or a procedure intended to mimic the active intervention. Excluded were RCTs that assessed medicinal products or dental interventions, non-randomised studies, reviews, editorials, letters and conference abstracts.

Searches conducted

Articles identified in a previous review [Wartolowska 2016] published between database inception and 14th of November 2014 were included (n=63). Searches using the same search terms and electronic databases (Ovid MEDLINE, Ovid EMBASE and CENTRAL) were conducted to identify RCTs published from 15th November to 31st December 2017. Additional articles, with no restriction on publication date, were identified by hand searching references of included articles and expert knowledge.

Screening articles

All articles retrieved from the current search (November 15th – December 31st 2017) were imported into an Endnote database (EndnoteTM, version X8.0.2). Titles and abstracts were screened for eligibility and full texts of potentially eligible articles were retrieved to confirm eligibility. Screening was conducted independently by two reviewers.

744 **Figure 1: ASPIRE checklist for the design and conduct of placebo-surgical controls in randomised**
745 **trials**
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ASPIRE Checklist

Rationale & ethics:

- ☑ Justify the scientific rationale for the use of a placebo-surgical control
- ☑ Justify how the use of placebo adheres to accepted ethical principles:
  - Is there equipoise?
  - Is it evaluating a novel surgical procedure in a condition for which there is no proven, effective surgical intervention or is it evaluating a procedure in common use for which the evidence base is poor?
- ☑ Weigh up the risk-benefit considerations underpinning the choice of a placebo-controlled design

Design:

- ☑ Identify who the trial is designed to inform (and thus whether the inclusion of a no intervention arm is also desirable)
- ☑ Identify the critical surgical element through adoption of the DITTO framework (using pilot and feasibility work as appropriate)
- ☑ Outline the placebo-surgical control in terms of its level of fidelity to the index surgical procedure
- ☑ Provide a clear and detailed description of the components of the placebo-surgical intervention
- ☑ Outline how mitigation of risk of the placebo-surgical control has been considered
- ☑ Engage key stakeholders (including patients, anaesthetists, physiotherapists and primary care physicians) in the design of the trial

Conduct:

- ☑ Avoid the use of terms such as “sham” or “fake” surgery
- ☑ Engage participants in the production of the trial including patient information
- ☑ Provide the following information in patient information leaflets:
  - a full description of the placebo and index surgical procedure
  - a statement that whilst benefit may accrue through undergoing a placebo-surgical procedure, that there is no known mechanism by which the placebo surgery should result in direct benefit for the indicated complaint
  - recognition that the use of the placebo-surgical procedure is being used predominantly for research purposes
  - information on the possible risks or discomforts linked to the index and placebo-surgical procedure
- ☑ In patient information leaflets, surgical placebos should not be described in terms that may unwittingly lead participants to believe that the placebo-surgery brings benefit in and of itself
- ☑ Ensure balance in the information provided on both the index surgical procedure and the placebo-surgical procedure
- ☑ Consider use of enhanced processes (eg decision-aids) to facilitate patient understanding of the pros and cons for them of participating in a placebo-surgical trial
- ☑ Consider use of enhanced recruitment processes (eg Quintet-type approaches) to facilitate and optimise recruitment processes
- ☑ Consider enhanced monitoring of the trial to allow early stopping if benefit or harms clearly observed early in the index surgical procedure group

- ☑ Consider action and communication to the patient at the end of the trial i.e. offer of different treatment

Interpretation & Translation:

- ☑ Prepare in advance for dissemination and implementation of findings from the trial
- ☑ Ensure early inclusion of key leaders from patient groups, professional associations and clinical communities, systematic reviewers/guideline makers, policy makers involved in routinely delivering the treatment under investigation
- ☑ Consider insights from implementation science for the effective translation of trial findings into change of practice (eg use of theory-informed, evidence-based strategies to address expected barriers to behaviour change)
- ☑ Consider the implications for shared decision-making and clinical practice early - including advice for patients about what alternative treatments are available if the implications are that it is anticipated that the procedure will be performed much less frequently as a result of the trial findings.

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