Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines)

David J Beard, Marion K Campbell, Jane M Blazeby, Andrew J Carr, Charles Weijer, Brian H Cuthbertson, Rachelle Buchbinder, Thomas Pinkney, Felicity L Bishop, Jonathan Pugh, Sian Cousins, Ian A Harris, L Stefan Lohmander, Natalie Blencowe, Katie Gillies, Pascal Probst, Carol Brennan, Andrew Cook, Dair Farrar-Hockley, Julian Savulescu, Richard Huxtable, Amar Rangan, Irene Tracey, Peter Brocklehurst, Manuela L Ferreira, Jon Nicholl, Barnaby C Reeves, Freddie Hamdy, Samuel CS Bowley, Jonathan A Cook

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of surgical interventions. The aim of this Review is to provide a summary of knowledge on placebo controls in surgical trials. A placebo control is a complex type of comparison group in the surgical setting and, although powerful, presents many challenges. This Review outlines what a placebo control entails and present understanding of this tool in the context of surgery. We consider when placebo controls in surgery are acceptable (and when they are desirable) in terms of ethical arguments and regulatory requirements, how a placebo control should be designed, how to identify and mitigate risk for participants in these trials, and how such trials should be done and interpreted. Use of placebo controls is justified in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale. Surgical placebos might be most appropriate when there is poor evidence for the efficacy of the procedure and a justified concern that results of a trial would be associated with high risk of bias, particularly because of the placebo effect. Feasibility work is recommended to optimise the design and implementation of randomised controlled trials. This Review forms an outline for best practice and provides guidance, in the form of the Applying Surgical Placebo in Randomised Evaluations (known as ASPIRE) checklist, for those considering the use of a placebo control in a surgical randomised controlled trial.

Introduction

Compelling evidence of efficacy and safety, ideally based on data from randomised controlled trials (RCTs), should underpin all routine clinical therapies, and surgical therapies are no exception. Although an RCT comparing surgical treatment to no surgical treatment provides evidence of overall efficacy, this comparison does not account for specific biases, especially the placebo effect. These potential biases are particularly likely 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 this control poses potential risk to the patient with little potential benefit and presents ethical, design, and trial conduct challenges.

Reviews of placebo-controlled surgical trials3–4 have included their use, issues of recruitment and feasibility, and effect on outcome and serious adverse events.5,6 These reviews have not, however, explicitly considered issues of trial design, such as the definition and content of placebo, when it is appropriate to use (or not use) a placebo control in a surgical trial, factors that should guide the choice of a placebo design, and the influence of that choice on intervention standardisation. Some information on the ethical implications of surgical placebo trials has been published.7,8 This Review aims to provide up-to-date knowledge on all aspects of placebo controls in the evaluation of surgery. The insights are mainly based on the outputs of a workshop funded by the UK’s National Institute for Health Research and Medical Research Council, which brought together an international team of interdisciplinary experts (with research experience in placebo surgery) and patients. The workshop included a systematic update of important literature, an in-depth discussion of case studies, and an explanation of direct experience and best practice. This work culminated in the production of practical guidance for researchers: the Applying Surgical Placebo in Randomised Evaluations (ASPIRE) checklist. In this Review, we have restricted our focus to studies of adults with capacity to consent to participate in surgical research.

Search strategy and selection criteria

Articles reporting randomised controlled trials (including long-term follow-ups and protocols) comparing an invasive procedure with a placebo procedure in living humans were included. Pilot randomised controlled trials retrieved by the review update search were included as a source of potentially useful information about methods. Interventional procedures that change the anatomy and require 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. Randomised controlled trials that assessed medicinal products or dental interventions, non-randomised studies, reviews, editorials, letters, and conference abstracts were excluded. Articles identified in a previous review (Wartolowska [2014]) published between database inception (1966) and Nov 14, 2014, were included (n=63). Searches using the same search terms (related to randomised controlled trials, invasive procedures, and placebo concepts) and electronic databases (Ovid MEDLINE, Ovid Embase, and CENTRAL) were done to identify randomised controlled trials published in English from Nov 15, 2014, to Dec 31, 2017. Additional articles, with no restriction on publication date, were identified by hand searching references of included articles and expert knowledge. All articles 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. Two reviewers independently screened.
What is a placebo in the context of surgical trials?

Understanding the placebo context

Knowledge of the placebo effect is dominated by two main psychological theories, both of which apply to surgery. These theories are broadly labelled as 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 response expectancy, in which the placebo effects are underpinned by the patient’s conscious or unconscious expectation that the placebo will have a particular effect. Colloca and Miller integrated the conditioning and response expectancy theories to suggest that patient expectations are the central psychological mechanism that mediate placebo effects. According to their model, the brain decodes the psychosocial context, formulating conscious or unconscious expectations about outcome that then trigger placebo responses. These expectations are shaped by learning mechanisms involving three types of signs (signs are things that convey specific meanings to individuals) within the psychosocial context. The signs are (1) indices that generate expectations through sensory or memory-based associations for individuals (in essence, a conditioned response), (2) symbols that generate expectations through culturally specific conventions including language, ritual, and doctor–patient communication, and (3) icons that generate expectations through perceived similarities with the object (expectations via social learning mechanisms).

The manner in which patients are informed about the placebo control also affects patients’ expectations. Any imbalance in the tone and quantity of information given about the benefits of the index procedure compared with that given for the placebo control can be obvious and influence outcome.

Further work has characterised the different domains of the psychosocial context of health care present in clinical trials and how these domains might affect the patient’s response to a surgical placebo. These key domains include the treatment, clinician, and patient characteristics, the health-care setting, and the patient–clinician interaction (panel 1).

With regard to the placebo response in general, there is some suggestion of genetic susceptibility and biomarkers indicate at least a moderate influence of genes on the response. Furthermore, the geographical and cultural differences between patients could influence the placebo response and is a largely unexplored aspect. Both such factors apply to pharmaceutical and surgical placbos and also apply equally across groups in a randomised design.

Definition of a surgical placebo

In this Review, surgery is defined as an invasive procedure in which access to the body is gained via an incision, natural orifice, or percutaneous puncture and instrumentation is used in addition to the puncture needle. One important distinction to highlight is between the concept of placebo for evaluation purposes (eg, an experimental placebo control as is described in this Review) and the notion of purposely using a placebo for benefit or treatment.

There is not a clear definition of an experimental placebo for surgical trials and classical definitions can introduce conceptual confusion rather than clarity. A surgical placebo is ill-defined within the published literature. The descriptions can vary from “a surgical intervention with theoretically little benefit” to so-called sham surgery (entirely simulated surgery or small superficial incisions only) to a surgical placebo intervention, a procedure in which there is routine delivery of most of the operation, but the presumed active components, or the essential or critical surgical element, are removed. However, identification of, and conceptual clarity in defining, the essential surgical element can be far from straightforward.

Rather than use of the all-encompassing and generic label 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. Varying levels of fidelity are possible and include low fidelity, in which there is little similarity to the complete surgical intervention (eg, skin incisions only, thus resembling what surgeons would have traditionally described as a sham treatment), and maximum fidelity, in which treatment occurs with a

Panel 1: Influences of different domains of the psychosocial context of health care on the placebo response

Treatment characteristics

A placebo surgical control that has highly similar characteristics to the real procedure might influence participants’ response to the placebo procedure.

Health-care setting

A surgical placebo procedure can involve additional and complex procedures for the participant and this might affect the participants’ response to the placebo.

Clinician characteristics

Participants’ response to placebo might be influenced by the perceived high status of the practitioner (the surgeon) operating.

Patient characteristics

A patient’s previous experience of undergoing surgery and how the surgery affected them might influence their response to a surgical placebo.

Patient–clinician interaction

If the surgeon has detailed and extensive interaction with the patient, this might influence the patient’s response to the surgical placebo.
complete set of surgical attributes (ie, the surgical procedure under evaluation). In between these extremes, a high fidelity placebo might have identical surgical content and attributes to the complete surgical procedure but does not have the presumed active or essential component. A medium fidelity placebo might have fewer surgical components and less resemblance to the complete surgical procedure. A no surgery control has no attributes of the index procedure.

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 might be identical surgery but without the removal of bone, a medium fidelity placebo might be very similar surgery but without the removal of bone and some other operative procedures (ie, just the insertion of an arthroscope), and a low fidelity placebo might be surgical skin incisions only. Similarly, in a study of endoscopic radiofrequency ablation in patients with dysplastic Barrett’s oesophagus, the normal or maximum fidelity placebo involved ablation using a catheter. Patients who were randomly assigned to the placebo intervention group underwent a lower fidelity procedure involving upper endoscopy, oesophageal intubation, and measurement of oesophageal inner diameter only.27

This working framework is dependent on the theoretical premises of the operation and postulation of an essential surgical element; however, especially for surgeries that create effect by a multimodal or an interacting set of procedures, the identification of the essential element is not always possible.

When are surgical placebo controls acceptable?

Surgical placebos might be most appropriate when 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 to use a surgical placebo control. Patients participating in a placebo-controlled surgical trial are at risk of a surgical intervention that does not have the presumptive causally effective element (ie, the essential surgical element). Therefore, participants are potentially subjected to some of the risks of surgery with fewer perceived benefits. Ethical standards suggest, however, that exposing research participants to such risks is allowed provided that clinical equipoise exists in the study groups, and study risks 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 establish 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 non-therapeutic procedures. However, for surgical placebos, this separation is not straightforward because a placebo intervention that does not have the essential surgical element might nonetheless induce physiological changes in the patient. In this Review, we differentiate warranted therapeutic procedures, in which the prospect of direct patient benefit is supported by evidence, from non-therapeutic procedures, in which no such warrant exists and the procedure is done for scientific purposes.

The analysis of benefits and harms in placebo-controlled surgical trials is further complicated because the placebo control includes both warranted therapeutic and non-therapeutic procedures. To address this, a two-step ethical analysis is required. First, one must consider whether the use of any placebo control is justified—ie, whether equipoise exists. 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”.

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 group the participant is placed into; given the state of knowledge at the beginning of the trial, all trial groups are deemed to be broadly consistent with competent surgical care.30 Use of a placebo control is permissible when evaluating a novel surgical procedure in a condition for which there is no proven, effective surgical intervention. Additionally, the case for placebo-controlled design for surgical trials becomes stronger and equipoise exists when the evidence base supporting a commonly used procedure is poor, such as for vertebroplasty.31 Thus, in both cases, the use of a placebo control is consistent with equipoise because there is sufficient uncertainty concerning whether surgery offers any advantage over non-surgical management alone.

If a placebo is justified, then the appropriate level of fidelity to the surgical intervention must subsequently be considered and this consideration is the second step in the two-step ethical analysis. To make this determination, two standards are relevant.30 First, the harms posed by the intervention must be minimised. Second, the risks posed by the placebo intervention must be outweighed by the value of the knowledge generated.30 The first standard considers whether the risks are necessary; the second standard considers whether the risks are proportionate to scientific value. Committees on research ethics frequently debate the assessment of scientific value, and use of the value–validity framework is recommended.31 This assessment of scientific value requires that the research question is clinically important, the hypothesis is justified by the current state of evidence, and the study is well situated in a research portfolio.32

The issue of patient consent is foremost in any discussion of placebo surgical trials. Surgical trials with a
placebo control are inherently complex; clearly conveying the risks involved to prospective participants is a challenge. There is a threat from so-called therapeutic misconception, whereby research participants systematically misunderstand research elements, such as randomisation or placebos, as being designed to benefit them directly.\textsuperscript{34} Full disclosure is therefore imperative to ensure the patient is aware that they might receive a surgical intervention without the presumptive essential surgical element. Informed consent must clearly identify which procedures have evidence of direct benefit and which are primarily done only to further science. Surgical placebos must not be described in therapeutic terms—eg, as treatment or active procedures—when there is no clinical indication for the placebo procedure. However, well founded doubts over the efficacy of the real procedure are most often the reason for doing these trials and so open doctor–patient communication about these uncertainties is also required.

As placebo surgical trials include a potentially non-therapeutic intervention, additional protections should be indicated. Adequate patient comprehension of the likely (absence of) benefit from placebo allocation must be ensured to reduce therapeutic misconception. Various techniques have been shown to improve comprehension in informed consent for research, such as enhanced consent forms (ie, simplified forms developed by an interdisciplinary team that includes patients, researchers, and clinicians) and additional discussion time.\textsuperscript{35} There is preliminary evidence that the modality of the information (eg, verbal, written, or audio–visual) and the person who presents the information (eg, the treating surgeon or an independent researcher) might also make a difference to participant comprehension in placebo surgical trials.\textsuperscript{36} Formal testing of participant understanding of key elements of consent, especially relevant to the potential participation in a placebo group, might serve to enhance comprehension and document understanding.\textsuperscript{37}

There are many arguments around the balance of the financial implications to design, conduct, report, and disseminate the findings of an RCT with placebo surgery versus the continued use of the surgery in question without high level evidence. However, without such a study, surgeries might continue that are ineffective, costly, risky, and resource-intensive, and replace other, more effective treatments.

**How have placebo surgical trials been used?**

We did a systematic review\textsuperscript{38} to update the published literature on surgical placebo rationale and methods (appendix pp 1–5). The review updated and extended a previously reported systematic review\textsuperscript{3} up to December, 2017.

Data were extracted for trial characteristics and methodological areas of interest and included the rationale for use of placebo interventions, patient information, intervention standardisation and fidelity, delivery of cointerventions and anaesthesia, trials offering treatment interventions to patients allocated to placebo, and how risk was minimised because of the invasive placebo. The findings of the review have been written up for publication separately,\textsuperscript{39} but we briefly summarise these findings in this Review.

An additional 50 articles were included in this systematic review compared with the review done by Wartolowska and colleagues\textsuperscript{1}, giving a total of 96 placebo surgical RCTs. Of these RCTs, 40 (42%) focused on gastrointestinal indications and 44 (46%) evaluated minimally invasive luminal endoscopic interventions. Over two thirds of studies (n=65, 68%) randomly assigned fewer than 100 patients and approximately a third (n=31, 32%) were done at a single site.

The most common reason given for use of placebo interventions was to quantify placebo effects (in response to perceived limitations of previous controlled trials without placebos and known or expected placebo effects associated with the surgical procedure under evaluation). Information provided to patients was variable. Very few trials reported information about the standardisation (n=7) and fidelity (n=4) of interventions. 64 of the 96 trials matched anaesthesia protocols between treatment and placebo groups and 36 offered treatment to patients in the placebo group after completion of the trial.

Reporting of the placebo surgery was scarce and variable. Therefore, there is a need for clearer and more consistent reporting of rationales for the use of placebos and cointerventions, patient information provision, and standardisation and the fidelity of interventions.

**How should a placebo intervention in surgery be designed?**

An in-depth understanding of the presumed essential surgical element is crucial for placebo trial design. Assessment of any potential risks to patients and strategies to ensure the placebo effectively mimics the treatment are also required. We also developed a framework to optimise the design and delivery of placebo interventions in surgical RCTs. The Deconstruct, Identify, Take out, Think risk, Optimise (known as DITTO) framework\textsuperscript{39} was developed from the systematic review\textsuperscript{38} of published literature and built on a previously published classification system (typology)\textsuperscript{39} for identifying the components and steps of any invasive procedure. In brief, the DITTO framework suggests that five stages are required in the formulation of a placebo surgical intervention (panel 2). Stage three of DITTO, involving identification of the essential surgical element, is exemplified 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 who were randomly assigned to the placebo group underwent diagnostic bronchoscopy but not valve
Panel 2: Stages of the Deconstruct, Identify, Take out, Think risk, Optimise framework (known as DITTO)

Stage one: Deconstruct
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 two: Identify
Identify the essential surgical element, which could be one or more components or steps in the surgical intervention, and identify which treatment components and steps are included or not in the placebo intervention.

Stage three: Take out
Omit the essential surgical element from the proposed placebo intervention.

Stage four: Think risk
Consider the potential risk to patients, feasibility, and the role of the placebo intervention within the randomised controlled trial (eg, as a control intervention to elucidate treatment mechanism). This stage might result in further components or steps being omitted from the placebo intervention.

Stage five: Optimise
Optimise the placebo throughout the design process (eg, sensory masking).

placement, which was deemed the essential surgical element of the procedure.41

Who is the surgical placebo trial being designed to inform?
When designing a surgical placebo trial, identifying at the outset who the trial is attempting to inform is important. This factor will influence the overall design of the study, such as decisions as to whether a third, no-treatment group should be included, and which outcomes to measure.

Policy makers can be divided into two broad groups: those who issue guidance about how interventions should be used in health care, and those who commission and pay for services (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. Decision makers might value information about the placebo effect of an intervention in a different way to clinicians and patients.

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

Should a surgical placebo trial have a no intervention group?
There are four broad possible categories of groups in a surgical placebo trial: the index surgical intervention being studied, a placebo control (with varying levels of fidelity from simulated surgery—eg, low fidelity, minimal skin incisions to near full fidelity procedures), non-operative care, and a no intervention group. The value of a no intervention group should always be considered.

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

A no-intervention group has the advantage of measuring the natural history of the condition without any treatment and is useful to show how beneficial any surgery can be compared with doing nothing at all. A change in outcome might still be observed in a no intervention group 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 of a difference, or the 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 of placebo vs normal surgery) is sufficient to conclude on surgical benefit overall remains a matter of debate.

A placebo trial including a no-treatment comparison might be scientifically superior to one without this comparison but, considering the resource requirement, might not always be possible or justified. Two-arm surgical trials can also be very useful and informative. Decisions on the number and type of groups should reflect the research question and involve consideration of sample size, analysis, ethics, and trial feasibility. A study with a focus on mechanism and an assumed subsequent efficacy can positively use a two-arm approach. A study
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 and colleagues found that surgical placebo-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 serious adverse events in placebo-controlled trials were similar between true intervention and placebo groups but raised a concern that trials of more invasive placebo interventions might entail substantial risks for study participants. This issue is highlighted by trials such as the ORBITA study in interventional cardiology, in which the placebo group was found to have a greater number of adverse events than in the treatment group, leading to difficulties and contention in interpretation of the results.

The risks of a surgical placebo control, especially in relation to fidelity, are complex and difficult to quantify. Inert treatments, such as low or minimal fidelity surgery, might seem to have less risk than a surgical procedure with higher fidelity (in which more tissues might be involved), but this model might be too simple. For example, despite this supposed higher risk, those undergoing a placebo surgical procedure might still experience apparent benefit (although this benefit is not achieved through any known, or theoretically causal, mechanism).

Similarly, the apparent safety of a minimal fidelity procedure, in which there is little tissue damage, is tempered by the risk of anaesthetic complications. 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 group). The situation in which a treatment’s risk in a low or minimal fidelity placebo surgery group can potentially outweigh the benefits of the study’s findings can be difficult to reconcile. How to balance the risks and benefits of a placebo surgery control group trial is unclear; this dilemma remains a complex area and will depend on individual procedure risk and routine surgical risk (eg, anaesthetic), with consideration of the perceived capacity to benefit from the specific surgery in question.

Previous published literature has suggested various strategies for risk mitigation: restriction of eligible patients to those with a low clinical risk profile (eg, restriction to American Society of Anesthesiology grades one and two); reducing the invasiveness of the surgical placebo (this forms part of the balance between fidelity and risk); review of the form of anaesthesia used for the placebo procedure; use of only experienced surgeons; and enhanced monitoring with oversight committees.

Therefore, explicitly outlining all means of risk mitigation before doing a surgical trial with a placebo control is important. For situations in which the overall risk of any placebo control in surgery 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 might continue unabated, meaning patients continue to be subjected to risks related to the procedure. In this situation, the riskier the procedure, the more urgent the need for a sufficiently robust (placebo surgical) trial.

Trial conduct issues for surgical trials with placebos

Nomenclature for patients

The nomenclature for patients in surgical placebo trials is important and patient representatives are uneasy with descriptors such as deception and sham for surgical evaluation. Although such terms might often be seen in a scientific or trial design context, they are less acceptable to patients because of their negative connotations and should be avoided. Reporting guidelines under TIDieR (Template for Intervention Description and Replication) are being updated for placebo control (J Howick, University of Oxford, personal communication).

Informed consent

As surgical trials with placebos pose an unusually high degree of non-therapeutic risk, ensuring enhanced, more comprehensive information for informed consent is important. Consenting material should include, but not be limited to: a full description of the surgical placebo procedure; a statement that although benefit might result from a surgical placebo procedure, 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 procedure is for research purposes; the need to avoid language in the consent process that might unwittingly promote any therapeutic misconception; and possible risks or discomforts linked to both the index and surgical placebo 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 to avoid therapeutic misconception in trials of this type. Any information should also clearly describe the standard index surgical procedure for the condition should the patient 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 systematic review found that slow recruitment, due to difficulties finding eligible patients who would agree to participate, was the major barrier to successful trial completion. The wider literature has also noted that individuals can have inherent beliefs and preferences about surgery as an intervention, which might consequently affect their willingness to participate in a surgical trial with placebos; however, this factor can be measured and accommodated for. Randomisation ensures that any such confounders (and indeed any other unknown confounders) are balanced across intervention groups.

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, both surgeons and patients might be reluctant to accept a 50% chance of placebo (for a two-arm trial), particularly when placebo involves invasive surgery. This reluctance could be partially mitigated by inclusion of a non-surgical treatment in a third arm, although this arm would increase trial complexity and cost.

Strategies are being developed to improve recruitment for surgical trials with placebos. Recruitment communication planning is crucial and 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 trial processes and performance. Donovan and colleagues have developed the Quintet Recruitment Intervention for optimising recruitment and informed consent for trials on the basis of identifying 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. The idea is to increase public buy-in of the trials by highlighting study prestige, worth, and legitimacy, indicating the worthiness of the placebo design. Empirical work has shown that when well informed, patients can be willing to take part in surgical placebo trials and give many positive reasons for doing so.

The preferences of patients and health professionals, including surgeons, can have a decisive influence on trial recruitment; however, many questions remain unanswered. These questions 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 random assignment, and whether or not surgeons should be allowed to restrict random assignment to eligible patients only when personally uncertain as to which intervention would be the best option for an individual patient. Patient engagement is also crucial 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 in helping patients to know both when and how they can access this information on unblinding.

One of the strategies noted by the review by Cousins and colleagues was to offer participants randomly assigned to the placebo control group the active intervention once the primary endpoint for that individual had been assessed. Although this approach appears ethical and is commonly used, the patient is essentially exposed to more risk (ie, the risks associated with the placebo surgery and then from an unproven intervention). For this reason, unless clinician autonomy appropriately overrides trial convention, the offering of the definitive treatment should probably be reserved until after a final analysis of the trial.

The issue of quality control also arises for the surgical procedure. If information on mechanism is required, as it mostly is from these studies, then the surgery should have a definite minimum quality and be done by experienced surgeons. In this scenario, the question of whether an intervention can work tends to have more primacy than the question of whether an intervention does work, and therefore mandates the use of highly competent surgeons. Evaluation of the surgical quality of all surgeries done in such studies might be needed for validation that the procedure was done appropriately.

Involvement and engagement of other key stakeholders
The public need to be better educated about surgical evidence and, despite several strong initiatives to improve the situation, there remains a paucity of high-quality evidence for surgical procedures. Engagement and acceptance from the public that these trials are required is essential. Research has highlighted the importance of identifying and engaging key stakeholders in addition to the participating surgeon (eg, patients, anaesthetists, operating theatre teams, ward nurses, health service managers, and policy makers) from the outset. For example, anaesthetists are key clinical stakeholders and have a crucial role in deciding how to minimise risk in the placebo surgical intervention. The time at which patients are at the greatest risk in placebo trials is the perioperative period and therefore this period receives the greatest focus from clinical, ethical, regulatory, and other risk management stakeholders.
Panel 3: The Applying Surgical Placebo in Randomised Evaluations (known as ASPIRE) checklist for the design and conduct of surgical placebo controls in randomised trials

Rationale and ethics
- Justify the scientific rationale for the use of a placebo surgical control.
- Justify how the use of a placebo adheres to accepted ethical principles:
  - Is there equipoise?
  - Is the trial evaluating a novel surgical procedure in a condition for which there is no proven, effective surgical intervention or 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 group is also desirable).
- Identify the essential surgical element through adoption of the Deconstruct, Identify, Take out, Think risk, Optimise framework (using pilot and feasibility work as appropriate).
- Outline the surgical placebo 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 the mitigation of risk of the surgical placebo 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 although benefit may accrue through undergoing a placebo surgical procedure, there is no known mechanism by which the placebo surgery should result in direct benefit for the indicated complaint.
- Recognition that 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 might unwittingly lead participants to believe that the placebo surgery brings benefit in 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 patients’ understanding of the advantages and disadvantages 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 harm are clearly observed early in the index surgical procedure group.
- Consider action and communication to the patient at the end of the trial (ie, offer of different treatment).

Interpretation and 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 or guideline makers, and 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 the procedure will be done less frequently as a result of the trial findings.

Interpretation and translation into change of policy and practice
In more than half of the placebo-controlled trials of surgery reported in peer reviewed literature, the results have shown no benefit of the definitive procedure compared with the placebo control.7 In many others, the placebo effect remains strong but is accompanied by a small, genuine treatment effect from the procedure. The presence of some effect from the index procedure is not surprising because of 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 because of the placebo effect.

Therefore, the investigators responsible for doing and reporting such trials must 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, negative reactions and resistance from clinicians and patients whose beliefs and convictions are being challenged by the results. These trials will also generate interest from other stakeholders, including funders (state-based and insurance-based),
press, and the media. Increasing the use of placebo controls for RCTs in surgery might help to elucidate mechanisms and eliminate redundant procedures.

Experience with placebo-controlled trials of knee arthroscopy suggest there can be a considerable lag between evidence becoming available and a 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.26 Similar resistance from the clinical community has been encountered with trials of vertebroplasty for osteoporosis12 and subacromial decompression for shoulder pain.25 Consistent features of the typical response include 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 an assertion that the surgeons involved in the trial were not sufficiently expert in the procedure. An illustrative example of resistance to these trials is the response from 15 combined Surgical Associations (of a single country) to the C4SAW placebo-controlled trial72 for subacromial decompression surgery, which stated that “contrary to previous reports, the C4SAW trial does not provide any new insights” and “for [this institution’s] Health System there are no consequences from the C4SAW study” (unpublished). By contrast, the National Health Service in the UK, despite not deimplementing subacromial decompression, moved to recategorise the procedure so that it can only be provided if preconditions are met.

In anticipation of these issues, planning for the implementation and effect 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 is important. 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 to address expected barriers to behaviour change.55

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 probable benefits of both the definitive and alternative treatments.

Key messages

Our Review has described how placebo controls might justifiably be used in RCTs of surgical interventions, provided that there is a strong scientific and ethical rationale for the study. A surgical placebo control is not appropriate for all evaluations of surgery but might be best reserved for operations associated with low surgical complication risk, potentially low efficacy, unjustified usage, and in which a clinically significant placebo response is expected. In expectation of a complex set of ethical issues, these trials need to have the greatest possible chance of answering the primary research question in a robust manner (high internal validity), with high generalisability for the relevant clinical community (high external validity). New surgical procedures of unknown value should also be evaluated and might benefit from placebo control investigation. Trials must be designed appropriately and any risks associated with the placebo surgical control procedure mitigated. Considering levels of fidelity to the index surgical procedure helps to conceptualise the construction of a surgical placebo and its associated benefits and risks. We present a practical checklist (ASPIRE) that summarises the learning points from the Review and represents the minimum standard researchers should attain and show when designing a placebo surgical trial (panel 3).

Contributors

All authors (except JMB, JS, and MLF) attended the workshop and contributed to the development and content of this Review. All authors reviewed, contributed specific expertise, and edited the manuscript before submission.

Declaration of interests

There are no competing interests for any author for the work under consideration. No author received payment or services from a third party for any aspect of the work. DJB has institutional research grants from Zimmer Biomet, the National Institute for Health Research, Versus Arthritis, and Action Research (including the Medical Research Council and the National Institute for Health Research grant for the workshop), declares institutional support from the Rosettes Trust and the Royal College of Surgeons of England, outside of the submitted work, and is a non-executive director of an unrelated Oxford University spin-out company, Pro-mapp. AC is employed by the University of Southampton to work at the National Institute for Health Research Evaluation Trials and Studies Coordinating Centre, which receives funding from the National Institute for Health Research to run several research programmes. AR has educational grants from DePuy J&J and research grants from the National Institute for Health Research and Orthopaedic Research UK. CW receives personal fees from Eli Lilly and Company, Canada. FH has unrelated grant income from the National Institute for Health Research and Cancer Research UK. JAC was joint lead applicant with DJB on the grant that funded the workshop that underpinned this Review. JP received grant funds from the Wellcome Trust. JS receives grant income from the Uehiro Foundation on Ethics and Education, Oxford Martin School, and the Wellcome Trust, and receives salary support and research centre funding from the Murdoch Children’s Research Institute and the Melbourne Law School. MLF reports grant income funds from the National Health and Medical Research Council of Australia. PB reports grant income from the Medical Research Council, National Institute for Health Research, and the Wellcome Trust and consultancy from AG Biostest. RB reports multiple grants from the National Health and Medical Research Council of Australia, grant funding from Arthritis Australia, travel expenses for speaking at conferences from the professional organisations hosting the conferences, and has been a member of the Australian Medical Services Advisory Committee since May, 2016. RB has previously published a placebo-controlled trial of vertebroplasty for acute osteoporotic spinal fractures. SCSR reports personal fees from the Medical Research Council and UK Research and Innovation, during the conduct of this Review, and personal fees from the Medical Research Council and UK Research and Innovation, outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

The work was co-commissioned and jointly funded by the Medical Research Council UK and the National Institute for Health Research UK.
Methodology Research Programme in response to a commissioned call for a workshop on this topic. The NIHR Biomedical Research Centres at the University Hospitals Bristol National Health Service Foundation Trust, the University of Bristol, Oxford Health National Health Service Foundation Trust, and the University of Oxford also funded this work. Applicants for the commission were: David Beard, Jonathan Cook, Marion Campbell, Jane Blazey, Andrew Carr, Thomas Pinkney, Brian Cuthbertson, Irene Tracey, Rachel Buchbinder, Julian Savulescu, Dair Farrar-Hockley, and Natalie Blencowe. As part of the process of
developing the guidance, a two-day workshop was held in St Anne's
College, Oxford in December, 2018. In addition to the applicants,
the academic workshop participants were: Jonathan Pugh, Pهلicity Bishop, Sian Cousins, Charles Weijer, Richard Hustad, Jon Nicholl, Pascal Probst, Peter Brocklehurst, Andrew Cook, Katie Gillies, Freddie Hamdy, Ian Harris, Naomi Lee, Stefan Lohmander, Amar Rangan, Barnaby Reeves, and Samual Rowley. Carol Brennan and
Dair Farrar-Hockley kindly participated and contributed as patient
representatives. Dair Farrar-Hockley was also a co-applicant on the
workshop grant application. Sian Cousins and Natalie Blencowe kindly
took detailed cross-referenced notes throughout and recorded the
workshop discussions. Katie Chegwin was responsible for administration
representatives. Dair Farrar-Hockley was also a co-applicant on the
workshop grant application. Sian Cousins and Natalie Blencowe kindly
took detailed cross-referenced notes throughout and recorded the
workshop discussions. Katie Chegwin was responsible for administration
and organisation. The views expressed are those of the authors and not
necessarily those of the National Health Service, the NIHR, the MRC,
or the Department of Health and Social Care. AC, FH, and JMB are NIHR
senior investigators.

References
1 Wartolowska KA, Garry S, Fekins BG, et al. A meta-analysis of
  temporal changes of response in the placebo arm of surgical
2 Gu AP, Gu CN, Ahmed AT, et al. Sham surgical procedures for
  pain intervention result in significant improvements in pain:
  systematic-review and meta-analysis: metaepidemiologic research
  controls in the evaluation of surgery: systematic review. BMJ 2014;
  348: g2353.
  in surgery: a systematic review and meta-analysis. Medicine (Baltimore)
  2016; 95: e3516.
  randomized controlled trials with a placebo arm: a systematic
6 Campbell MK, Entwistle VA, Cuthbertson BH, et al. Developing a
  placebo-controlled trial in surgery: issues of design, acceptability and
7 Savulescu J, Wartolowska K, Carr A. Randomised placebo-controlled
9 Horng S, Miller FG. Ethical framework for the use of sham
  The ethics of sham surgery in clinical orthopaedic research. J Bone Joint
11 Miller FG. Sham surgery: an ethical analysis. Am J Bioeth 2003;
12 Rogers W, Hutchison K, Skea ZC, Campbell MK. Strengthening
  the ethical assessment of placebo-controlled surgical trials: three
13 Stewart-Williams S. The placebo puzzle: putting together the pieces.
14 Colloca L, Miller FG. How placebo responses are formed: a learning
15 Colloca L. Learned placebo analgesia in sequential trials: what are
  the pros and cons? Pain 2011; 152: 1215–16.
16 Wickramasekera I. A conditioned response model of the placebo
  effect predictions from the model. Biofeedback Self Regul 1990;
  5: 3–18.
17 Kapchuk TJ. Placebo studies and ritual theory; a comparative
  analysis of Navajo, acupuncture and biomedical healing. Philos
18 Colloca L, Benedetti F. Placebo analgesia induced by social
19 Bishop FL, Adams AE, Kapchuk TJ, Lewith GT. Informed consent
  and placebo effects: a content analysis of information leaflets to
  identify what clinical trial participants are told about placebos. PLoS
  One 2012; 7: e39661.
20 Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of
  context effects on health outcomes: a systematic review. Lancet
21 Bishop FL, Coghlan B, Geraghty AW, et al. What techniques might
  be used to harness placebo effects in non-malignant pain? A
  literature review and survey to develop a taxonomy. BMJ Open 2017;
  7: e015516.
22 Hall KT, Lonsalzo J, Kapchuk TJ. Genetics and the placebo effect:
23 Cousins S, Blencowe NS, Blazey JM. What is an invasive
  procedure? A definition to inform study design, evidence synthesis
  decompression for subacromial shoulder pain (CSAW): a
  multicentre, pragmatic, parallel group, placebo-controlled,
26 Mowhray CT, Holter MC, Gregory B, Teague G, Bybee D. Fidelity
criteria: development, measurement, and validation. AJE 2003;
  in Barrett’s esophagus with dysplasia. N Engl J Med 2009; 360:
  2277–88.
28 National Commission for the Protection of Human Subjects of
  Biomedical and Behavioral Research. The Belmont report:
  ethical principles and guidelines for the protection of human
29 The World Medical Association. WMA Declaration of Helsinki—
  ethical principles for medical research involving human subjects.
  July 9, 2018. https://www.wma.net/policies-post/wma-declaration-of-
  helsinkis-ethical-principles-for-medical-research-involving-human-
30 Weijer C, Miller PB. When are research risks reasonable in relation to
  1987; 317: 141–45.
32 Hey SP, Weijer C. What questions can a placebo answer? Monash
33 Binik A, Hey SP. A framework for assessing scientific merit in
34 Appelbaum PS, Grisco T. Assessing patients’ capacities to consent to
35 Nishimura A, Carey J, Erwin PJ, Tildurt JC, Murad MH, McCormick JB.
  Improving understanding in the research informed consent process:
  a systematic review of 54 interventions tested in randomized
36 Hare KB, Lohmander LS, Roos EM. The challenge of recruiting
37 Cousins S, Blencowe NS, Tsang C, et al. Reporting of key
  methodological issues in placebo-controlled trials of surgery
  needs improvement: a systematic review. J Clin Epidemiol 2019;
38 Cousins S, Blencowe NS, Tsang C, et al. Optimising the design of
  invasive placebo interventions in randomised controlled trials.
39 Blencowe NS, Mills N, Cook JA, et al. Standardizing and
  monitoring the delivery of surgical interventions in randomized
  reduction with endobronchial valves for patients with heterogeneous
  emphysema and intact interlobar fissures (the BeLieVeR-HIFi
41 The National Institute for Health and Care Excellence. Process and


© 2020 Elsevier Ltd. All rights reserved.