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# Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop

*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 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 Rowley, Naomi Lee and Jonathan A Cook*





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The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop

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**Background:** The use of placebo comparisons for randomised trials assessing the efficacy of surgical interventions is increasingly being considered. However, a placebo control is a complex type of comparison group in the surgical setting and, although powerful, presents many challenges.

**Objectives:** To provide a summary of knowledge on placebo controls in surgical trials and to summarise any recommendations for designers, evaluators and funders of placebo-controlled surgical trials.

**Design:** To carry out a state-of-the-art workshop and produce a corresponding report involving key stakeholders throughout.

**Setting:** A workshop to discuss and summarise the existing knowledge and to develop the new guidelines.

**Results:** To assess what a placebo control entails and to assess the understanding of this tool in the context of surgery is considered, along with when placebo controls in surgery are acceptable (and when they are desirable). We have considered ethics 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 carried out and interpreted. The use of placebo controls is justified in randomised controlled trials of surgical interventions provided that there is a strong scientific and ethics 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 a high risk of bias, particularly because of the placebo effect.

**Conclusions:** The use of placebo controls is justified in randomised controlled trials of surgical interventions provided that there is a strong scientific and ethics rationale. Feasibility work is recommended to optimise the design and implementation of randomised controlled trials. An outline for best practice was produced in the form of the Applying Surgical Placebo in Randomised Evaluations (ASPIRE) guidelines for those considering the use of a placebo control in a surgical randomised controlled trial.

**Limitations:** Although the workshop participants involved international members, the majority of participants were from the UK. Therefore, although every attempt was made to make the recommendations applicable to all health systems, the guidelines may, unconsciously, be particularly applicable to clinical practice in the UK NHS.

**Future work:** Future work should evaluate the use of the ASPIRE guidelines in making decisions about the use of a placebo-controlled surgical trial. In addition, further work is required on the appropriate nomenclature to adopt in this space.

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# List of boxes

**BOX 1** ASPIRE checklist for the design and conduct of placebo surgical controls in randomised trials

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## List of abbreviations

ASPIRE	Applying Surgical Placebo in Randomised Evaluations	NIHR	National Institute for Health Research
CSAW	Can Shoulder Arthroscopy Work?	PPI	public and patient involvement
DITTO	deconstruct, identify, take out, think, optimise	QALY	quality-adjusted life-year
KORAL	Knee Osteoarthritis: Role of Arthroscopic Lavage	RCS	Royal College of Surgeons
MRC	Medical Research Council	RCT	randomised controlled trial
		SUcceSS	SURgery for Spinal Stenosis



# Plain English summary

## What was the research about?

One of the best ways to prove that a new medicine really works is to use a scientific test called a 'placebo-controlled trial'. In this type of test, half of the participants are given a new pill and the other half are given a 'placebo', which is a dummy pill (usually a sugar pill) that is made to taste and look the same as the active pill, but has no active ingredients. The results are then compared.

Just like medicines, new surgical procedures need to be tested to show that they are safe and benefit patients. Ideally, they would also be tested using the 'placebo-controlled trial' approach, but asking patients to have 'dummy' surgery is not the same as asking people to take a dummy pill. Placebo surgery raises lots of ethics questions and is controversial. As it is controversial, guidelines are needed to recommend when placebo surgery studies can be used (if at all) and what special considerations need to be taken into account. Our research team was commissioned to develop these guidelines.

## What did we do?

We summarised, to the best of our knowledge, all previous research that had used placebo surgery and reviewed all the ethics literature on this topic. We also looked at the latest scientific understanding of how placebos work.

We then held a workshop to discuss and summarise the existing knowledge and to develop the new guidelines. This involved an international team of patients, surgeons, researchers, ethicists, psychologists, physiologists and funders.

We published the guidelines [i.e. the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) guidelines] in an influential medical journal and also wrote several other publications. This report provides a slightly more detailed version of our findings and recommendations.

## Who will this help?

The guidelines will help researchers and doctors know when, and how, to best design placebo surgery studies in the future.



# Scientific summary

## Background

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of complex interventions, including surgery. A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting.

## Aim

The aim of this workshop and report was to extract and summarise the current knowledge on the use and appropriateness of placebo controls for surgical trials. It was intended to provide advice for researchers, clinicians, patients and funders when considering or designing a placebo surgical study or involvement in such a study.

## Structure and content of report

This report outlines the background to placebo control for surgery and what a placebo surgical control entails and provides a summary of the up-to-date understanding of the placebo phenomenon in the context of surgery. Placebo controls for surgical evaluation are not always acceptable, nor are they always the most desirable or optimal option. The nature of surgical placebo is explored in terms of ethics arguments and regulatory requirements. The design of a placebo surgical control is also complex and consideration is given to this with clear guidelines on process. As placebo surgery is not without risk, methods are outlined on how to identify and mitigate risk for participants in placebo-controlled surgical trials. Last, attention is given as to how the results of such trials should be interpreted.

## Findings

The use of a placebo control for the evaluation of a surgical procedure is justified provided that a strong scientific and ethics rationale can be provided. Feasibility work is recommended to explore the value of placebo randomised controlled trial (RCT) design and optimise the conduct. The workshop and ensuing publications provide an outline for best practice in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) guidelines.

## Conclusions

The guidelines are advised reading for those considering the use of a placebo control in a surgical RCT.

## Outputs

The workshop has, to date, produced three substantial publications in high-impact journals, and the content of each helps to guide placebo control comparison and trial design in surgical trials [Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, *et al.* Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). *Lancet* 2020;**395**:828–38; Cousins S, Blencowe NS, Tsang C, Chalmers K, Mardanpour A, Carr AJ, *et al.* Optimizing the design of invasive placebo

interventions in randomized controlled trials. *Br J Surg* 2020;**107**:1114–22; and Cousins S, Blencowe NS, Tsang C, Lorenc A, Chalmers K, Carr AJ, *et al*. Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol* 2020;**119**:109–16].

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# Chapter 1 Introduction and background

A preliminary and over-riding ethos for this work is that surgical interventions must be fully evaluated before being introduced into clinical practice, including existing interventions without compelling evidence to underpin their use. The present gold standard for such evaluation of clinical efficacy remains the randomised controlled trial (RCT) using a comparator treatment or group. Furthermore, using a placebo control is often thought as the 'best' trial design approach to investigate health-care interventions, as it minimises the risk of bias. Such bias can arise from several sources, including expectation bias and confirmation bias, and could undermine the validity of a comparative study's findings. The use of a surgical placebo control is, understandably, highly controversial for ethics and trial design reasons. The construction or development of a placebo surgical intervention, the achievement of satisfactory participation/acceptance by surgeons and other key personnel (e.g. anaesthetists), the participation of patients, and the interpretation of the trial results can all be challenging.

It could be argued that placebo designs are especially important for surgery for two main reasons. First, surgical interventions have undergone far less rigorous evaluation than drug treatments.<sup>1</sup> Second, bias is particularly high, with surgical interventions anticipated to have a larger placebo effect than other treatments, given the orchestration and personalisation around the intervention delivery. Recent work has shown the substantial magnitude and duration of surgical placebo effects.<sup>2,3</sup>

Placebo trials in surgery can be, and have been, carried out in a number of circumstances.<sup>2-6</sup> It is crucial that triallists, patients and surgeons understand the circumstances in which a surgical placebo control could or should be used and, if this is to be used, what type of placebo control would be appropriate. There is a need for clear advice to aid triallists, funders, patients, journal editors and regulators.

Previous reviews of placebo-controlled surgical trials<sup>3-6</sup> have examined the characteristics of such studies, and have raised issues related to recruitment and feasibility, impact on outcome and serious adverse events.<sup>7,8</sup> These reviews, however, have not considered, in detail, trial design issues, such as when it is appropriate to 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 (and fidelity assessment)<sup>9</sup> and the selection and use of co-interventions. Further practical consideration of the ethics implications is needed.<sup>10,11</sup> How placebo comparators are developed and piloted before use in a main trial has also not been considered. Beyond placebo analgesia studies using neuroimaging, there is little supporting information on the neurophysiological effects of placebo. Trial conduct specifically for placebo-controlled surgical trials has received little focus, with key areas including qualitative aspects and recruitment. Guidelines around core methodological considerations are urgently required to ensure that triallists can design (and funders can appropriately assess and fund) the optimal placebo-controlled surgical trials of the future.

This report comes out of a project funded by the National Institute for Health Research (NIHR) and the Medical Research Council, which brought together leading national and international experts to produce state-of-the-art thinking and knowledge on placebo controls in surgical evaluation. The expert interdisciplinary team of triallists, surgeons, anaesthetists, methodologists and ethicists all had a strong track record of successful research in this field, including surgical placebo-controlled trials. The work also brought together four of the leading UK centres of excellence in surgical trial design and methodology (i.e. Oxford, Bristol, Birmingham and Aberdeen). The study group provided strength and depth in the design and conduct of surgical trials, ethics expertise, organisation of consensus workshops, development of trials methodology guidelines and a deep awareness of the clinical, regulatory and practical trial contexts in which guidelines will be applied. The group also has extensive active collaborations with practising surgeons and key stakeholders in the UK and overseas [i.e. the Royal Colleges of Surgeons (RCS) of England (London, UK), Scotland (Edinburgh, UK) and Ireland (Dublin, Ireland), the Royal Australasian College of Surgeons (East Melbourne, VIC, Australia) and the American College of Surgeons (Chicago, IL, USA)].



The output is a set of methodological guidelines, known as the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) guidelines, to inform the future design of surgical trials and, specifically, the role and optimal design of placebos in surgical trials.

The structure of the report consists of seven relatively brief, but discursive, elements:

1. What is 'placebo' in the context of surgical trials?
2. The current regulatory requirements for placebo-controlled surgical trials.
3. Systematic literature review update for placebo-controlled surgical trials.
4. Ethics considerations for placebo-controlled surgical trials.
5. Design aspects of placebo-controlled surgical trials.
6. Trial conduct and recruitment in surgical trials.
7. Interpretation of placebo-controlled surgical trials and changing practice.

The salient aspects are then given in point form in:

8. Summary guidelines for researchers, reviewers and funders (i.e. the ASPIRE guidelines).

The methodology for translation of the pre-workshop work and workshop proceedings into guidelines was as follows.

The results from the preparatory work were collated and summarised. This included an updated systematic review of placebo-controlled surgical trials, extension of a previously published surgical taxonomy to allow the characterisation and optimisation of aspects of placebo controls, and a scoping review of regulatory guidance on placebos and collation of up-to-date literature on ethics, methods and conduct of placebo-controlled surgical trials.

The transcripts of the workshop and the facilitator/rapporteur notes taken at each session formed the documentary and evidence sources available and informed the final guidelines. Each session subteam contributed and reviewed the transcripts and notes from their sessions using emergent themes for integration into the final guidelines. A draft of the guidelines was circulated to the workshop attendees for feedback and to ensure international generalisability of recommendations.

The work has now been published,<sup>12</sup> and the authors and relevant stakeholders have been approached to ensure that the guidelines meet their needs.

### **Public and patient involvement**

Public and patient involvement (PPI) was important for the workshop from its inception. Following the NIHR call for a workshop, the submission team was selected from a group of appropriate international experts, scientists and clinicians. A PPI member (DF-H) was part of the submission team and contributed to all PPI work and submission documents. On award, a further PPI attendee was invited to the workshop. This PPI attendee had experience and understanding of placebo-controlled surgical trials. Both patient representatives had been involved in the CSAW (Can Shoulder Arthroscopy Work?) placebo-controlled surgical trial<sup>13</sup> from Oxford. One patient, who had previously undergone decompression shoulder surgery, had been the patient representative on the Trial Steering Committee for CSAW. The other patient had been an enrolled patient on the same trial.

Public and patient involvement members were involved in all stages of the work. Both members attended the workshop and contributed substantially to discussions from a patient perspective and, based on their involvement in similar previous trials, also as knowledgeable individuals on aspects of the methodology. The chairperson made every effort to include the PPI members on most discussion points.

The PPI members also provided a presentation alongside the other scientific presentations being delivered. Both members participated in report writing and editing content. *Chapter 8, Placebo-controlled surgical trials: the patient's perspective*, has a section dedicated to the 'patients' perspective', written by the PPI members. This exemplifies the impact and dissemination features of the PPI input. It may have been useful to have a further PPI representative outside the Oxford group or perhaps from overseas, but travel costs were considered in relation to the extra benefit.



## Chapter 2 What is ‘placebo’ in the context of surgical trials?

The origin of the word ‘placebo’ is from the Latin *placere*, ‘to please’.

Various definitions of placebo exist, including a medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect, and a substance that has no therapeutic effect and is used as a control in testing new drugs.

There is an important distinction between the known placebo effects within established treatment and those that are formally, and somewhat artificially, devised for evaluation purposes, as per control in a clinical trial. This document refers to ‘placebo’ in the context of evaluation purposes (in surgery) only.

Early distinctions must also be made between the classical (pharmacological)-derived definitions and those modified for placebo-controlled evaluations of surgery. Definitions for placebo surgical intervention vary from ‘a surgical intervention with theoretically little benefit’ to ‘sham’ surgery or ‘placebo surgical intervention’, a procedure in which presumed ‘active’ components of the procedure or the critical surgical element were removed. Many of these terms are used interchangeably and often without an ascribed clear meaning. After consideration, the word ‘placebo’ for surgical evaluation has been used in the report along with the concept of a ‘critical surgical element’.

Further distinction is observed between a completely ‘sham’ or ‘dummy’ treatment (i.e. an entirely pretend surgery or small superficial incision only) and varied levels of placebo ‘intervention’ in which some part of the surgery is delivered, with or without additional known benefit. However, rather than ascribing hard boundaries, a concept in which the placebo intervention is described in levels of fidelity<sup>14</sup> to the complete surgical intervention may be helpful. A placebo intervention can be either low fidelity [i.e. there is little similarity with the complete surgical intervention (sham surgery being a category of overall least fidelity)] or high fidelity (i.e. the surgical intervention has most components of the complete treatment, but perhaps without the presumed active or critical component). The complete treatment (no placebo) has full fidelity. A schema is given in *Table 1*, which can also be used in cross-reference to the DITTO (deconstruct, identify, take out, think, optimise) method for deconstruction, as reported in *Chapter 7*.<sup>15</sup>

The nomenclature is important. Although all placebo-based interventions (in a surgical trial) have some form of intentional ‘deception’ to support the methodology (i.e. where knowledge of the intervention received is kept hidden), patient representatives have expressed uneasiness with this descriptor. Likewise, terms such as ‘magic’ and ‘simulated surgery’ are considered inappropriate. ‘Sham’, although much used as a descriptor (scientifically), is also considered unacceptable to use with patients because of its negative connotations with regard to quality of clinical practice/caregivers.

TABLE 1 Levels of fidelity to the complete surgical intervention for placebo-controlled surgical trial design

Fidelity level	Descriptor
Index procedure	Complete surgical intervention (not placebo)
Placebo: high fidelity	Near-complete attributes of the procedure under investigation
Placebo: low fidelity	Few attributes of the procedure under investigation
Placebo: minimal fidelity	Minimum or no attributes of the procedure under investigation (i.e. sham, skin incisions only)



# Chapter 3 The psychological and physiological aspects of placebo for surgical trials

## The psychological aspects of placebo

Classical definitions of placebo can introduce conceptual confusion rather than clarity when considering the mechanisms underpinning placebo effects. For example, defining placebos as inert substances leads one paradoxically to define placebo effects as the effects of inert substances. These difficulties may stem from a focus on placebo as a substance rather than placebo as a process.<sup>16</sup> Indeed, current definitions now invoke notions of process. For example, placebo effects have been defined as changes in a person's health status that result from the meaning and hope that the person attributes to a procedure, event or interaction in a health-care setting.<sup>17,18</sup> Colloca,<sup>19</sup> a leading commentator on the placebo phenomenon, goes further in linking placebo effects to a specific mechanism, defining them as 'powerful determinant[s] of health outcomes across many different diseases and encounters; the placebo effect is due to the expectancy of positive treatment outcomes'.<sup>19</sup>

Two main theories dominated early work on the psychological mechanisms underpinning placebo effects: (1) learning theory, specifically conditioning (i.e. placebo effects are underpinned by associative learning when placebos are paired with an active drug that triggers a physiological response); and (2) response expectancy theory (i.e. placebo effects are underpinned by the patient's conscious or unconscious expectation that the placebo will have a particular effect). Experiments were designed to test competing hypotheses derived from these theories and the evidence amassed suggested that both conditioning and expectancy were involved in placebo effects in different circumstances.<sup>20</sup>

Less divisive accounts of placebo mechanisms have now been proposed. Benedetti<sup>21</sup> emphasises the importance of considering disease- or system-specific placebo mechanisms, particularly when considering mechanisms at the physiological level. Colloca and Miller<sup>22</sup> integrate insights from learning theory and response expectancy theory, arguing that patient expectations are the central psychological mechanism that mediates placebo effects. According to this model, the brain decodes the psychosocial context, formulating (conscious or unconscious) expectations about outcome that then trigger placebo responses.

Colloca and Miller<sup>22</sup> drew on previous work to suggest that expectations are shaped by learning mechanisms around three types of sign (or triggers) in the psychosocial context:

1. indices, which generate expectations through sensory- or memory-based associations for individuals (e.g. tablets can be indices when patients become conditioned to expect symptomatic benefit from taking them)<sup>23</sup>
2. symbols, which generate expectations through culturally specific conventions, including language (e.g. the ritual and doctor-patient communication around surgery and the operating theatre foster particular expectations of benefit)<sup>24</sup>
3. icons, which generate expectations through perceived similarities with the object (e.g. observing a similar person with similar symptoms responding to an intervention can foster positive expectations through social learning mechanisms).<sup>25</sup>

Understanding the influence of these different elements on placebo effects within clinical trials can then inform attempts to design, manipulate and control placebo effects in surgery trials.

Five domains of the psychosocial context of health care that may influence patient outcomes have been suggested from reviews of the literature.<sup>26</sup> A recent review further explored how each of the five contextual domains are at play in clinical trials and identified specific design features and methods that might shape patient expectations and, therefore, placebo effects in trials<sup>27</sup> (Table 2).

Qualitative research methods are helpful for exploring the psychosocial context of clinical trials and understanding the myriad influences and dynamic processes involved in shaping patients' expectations. For example, interviews in a placebo-controlled trial<sup>28</sup> of acupuncture for osteoarthritis revealed that participants derived empathy not only from the acupuncturists themselves, but also from other trial personnel, from the friendly and polite reception staff and from the ease of making convenient appointments, all of which made the patients feel cared for.

How patients are informed about placebo surgery might be a key component of the psychosocial context of clinical trials that could shape patients' expectations. Patient information leaflets in placebo-controlled trials typically seem to explain placebo effects in quite negative terms, if at all, with most devoting considerable space to describing the potential benefits and mechanisms of action of the trial treatment while describing placebos as 'a 'dummy treatment, which looks like the genuine medicine but contains no active ingredient'.<sup>29</sup> This is important because, arguably, it does not adequately inform patients about the potential for positive or negative outcomes from the placebo intervention.<sup>29</sup> Another acupuncture trial,<sup>30</sup> this time for irritable bowel syndrome, identified four main ways that patients conceptualised placebo effects: (1) placebos are necessary for research, (2) placebo effects are fake, (3) placebo acupuncture is not real acupuncture and (4) placebos have real effects mediated by psychological mechanisms. Negative views of placebos as fakes or illusory are potentially problematic for patients who receive a placebo intervention and experience real tangible benefit from it, as they may then struggle to make sense of this and integrate it into a coherent narrative that does not entail them feeling tricked or gullible.<sup>30,31</sup>

Patient expectations are central to placebo effects and are driven by multiple components of the psychosocial context, including interpersonal interactions with clinicians and trial personnel, and information about the trial interventions. It is important to consider this when designing and conducting placebo-controlled trials in surgery.

TABLE 2 Different domains of the psychosocial context of health care on the surgical placebo response<sup>26,27</sup>

Domain context; Characteristics of	Placebo-surgery relevant examples influencing the placebo response
Treatment	A placebo-surgical control treatment that is very similar in characteristics to the definitive procedure
Health-care setting	A placebo-surgical procedure conducted in the same setting (i.e. an operating theatre), with all the associated cues
Clinician	The perceived status of the practitioners (surgeons, nurses) performing the placebo surgery in surgical gowns
Patient	Previous experience of undergoing surgery
Patient-clinician interaction	A previous interaction with the patient

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## The physiological aspects of placebo

The scientific overlap between the physiological and psychological aspects of placebo is significant and far from straightforward. Most work has been completed in the context of pain and pain relief, rather than methodological considerations for comparative groups in surgical trials. Therefore, direct application has limitations. However, in the context of pain modulation, it is well established that the mechanisms of placebo analgesia involve the antinociception brainstem pathway and spinal inhibition.<sup>32</sup> Functional magnetic resonance imaging work has also linked observed placebo effects to the anticipation of reward.<sup>33</sup> If these effects are substantial for an intervention such as surgery, it is critical that they are taken account of in any trial design to enable fair comparison or deeper understanding of mechanism.

Furthermore, there is evidence from investigations of the mesolimbic reward system that certain personalities are more susceptible to such analgesic responses and placebo effects.<sup>34</sup> Many of the more qualitative features of placebo (e.g. expectancy, prior experience and belief systems) can influence various opioid and dopamine receptor systems to produce an effect,<sup>35</sup> giving physiological credence to centuries-old medical teaching (Galen) regarding the need for 'confident' physicians. The therapeutic setting can also produce very similar physiological changes using the same pathways.<sup>35</sup> What should not be forgotten is that the powerful antinociceptive or positive effects can also be mirrored with negative expectancy and 'anxiety amplification', the understanding of which continues to be driven by rapidly developing functional magnetic resonance imaging research.<sup>36</sup> Such nocebo or negative placebo effects also have a place in clinical trial design, depending on the research question being asked. It is likely that with large data set and machine learning input our understanding of these physiological areas will increase.





## Chapter 4 The current regulatory requirements for placebo-controlled surgical trials

It is a requirement for all clinical trials not only to be scientifically rigorous and ethically sound, but also to be conducted in accordance with all relevant regulatory requirements. This is particularly the case for placebo-controlled surgical trials, for which regulatory constraints may be especially stringent, given the invasive nature of the placebo and the complex nature of the trial design. Where available, regulatory guidance outlines the circumstances under which placebo-controlled surgical trials are permissible and any extra conditions imposed on the conduct of such a design. The most widely used regulatory guidance to date has been that of the American Medical Association (Chicago, IL, USA),<sup>37</sup> which outlines that surgical placebo-controlled trials are permissible when existing surgical procedures are being tested for efficacy or where there is no known surgical treatment currently available or non-operative treatment options are known not to be acceptable to patients. However, it highlights that additional safeguards must be included in the consent process if a placebo procedure is to be used.

Regulatory guidance has been noted to have two main roles for those designing placebo-controlled trials in surgery: (1) to constrain the inappropriate use of placebo surgical controls and (2) to justify the acceptability of a placebo surgical design under key circumstances. A more detailed description of this dual purpose to regulatory guidance can be found in the report of the KORAL (Knee Osteoarthritis: Role of Arthroscopic Lavage) trial<sup>38</sup> (a proposed surgical placebo-controlled trial of knee arthroscopic lavage).

A scoping review of relevant international regulatory guidance was undertaken. This involved a systematic electronic search for published regulatory guidance, an augmented text search of major medical/surgical association websites (including electronic codes of practice/ethics codes), a review of other known statements (e.g. the RCS of England statement on placebo surgery trial<sup>39</sup>) and direct contact with surgeons in different jurisdictions.

Most medical/surgical associations had only very generic references to the design and conduct of clinical trials. Where placebo controls are mentioned, they are primarily discussed in the context of placebo drug trials. The American Medical Association,<sup>37</sup> the Canadian Medical Association (Ottawa, ON, Canada),<sup>40</sup> the German Medical Association (Berlin, Germany)<sup>41</sup> and the RCS of England<sup>39</sup> did, however, explicitly discuss surgical trials (and surgical placebos). In addition, the New Zealand Medical Association (Wellington, New Zealand)<sup>42</sup> described the circumstances under which placebo controls could be used for testing 'therapeutic procedures' (which could encompass surgical procedures).

Regulatory guidance suggests that the use of a surgical placebo control needs to be carefully considered on a case-by-case basis. The risk of subjecting participants to a potentially harmful placebo intervention needs to be weighed up against the expected individual and societal benefits of undertaking the trial.

Where the balance of risks to benefits is deemed to be acceptable to clinicians and patients, regulation suggests the following:

- The use of a surgical placebo is justifiable to test the efficacy of a new surgical intervention.
- The use of a surgical placebo is justifiable to test the efficacy of existing surgical interventions (where doubts exist over benefits and where evidence of efficacy is lacking).
- The use of a placebo surgical control is not considered appropriate when a standard treatment that is known to be efficacious and acceptable to the patient exists or where the surgical technique under evaluation represents only a minor modification of an existing evidence-based surgical procedure.

In the circumstances where surgical placebos are deemed justifiable, regulation further suggests that:

- triallists should formally document the justification for their use of a placebo surgical control
- triallists rigorously consider the composition of the proposed placebo procedure and ensure that components are well specified and explicitly documented
- triallists explicitly consider the level of risk to the patient from the placebo and outline ways in which risks can be mitigated
- trials with a placebo surgical control arm provide enhanced information to participants and consider any expanded consent needs
- trials with a placebo surgical control arm consider enhanced monitoring with an option for early termination should the active intervention show effectiveness at any stage before the end of the trial.

## Chapter 5 Systematic literature review update for placebo-controlled surgical trials

As preparatory work for the workshop, we undertook a systematic review of previously conducted surgical RCTs in humans. This was an update of a previous review by Wartolowska *et al.*<sup>5</sup> until December 2017. (Although the review search strategy was completed in December 2017, we are not aware of substantive changes in the literature since that time.) The complete methods, findings and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) inclusions have been published separately.<sup>43</sup> The work is summarised here.

Data were extracted for trial characteristics and methodological areas of interest, including rationale for the use of placebo interventions, patient information, intervention standardisation and fidelity, delivery of co-interventions and anaesthesia, trials offering treatment interventions to patients allocated to placebo and how risk is minimised because of the invasive placebo.

Of 1864 newly screened articles, 50 were included (resulting in 96 RCTs in total). A large number of trials were gastrointestinal based ( $n = 40$ , 42%) and evaluated minimally invasive luminal endoscopic interventions ( $n = 44$ , 46%). Two-thirds of trials ( $n = 65$ , 68%) randomised fewer than 100 patients and approximately one-third of trials were conducted at a single site ( $n = 31$ , 32%).

### Rationale for use of a placebo intervention

Most trials did not provide an explicit rationale for using a placebo intervention. Some trials discussed the need to quantify potential placebo effects ( $n = 27$ , 28%)<sup>13,44-69</sup> and the role of placebo interventions in reducing bias ( $n = 9$ , 9%).<sup>13,45,50,61,65,67,70,71</sup> Using a placebo intervention to elucidate the mechanism of treatment action was seldom explicitly reported. However, 10 articles (10%) acknowledged that there was uncertainty as to which treatment components were responsible for the mechanism of action.<sup>13,50,53,63,69,72-76</sup>

### Patient information

Eleven trials<sup>8,13,44-46,63,70,72,77-79</sup> (11%) reported details of placebo-specific information given to patients. Three trials<sup>72,77,78</sup> specified that the placebo surgery would not treat the patient's condition. In contrast, one trial<sup>79</sup> informed patients that the placebo might improve symptoms. Four trials<sup>13,44,45,63</sup> did not use the term 'placebo' in patient information, with three of these trials instead describing the characteristics of both treatment and placebo procedures.<sup>13,44,45</sup> The remainder informed patients of the 'blinded' nature of the study. Two trials<sup>46,70</sup> reported that patients were informed that they might not receive the treatment intervention.

### Intervention standardisation and fidelity

Attempts to standardise interventions were reported in seven trials<sup>47,48,78,80-83</sup> (7%). Four trials<sup>47,48,80,81</sup> were delivered in accordance with a standardised protocol. One trial<sup>82</sup> agreed a standard approach by consensus with participating investigators. One trial<sup>83</sup> achieved standardisation by ensuring that all interventions were delivered by one clinician. One trial<sup>78</sup> said that a protocol 'was discussed in the minutest detail to ensure that it would be adhered to in a similar manner', although no specific detail of intervention delivery was given.

Four trials<sup>47,49,78,82</sup> (4%) reported strategies to monitor the delivery of interventions (fidelity), including videotaping ( $n = 3$ )<sup>47,49,78</sup> and 'monitoring of adherence to technique by the study chairman' (no further details given).<sup>82</sup>

## Delivery of co-interventions and anaesthesia

Pre-, peri- and postoperative co-interventions were reported in 45 (47%),<sup>45,47,48,50,51,55-64,67,71,73,74,76,78,79,82,84-105</sup> 31 (32%)<sup>13,48,50,51,55-57,59,60,62,67,71,73,74,76,81,83,85,92,94,99,106-115</sup> and 64 (67%)<sup>8,45,46,48-50,54-64,66,67,69,70,72-75,77-79,83,84,87,88,90-96,98-102,105-107,111,112,115-128</sup> trials, respectively, with details being matched between the treatment and placebo groups in 42,<sup>45,47,48,50,51,55-63,67,71,73,74,76,78,79,82,84-93,95-102,104,105</sup> 27<sup>13,48,51,55,56,59,60,62,67,71,73,74,76,81,83,85,92,99,106,108-115</sup> and 61<sup>8,13,45,46,48-50,54-64,66,67,70,72-75,77,78,83,84,87,88,90-95,98-102,105-107,111,112,115-121,123-128</sup> trials, respectively. Anaesthesia protocols were matched between groups in 64 (67%) RCTs.<sup>8,13,45,46,48,50-54,56,57,59,60-62,64,66,67,69-71,73,76,78,79,81,83,84,86,88,90-95,97,98,100,102-104,106,107,109,111,112,114,116,121-124,126,127,129-135</sup>

## Trials offering the treatment intervention to patients allocated to placebo

Forty-three (45%) trials<sup>45-49,51,54-56,58,59,61,62,64,66,68-71,73-75,77,78,84,85,88-90,95,97,99,107,109,111,112,114,119,121,122,124,125,132</sup> reported that the treatment intervention was offered to patients in the placebo group. Seven trials<sup>59,73,74,85,109,112,119</sup> were formal crossover trials and one<sup>112</sup> had a four-group trial design that randomised the order of intervention delivery. Rationales were given by 16 (37%) trials.<sup>48,55,56,58,61,62,64,68,69,73,75,78,85,95,112,122</sup> This included if patients had continuing symptoms ( $n = 7$ )<sup>48,55,56,62,69,78,122</sup> and for ethics ( $n = 5$ )<sup>62,68,75,95,122</sup> and methodological reasons ( $n = 3$ ),<sup>62,85,112</sup> such as reducing the likelihood of patients seeking treatments outside the study.

## Minimisation of risk

The degree of operator skill was reported in 22 trials (23%),<sup>13,47,50,51,55,59,69,70,74,78,79,83,85,91,94,99,100,105,110,121,123,128</sup> independent data monitoring was reported in 28 trials (29%)<sup>13,45,46,52,55,57,60,61,68,69,71,72,78,82,84,97-100,103,104,106,113,114,121,125,128,136</sup> and an unblinding protocol was provided in one study.<sup>84</sup>

Ninety-six placebo-controlled surgical trials were identified.<sup>8,13,44-79,81-83,85-138</sup> Most were small (< 100 patients), focusing on minimally invasive endoscopic techniques. Quantifying placebo effects was the most common reason given for using placebo interventions. The information provided to patients was variable. A small number of trials reported minimal information about standardisation and fidelity of interventions. Two-thirds of trials matched anaesthesia protocols between the treatment and placebo groups and nearly half of the trials offered treatment to placebo patients.

Reporting of placebo surgical RCTs is limited. Specifically, there is a need for clearer rationales for placebo use, patient information provision, standardisation and fidelity of interventions and the use of co-interventions. Standardised reporting guidelines may be useful. In addition, consideration for how to minimise risk and whether or not patients in the placebo group should be offered the treatment intervention is necessary.

## Chapter 6 Ethics considerations for placebo-controlled surgical trials

Some of the text in the following section is reproduced with permission from Hey *et al.*<sup>139</sup> Reprinted by permission from Springer Nature, *Monash Bioethics Review*, Hey SP, Weijer C. What questions can a placebo answer? *Monash Bioeth Rev* 2016;**34**:23–36. Copyright 2016.<sup>139</sup>

Unlike patients treated in routine clinical practice, participants in research are exposed to risk primarily for the benefit of others.<sup>140</sup> It is this feature of research that drives the need for the ethics protection of participants. The use of placebo controls in RCTs in surgery illustrates this well.<sup>11,141</sup> When surgical interventions that lack an evidence base are used, there are compelling scientific reasons to evaluate them in comparison with a placebo control. However, should participants be exposed to the risks of a placebo surgical intervention that lack the presumptive causally effective element? On the surface, at least, such participants are being exposed to all of the risks of surgery, with none of the benefits.

Empirical research indicates that key stakeholders believe that placebo-controlled surgery trials can be ethically defensible. One study<sup>142</sup> found that a majority of the doctor respondents believed placebo controls to be necessary and such trials to be ethically permissible, although there was less agreement about the permissible degree of invasiveness and about the appropriateness of open trials. Another study<sup>143</sup> found that, despite some initial misgivings, researchers also accept the rationale for placebo controls. Patients' views appear to vary, as studies involving patients both with and without Parkinson's disease suggest.<sup>144</sup> Patients without Parkinson's disease appear more willing to participate in such research directed at this condition than those with the condition. This may be associated with members of the latter group having adapted to the condition, the personalities of the different respondents or the relative ignorance of those in the former group.<sup>144</sup> However, patients with Parkinson's disease have endorsed placebo trials, especially once educated about such trials.<sup>144</sup> Another study<sup>145</sup> found a small majority of such patients to be in favour. This was associated with their support for research generally, which indicates a need for potential participants to trust in the research endeavour and in the researchers themselves.<sup>145</sup>

To earn the trust of participants, it is important that placebo trials conform to acceptable ethics standards. The Belmont Report<sup>146</sup> outlines internationally accepted ethics principles for human participants research: (1) beneficence, (2) justice and (3) respect for persons. The principle of beneficence requires researchers to ensure that the benefits and harms of study participation stand in reasonable relation. The principle of justice concerns the fair distribution of the benefits and burdens of research. This means that researchers should ensure adequate protections for vulnerable participants and that the results of medical research should benefit society broadly. Finally, the principle of respect for persons enjoins researchers to take seriously the autonomous choices of participants and to protect those participants who lack the capacity to make their own decisions.

The use of any kind of placebo in research raises an ethics tension between the researcher's duty of care to those participating in the trial and society's interest in scientifically valid medical research. The reason for this is that, although the use of a placebo control may be required for a study to provide a scientifically valid answer to a particular research question, it is not immediately clear how the use of placebos can be compatible with the ethics principles articulated in The Belmont Report.<sup>146</sup> Therefore, how can one reconcile the use of placebos in surgical trials with ethics principles?

Placebo surgical control for a randomised trial aligns with the principle of beneficence, provided that the risks are considered and reasonable and potential benefits exist.<sup>11</sup> A component analysis can be used to determine the ethical acceptability of any potential benefits and risks of a trial.<sup>147</sup> In such an analysis, therapeutic procedures within the intervention must be considered separately from any

non-therapeutic procedures. This clear disconnect is not always possible, as a placebo surgical intervention may have added physiological effects, despite lacking the critical surgical element. Therefore, any surgical placebo control usually includes both warranted therapeutic and non-therapeutic procedures.

Therapeutic procedures (e.g. drugs or surgical interventions) must fulfil the ethics requirement of clinical equipoise. Clinical equipoise is defined as a state of 'honest, professional disagreement among expert clinicians about the preferred treatment'.<sup>148</sup> This disagreement (or uncertainty) is best understood as grounded in absent, preliminary or contradictory evidence regarding the safety and effectiveness of a treatment. The point is that, if equipoise obtains, then it does not matter 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 medical care.<sup>147</sup>

Non-therapeutic procedures (e.g. non-clinically indicated questionnaires or blood draws) must fulfil two different standards.<sup>147</sup> First, the harms posed by the intervention must be minimised and consistent with sound scientific design. Second, the risks posed by the non-therapeutic intervention must be outweighed by the value of the knowledge generated. The first standard asks us to consider whether or not the risks are necessary and the second standard asks us to consider whether or not the risks are proportionate.

Placebos in surgical trials comprise both therapeutic and non-therapeutic elements.<sup>149</sup> Insofar as the surgical placebo is a therapeutic intervention, it is best regarded as a no-treatment intervention, given that it lacks the presumptive causally effective element of the surgical intervention. No-treatment interventions are compatible with clinical equipoise when:

1. *there is no effective treatment for the condition;*
2. *the trial population is enriched for treatment-resistant patients;*
3. *the study is a test of an add-on treatment versus placebo and all patients receive at least standard of care;*
4. *treatment exists, but non-treatment is still consistent with competent care; or,*
5. *the effectiveness of the standard of care has been called into question either by new evidence or by doubts about the supporting body of existing evidence.*

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The last criterion is particularly relevant to the assessment of surgical procedures in common use. When the evidence base supporting a procedure in common use is poor, such as for arthroscopic repair of injured shoulders, the use of a placebo control is consistent with clinical equipoise.

The ethical principle of justice requires that researchers ensure that adequate protections are in place for vulnerable participants. Vulnerability may be defined as an increased risk of being wronged in research, where wrongs encompass autonomy, welfare and justice wrongs.<sup>150</sup> Persons who are unable to provide informed consent for participation in a surgical trial are at risk of an autonomy wrong. Generally, their participation is permissible only when (1) the study hypothesis requires their inclusion, (2) surrogate consent will be obtained from a legally authorised representative and (3) study participation involves no more than minimal risk. When surgical placebos involve procedures such as an incision, anatomical dissection, insertion of an arthroscope into a joint and anaesthesia, they will pose risks that predictably exceed those of the daily life of healthy persons. In such cases, the inclusion of persons who cannot consent to research participation, including children and incapable adults, is impermissible. Moreover, justice might also require, where a trial establishes the utility or success of a particular intervention, that this should be provided to all of the trial participants. This was certainly the view advanced by researchers.<sup>143</sup>

Finally, can the principle of respect for persons be satisfied in placebo-controlled surgical trials? Surgical trials with a placebo control are inherently complex studies and clearly conveying to prospective participants what is at stake is a challenge. Empirical research reveals that researchers are, perhaps unsurprisingly, well informed about placebo designs and their rationale.<sup>143</sup> Patients' understanding appears to vary. The same research suggests that some would be willing to participate because of disease severity or desperation (due to a lack of effective treatment or experimental interventions being restricted to trial participants). The researcher queries whether or not participation on such bases is sufficiently voluntary and, therefore, autonomous.<sup>145</sup>

Employing a rigorous informed consent process can help to satisfy concerns about autonomy. Naturally, the scientific validity of a placebo-controlled study will require that participants are blinded to treatment allocation. When participants are blinded, respect for persons requires that they be informed of the treatment that they received at the end of the study.

One obstacle to obtaining valid informed consent to research participation is the so-called therapeutic misconception, whereby research participants systematically misunderstand research elements, such as randomisation or placebos (whose purpose is solely to further the ends of science) as being designed to benefit them directly.<sup>151</sup> Qualitative research has found that a majority of individuals with Parkinson's disease and their relatives would wish to be in the active treatment arm of a placebo-controlled surgical trial, as they believe this means that they would be most likely to benefit.<sup>145</sup> This might suggest a lack of understanding of trials.<sup>145</sup> Just as component analysis requires the clear separation of therapeutic and non-therapeutic procedures in a trial for benefit-harm analysis, so too must informed consent clearly identify which procedures hold out the realistic prospect of direct benefit and which are performed to further science only. Inter alia, it is important that surgical placebos are not described in therapeutic terms, such as 'treatment', 'active' or 'diagnostic', when there is no clinical indication for the placebo procedure.

As some placebo-controlled surgical trials pose an unusually high degree of non-therapeutic risk, additional protections may be indicated. 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.<sup>152</sup> Testing research participants' understanding of consent information is a useful means to document understanding.

## Key ethics messages

- Placebo controls may be used in RCTs of surgical interventions provided that there is a strong scientific and ethics justification for the study.
- Clinical equipoise must be obtained among the study arms. Clinical equipoise may permit a placebo control when a surgical intervention is widely used but lacks an evidence base.
- The non-therapeutic risks of a surgical placebo can be justified only if (1) the study question cannot be answered with a different design and (2) the risks are outweighed by the importance of the knowledge to be gained.
- Generally, surgical trials with a placebo control may not enrol children or incapable adults unless the risk to the participants can be demonstrated to be minimal.
- In the informed consent process, surgical placebos should not be described in terms that may unwittingly lead participants to believe that they are clinically indicated.
- Informed consent procedures may be augmented with enhanced consent forms, additional discussion time and testing of participant understanding.
- Participants should be informed of the intervention to which they were allocated when the study is complete.
- Where a trial establishes the utility or success of a particular intervention, the intervention should be provided to all the trial participants.





## Chapter 7 Design of placebo-controlled trials in surgery

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There are several generic trial design issues that have a particular importance in the context of surgical placebo trials, including the content of the intervention, the choice of comparison arm or arms, whether to use a two- or three-arm trial design (with related multiplicity consideration), achieving sufficient statistical precision and the consideration of risk. These inter-related topics are considered below.

### Designing invasive placebo interventions: content of the intervention

The design and content of the placebo are important aspects of placebo-control methodology in surgical trials. As part of this work, we undertook an in-depth review and extension of a previously published surgical taxonomy to allow the characterisation and optimisation of a surgical placebo. The work has been written up in detail separately.<sup>15</sup>

In summary, the process involves deciding what aspects of the treatment intervention need to be delivered as part of the placebo, providing a framework to enable its adequate description. Equally, it is important to describe what parts of the intervention can or need to be omitted (i.e. identifying and removing the 'critical surgical element') (see *Chapter 2*). The choice involves consideration of any risk to patients by addition or omission of components and any strategies required to ensure that the placebo sufficiently mimics the treatment in question.

The work, led by Cousins *et al.*,<sup>15</sup> provides a comprehensive framework to deconstruct the surgical intervention into its component elements. This allows the critical surgical element to be identified and removed to generate the placebo. The resulting DITTO framework consists of five stages (*Table 3*).

This newly developed framework can help in the design of high-quality RCTs and to standardise intervention content.

TABLE 3 The DITTO schema<sup>15</sup>

DITTO stage	Description
D	Deconstruct treatment intervention into constituent components and co-interventions
I	Identify critical surgical element(s)
T	Take out the critical element(s)
T	Think risk, feasibility and role of placebo in the trial when considering remaining components
O	Optimise placebo to ensure effective blinding of patients and trial personnel

The intervention group should always represent the surgical procedure being studied, but the level of standardisation of the surgical technique can vary according to the aims of the study design [i.e. where the study lies on the spectrum of explanatory (tightly controlled) to pragmatic (usual care, often with some differences between surgeons, but with greater generalisability)]. The surgical intervention should also take account of adjunct treatments, such as rehabilitation and medical treatment.

## Comparisons and control groups in placebo-controlled surgical trials

At its simplest level, two basic alternative trial designs have been proposed for placebo-controlled trials: (1) a two-arm comparison of placebo with active intervention and (2) a three-arm trial that has the same two arms supplemented by a third, no-treatment, arm. The surgical equivalence is illustrated by the FIMPACT (Finnish Subacromial Impingement Arthroscopy Controlled Trial)<sup>153</sup> and CSAW trials.<sup>13</sup>

The two-arm study is a relatively straightforward proposition and is a direct evaluation of the effect of inclusion of the critical or active surgical component of the procedure. The difficulties surrounding this comparison involve patient consent and equipoise (see *Chapter 8*).

The three-arm trial, with inclusion of a no-treatment arm (for a three-way comparison), does add complexity, but can be a particularly useful design to track and compare against natural history/recovery. It also can provide information for quantifying the scale of potential placebo effect for the procedure. However, the three-arm (or more) trial can be particularly challenging in terms of both analyses and trial conduct. One of the main challenges is obtaining parallel start times for the intervention in all groups. For various reasons, intervention can be delayed under some health-care systems (including routine waiting times for receiving surgery within the clinical setting in some health-care systems). By definition, 'no treatment' is never delayed and there is also the possibility of 'crossover' to a more active intervention group during the trial, either for rescue or because of lack of benefit.

In reality, placebo-controlled surgical trials offer several possibilities for the content of the control group, depending on the intervention and the research question. The pros and cons of each control group option are listed below. Although in some circumstances many comparison control groups may be desirable, this must be weighed against the logistics and cost of a multiarm trial, along with the complexity of analysis and difficulty with interpretation of multiarm studies, which may provide complex and mixed messages for the reader and, therefore, affect the ability to change practice.

Altogether, there are four possible control groups (arms) with different content for a surgical placebo trial, and each is listed below. The SUCceSS (SUrgery for Spinal Stenosis) trial,<sup>154</sup> which tested spinal canal decompression by laminectomy (for spinal stenosis), will be used as the exemplar.

### *High-fidelity placebo surgery*

High-fidelity placebo surgery is placebo surgery that contains all elements of the surgical procedure, but with the critical element removed (as discussed, see the *Scientific summary* and *Chapter 3, The psychological aspects of placebo*). For a trial testing spinal canal decompression, this would involve anaesthesia, a skin incision and full muscle dissection, but not the removal of bone to decompress the spinal canal. Other intraoperative and postoperative care would be identical to the intervention group. The advantage of using this comparator is that it tests the effect of the active component of the surgery (decompressing the spinal canal) and tightly controls for all other factors. The disadvantage is that it may carry some benefit itself (e.g. through denervation of the posterior elements of the spine), such that if the two groups are similar in effectiveness then this does not tell us if both interventions are effective or if both are ineffective. The content of the placebo treatment and similarity to the intervention should be considered both in terms of fidelity and the DITTO framework.

### **Low-fidelity placebo surgery**

The lowest fidelity is a placebo surgery with no or minimal intervention (see the *Scientific summary* and *Chapter 3, The psychological aspects of placebo*). This has been called 'sham' in the past, although, as previously stated, this term is not helpful for recruitment purposes. It may, for example, involve a skin incision only. The advantage of using this comparator is that it minimises the risks associated with placebo surgery by minimising the extent/invasiveness of the surgery. It also tests more of the overall surgical procedure (e.g. muscle dissection and decompression) and not just the critical element. The disadvantage is that it does not test the critical element in isolation, as a high-fidelity comparison might do. A further issue, as potentially observed in trials such as SUCceSS,<sup>154</sup> is the potential for unblinding with a low-fidelity model. Difference in surgical duration, pain/discomfort after surgery and postoperative care could be different between groups and the risk of unblinding is high. A low-fidelity placebo surgical intervention should not be confused with non-surgical care.

### **Best non-surgical care**

Best non-surgical care has the advantage of testing the entire surgical procedure and of reflecting the real-life alternatives (surgery vs. best non-operative care). 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.

### **No treatment**

No treatment has the advantage of measuring the natural history of the condition without new treatment and is an important control group when ascribing improvement in any of the other groups to the intervention received (e.g. it would test if best non-operative care is superior to no care). This has the disadvantage of not allowing for improvements potentially due to placebo, concomitant treatment or non-operative care. It is important to note that a 'no-treatment' group, in this context, is really no surgery or 'no additional treatment', as patients are allowed to continue with existing non-surgical modalities, such as medication, albeit in a regulated and usually monitored way.

## **Analysis features in the design of surgical placebo-controlled trials**

A further challenge related to the three-arm trial is the issue of multiplicity of comparisons.<sup>155</sup> Typically, pairwise comparisons would be considered the most informative (allowing direct contrasts and quantification of the treatment effect). The three-arm design, unlike the two-arm design, offers options with the associated potential for formal statistical adjustment for multiplicity (i.e. various approaches could be adopted). Some authors have provided compelling arguments not to penalise different comparisons that relate to different research questions.<sup>155</sup> In the context of surgical placebo control, it raises the issue of whether or not a surgical placebo intervention is considered a valid interventional option in its own right. In terms of multiplicity and wider considerations, is the contrast of the surgical placebo intervention and no treatment a valid one to undertake?

In the context of surgery, compliance with treatment allocation is another concern for placebo-controlled studies, given the potential explicit or implicit preferences of surgeons. This potential lack of equipoise and its effect on trial conduct should be considered at the design stage.

Last, a trial design issue within the context of placebo-controlled surgical trials is the legitimate concern about whether or not these trials are of sufficient size to identify the meaningful effect. A recent systematic review<sup>43</sup> identified the median trial size to be small, with only 65% of all studies randomising > 100 patients. Only a handful of trials have had > 200 participants in the surgical arms. When such a sample size is translated to target differences that can be detected under standard conditions (i.e. two-sided significance level of 5% and statistical power of 80% or 90%), only large effects can be confidently be detected. Offsetting this concern is perhaps the general expectation that, at least for most of surgery, the benefit of the active intervention should be large enough to justify the risk. However, such considerations do reaffirm the need to for care in the choice of outcomes and the primary outcome in particular.

## Is placebo intervention risky and how to mitigate risk

The ethics arguments previously presented on the use of placebo surgical controls highlights the need for mitigation of potential risk from placebo interventions. There are opposing views on the degree of risk for surgical placebo interventions. Wartolowska *et al.*<sup>5</sup> showed that trials (albeit in endoscopic or minimal access interventions) that included a placebo surgical control had no greater risk than other treatment or control groups. Although work from the German Society of Surgery (Berlin, Germany) showed that the frequency of serious adverse events was comparable between true intervention and placebo, they expressed concern that trials of more invasive placebo interventions might entail a greater risk for study participants.<sup>6</sup> The ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) study in interventional cardiology is a good example of a study in which the frequency of adverse events was higher in the placebo group than in the normal treatment group.<sup>45</sup>

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 the risks of a surgical treatment 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 (e.g. anaesthetic), 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 American Society of Anesthesiologists grades 1 and 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 experienced surgeons only who are familiar with the surgical intervention under evaluation
- enhanced monitoring with oversight committees.

Therefore, it is important that all means of risk mitigation are explicitly outlined before undertaking a placebo-controlled surgical trial. When 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 riskier the procedure then the more urgent the need for a sufficiently robust (placebo-controlled surgical) trial.

If the use of a placebo control is scientifically justified then the next step is to mitigate the risk of this incomplete surgery by reducing its invasiveness as far as possible. As previously stated, an unintentional unblinding should be guarded against to avoid loss of the methodological advantages of a placebo comparator (and, therefore, making its use and the whole trial futile).

## Chapter 8 Trial conduct and recruitment in surgical trials

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### Patient information for placebo-controlled surgical trials

The ethics and legal requirements for potential participants to provide informed consent for inclusion in a randomised trial are well established. These include both verbal and written information explaining the purpose of the trial, research procedures, risks and benefits, end-of-trial provisions, source of funding, conflicts of interest, and institutional affiliations.<sup>156</sup> Potential participants should be made aware of refusal rights and the ability to withdraw their consent at any time.<sup>156,157</sup> This routine regulatory guidance does not contain explicit requirements for placebo surgery trials. Both the European Medicines Agency's Guideline for Good Clinical Practice E6 (R1)<sup>158</sup> and the US Food and Drug Administration's guidance for informed consent<sup>159</sup> information sheets contain only general requirements about placebo trials, mostly designed for drug trials and not placebo-controlled surgical trials.

Section 2 in this guidance<sup>158</sup> on the current regulatory requirements for placebo-controlled surgical trials highlights the suggestion from several medical associations that trials with a placebo surgical control arm should provide enhanced information to participants and consider any expanded consent needs. However, the details of how this should be operationalised in terms of exacting information for placebo-controlled surgical trials has not been specified. There are some broad items of content information for placebo-controlled trials that could be considered:

*A full description of the placebo-surgical 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;*

*Possible risks or discomforts linked to both the index and the surgical placebo procedure.*

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It is, however, important to recognise that these items may not be applicable to all placebo-controlled surgical trials and will be dependent on the nature of the placebo. For example, when considering a placebo with no fidelity (i.e. a sham procedure) (see *Table 1*), it would be necessary to inform potential participants that allocation to the placebo may not result in personal benefit. The converse, a high-fidelity placebo, may confer some potential benefit on the participant and so needs to be framed accordingly. The fidelity spectrum for placebo controls will be key in considering what information should be included in the information provided to and shared with potential trial participants. This should help to address concerns over the therapeutic misconception in trials of this type.

In addition to the information provided to potential participants on the placebo comparator in surgical trials, it is important to consider how to present information on the surgical intervention being evaluated to promote informed choice about participation. The surgical intervention will probably be the current standard of care and what the patient will receive should they choose not to participate in the trial. The information provided on the risks of the surgical intervention needs to be considered equally with regard to the placebo comparator. For example, the risk of a general anaesthetic for both the surgical intervention and the placebo should be considered alongside the risk of surgical site infection, especially when the placebo comparator is of low fidelity.

Methods to specify core content for patient information for trials while working with potential participants are available.<sup>160</sup> These opportunities for the co-production of information in advance of the trial will be key for developing patients' information for placebo-controlled surgical trials that is fit for purpose. In addition to the core content, considering how the information is provided to enable support for decision-making is also important. Rogers *et al.*<sup>161</sup> have proposed the use of decision support tools (namely decision aids) to help potential participants deliberate over their participation in placebo-controlled surgical trials by improving research literacy and attending to potential concerns over therapeutic misconceptions. There is preliminary evidence that the medium (e.g. verbal, written, audiovisual) and who (e.g. the surgeon) presents the information may also make a difference to potential trial participants in placebo-controlled surgical trials.<sup>162</sup>

As well as information provided to potential trial participants at the point of considering participation in a trial, written (and often verbal) information is provided throughout the trial in the form of follow-up questionnaires, newsletters and trial results. Each interaction with a participant requires consideration regarding the information being shared with them and how that may have an impact on aspects of the placebo-controlled surgical trial that are important for conduct and analysis (i.e. considering the information continuum across the lifetime of the trial).

### Maximising recruitment

Overestimation of the pool of available eligible patients is common, and especially true for placebo-controlled surgery trials. A systematic review<sup>7</sup> of placebo surgery trials (63 studies published between 1959 and 2014) found that slow recruitment that was directly attributable to eligibility was a substantial barrier to trial completion. It was found that approximately five people needed to be screened to identify one eligible person. In an Australian placebo-controlled trial<sup>50</sup> of vertebroplasty, performed before the procedure was widely available in that setting, only 34% (of 468 people screened) were eligible. Almost half (49%) of those found to be eligible agreed to participate.<sup>50</sup> A recruitment strategy that included direct-to-consumer adverts using a range of media failed to substantially improve the pool of eligible people. A more focused approach to doctors who manage vertebral fractures across primary to tertiary care was more successful.

Recruitment into placebo-controlled trials testing treatments that are already widely accepted, available and affordable, despite an absence of high certainty evidence supporting their use, is especially challenging. Both surgeons and patients may be reluctant to accept a 50% chance of placebo, particularly when placebo involves invasive surgery. In any case, recruitment planning of both surgeons and participants must necessarily start early, as it is essential to determining the feasibility of the trial.

Several recent initiatives have developed frameworks for strategic recruitment planning, and these highlight the need for realistic budgets and resources to support recruitment.<sup>163</sup> At the trial design and protocol development phase, Huang *et al.*<sup>163</sup> have highlighted that it is essential to identify and engage all stakeholders, ensure the relevance of the scientific question and have realistic eligibility criteria. Trial feasibility requires evidence-based feasibility analyses, having realistic metrics and milestones, and ensuring appropriate site selection and performance monitoring.

Recruitment communication planning can strongly facilitate a trial. It involves identification and engagement of all relevant stakeholders, clarifying treatment pathways, developing and testing tailored and creative messages/materials, and monitoring and evaluating process and performance. The QuinteT Recruitment Intervention system for optimising recruitment and informed consent pioneered by Donovan *et al.*<sup>164</sup> has been very successful and is based on identification of the motivators of and barriers to trial participation.

Increasingly, business models and modern marketing theory and techniques have also been used to inform strategies for recruitment.<sup>165–167</sup> For example, McDonald *et al.*<sup>166</sup> recommends developing and building brand values that gain prestige and legitimacy and signal worthiness of the trial; developing an explicit market plan, including strategies for overcoming resistance; making the ‘sale’ through achieving public buy-in, delivery of a multiaudience, multilevel message and engaging champions and change agents; and maintaining engagement via provision of frequent positive reinforcement and facilitating incorporation of recruitment into usual routines.<sup>166,168</sup>

Embedding recruitment intervention studies and sharing the results will also ensure advancements in trial recruitment for placebo surgery trials, but there is currently a paucity of data in this space. For example, a 2018 Cochrane review<sup>168</sup> investigating strategies to improve recruitment into clinical trials included 68 RCTs; however, none of the RCTs was a placebo surgery trial. Likewise, a review published in 2015 included 17 trials investigating training programmes for recruiters to RCTs also failed to identify any programmes specifically for recruiters of placebo surgery trials.<sup>169</sup> The latter review found that, although training increased recruiters’ self-confidence in communicating key trial concepts to potential participants, there was little evidence that it increased recruitment rates.

Furthering our knowledge about how to optimise recruitment into placebo surgery trials, including the information that is provided for potential trial participants and who should provide that information, is crucial. It is well known that the preferences of patients, as well as health professionals, including surgeons who provide the treatment, can have a decisive influence on trial recruitment:<sup>170</sup>

*These questions include whether transmission of preference can be mitigated if consent is obtained by a trained and ideally neutral recruiters; whether well-informed patients are more or less likely to accept random assignment to; 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.*

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## Placebo-controlled surgical trials: the patient’s perspective

The patient’s perspective is crucial to the design, conduct and analysis of placebo-controlled surgical trials. The patients’ partners gave this critical reflection:

*As patients and patient representatives, it was a privilege for us to be invited to the Workshop; to contribute but also to learn more about the fascinating world of placebo surgery trials.*

*The patient follows a journey: through development of symptoms, to medical consultation, enrolment in the trial, treatment (or pseudo treatment), follow-ups, recovery (or not) and ultimately ‘unblinding’. Patients join clinical trials for a variety of reasons and for each there may be a mixture of altruism, self-interest and curiosity. Many patients will have reached a point where they feel desperate to find a solution to their symptoms. Any observations about the process of recruitment are necessarily personal and anecdotal. This said, clear and simple explanations of what participation will involve answering questions, enabling a dialogue and, significantly, clarifying what options are open to the patient during the trial. It is obvious that at no point should the participant feel that they were deceived about any aspect of the trial.*



*All patients benefit from being informed, supported and having a good relationship with their clinicians. It is the same for participants in clinical trials and perhaps not more or less for those in placebo surgery trials. There must be trust and confidence not only in the lead clinician, but in the whole team administering the trial. Some patients felt that, having had potential participation broached to them by their surgeon, it was helpful for more detailed discussions and decision-making to take place separately, with a different member of the team.*

*The 'unblinding' stage is a key one and it is important that patients know both when and how they can access this information. Not all will be familiar with electronic communication and more traditional methods, such as letters, should be offered. This also applies to the published results of their trial. This is of great importance to participants and so it must be presented in an easily digestible form.*

*Any participants whose symptoms are persisting will need continued treatment and support.*

*Friends and family tend to be very interested in the experiences of participants and favourable reports to them may open the door to future volunteers.*

These reflections echo the conclusions from the ethics and trial literature that communication is key, and that potential risks and benefits of participation need to be clearly laid out (as identified in *Chapter 4*). Timely and direct feedback of trial results is also crucial.

### **Placebo-controlled surgical trials: the surgeon's perspective**

The surgeon's position with regard to a placebo trial can be a difficult one. Surgeons who are investigators for the study and fully believe in the utility of the placebo-control methodology often have different perspectives from those who are simply recruiting to the trial. The recruiting surgeons must explore and satisfy their own position of equipoise. This is not straightforward, as surgeons have been trained to make clear-cut decisions and, as a rule, do not sit easily in a landscape of uncertainty, especially the uncertainty that a postulate of a placebo-controlled surgical trial brings. The patient is expecting their surgeon to express confidence and reassurance about the operation they are about to perform, and the reason for doing it, but is told that they can be recruited to a study that questions the very benefit of the proposed treatment. Both surgeon and patient are asked to accept that the evidence for the treatment is insufficient and this can generate concerns for both groups. The explanation of a control treatment of surgery that may have some risk without necessarily any benefit is an added layer of complication to convey to a vulnerable patient.

Reconciliation of these positions can take substantial consideration. Ultimately, as the ethics literature in *Chapter 2* highlighted, the surgeon has to believe that the evidence for the intervention under assessment is insufficient and that a placebo design is the best, or the only, way of providing the evidence. Only then can surgeons discuss the merits and issues with a patient and recruitment be successful and fully informed. Qualitative research in these areas can help considerably with this process, as has been seen in the ProtecT (Prostate Testing for Cancer and Treatment) study in urology,<sup>171</sup> the CSAW study<sup>13</sup> and the wider area of trials recruitment involving surgeons.<sup>164,172</sup>

There is an increasing acceptance among the surgical community that surgery and surgical intervention requires more comprehensive and rigorous evaluation, and this is helping surgeons become familiar with the needs for involvement and recruitment to surgical trials. It is essential that surgeons involved in placebo-controlled trials are fully knowledgeable of the rationale, conduct and implications of these types of studies, especially the teachings on community equipoise and uncertainty.

## Placebo-controlled surgical trials: the anaesthetist's perspective

A theme that appeared in this previous work in this field was the identification that key stakeholder groups for such trials are broader than previously understood and that previously less prominent stakeholder groups are very influential. An important example of this is anaesthetists.

Anaesthetists do not necessarily have major involvement in the diagnosis, prognostication or identification of treatment trajectories and outcomes in patient groups that may be considered for such trial methodologies (e.g. patients with osteoarthritis), but are key clinical stakeholders when it comes to patient safety around the perioperative period. Importantly, the perioperative period is where the greatest risk to patients lies in placebo trials and, therefore, the area where the greatest focus comes from clinical, ethics, regulatory and other risk management stakeholders.

An interesting example of this comes from the KORAL study.<sup>38</sup> It might be thought that anaesthetists would consider sedation and local anaesthesia, or perhaps regional anaesthesia, to be the safest anaesthetic techniques to use when delivering a trial intervention, as these appear on the face of it to be relatively low-risk techniques. However, when asked, a significant majority of anaesthetists taking part in a focus group thought that general anaesthesia with full control of the airway was the safest procedure, and, importantly, they also pointed out that general anaesthesia would supply the highest fidelity placebo for the proposed study intervention. According to the anaesthetists, intravenous sedation techniques have been reported in the medical literature to be unsafe, and their own experience showed that local anaesthesia techniques are often insufficient for surgery, with implications for both patients and control group fidelity. These conclusions were the opposite to those drawn by the lay reviewer and by trial team members from medical backgrounds other than anaesthesia (e.g. the surgeons), showing the benefit of such expert engagement. Conversely, if anaesthetists are to assess the risk-to-benefit ratio in proposed placebo surgery trials, they need to understand the potential benefit of the proposed surgical procedures so that they can weigh this against the risks of anaesthesia from the perspective of their own clinical expertise.

To allow such high-level engagement, anaesthetists must be integrally involved in the acceptability phases of future proposed studies (e.g. in the design and piloting of the intervention, as well as informing the ethics and regulatory decision-making from the perspective of patient safety). Anaesthetists are identified as key stakeholders in all future research involving local or general anaesthesia, as well as intravenous sedation, for placebo trials.



# Chapter 9 Interpretation of placebo-controlled surgical trials and changing practice

## The statistical analysis plan and potential results scenarios

All clinical trials should have a statistical analysis plan. This gives an a priori opportunity to review potential scenarios for the results of the trial, what the results might mean and how this is translated into clinical interpretation. This process is especially important for placebo-controlled trials. The complexity of a multigroup design, perhaps with a no-treatment arm, brings about many possible interpretation permutations (see *Chapter 3, The physiological aspects of placebo*). The surgery can be shown to have more benefit than placebo or no treatment, or maybe no added benefit. A hierarchy of benefit may be proposed perhaps with surgery being more beneficial than both placebo and no treatment.

One of the advantages of outlining the various possible results scenarios is to prepare for any clinical conclusions and potential obstructions to change of practice (outlined below). Early consideration of difficult commissioning decisions can be shared upfront with the surgical community conducting the trial if the options are reported. Sudden realisation from surgical personnel that they have been involved in a study that questions the value of an established procedure can be alarming and have negative influences on any change of practice and acceptance of that change.

A further stage for the future might be to fully explore what the trial results might mean with all parties before the trial has even started. The discussion around whether or not a placebo treatment still has sufficient benefit or merit to be commissioned or provided as a treatment in itself could also be had at this time.

## Translation into change of policy and practice

Many of the placebo-controlled trials of surgery reported to date have shown no benefit of the definitive procedure over the placebo-controlled intervention. The design is popular and used frequently to explore treatments with suspicious efficacy and effectiveness. Bearing in mind the ethics and academic justifications required (see *Chapters 6 and 7*) for a surgical placebo control, reasonable preliminary evidence is, therefore, required to show that part or all the treatment effect of the surgical procedure under investigation might be due to the placebo effect. As previously reported, investigation of a treatment that has no such placebo component, or even a general belief that surgery has no placebo effect at all (Dr Teemu V Karjalainen, Central Hospital, Finland, 2020, personal communication), would not require a placebo-controlled evaluation.

With this backdrop and focus on established, if questionable, procedures, investigators responsible for undertaking such trials must anticipate that any 'no difference' results of the trial will be disruptive to accepted clinical care pathways and guidelines. Investigators should also expect, and be prepared for, resistance from clinicians and patients whose beliefs and convictions are being challenged by the findings. Such trials will also generate interest from payers (state and insurance based), press and media.

Once change is indicated, there can be a long lag between research findings and change in practice, as exemplified by trials of knee arthroscopy. In the case of knee arthroscopy for osteoarthritis, although the original publication was in 2002,<sup>72</sup> it took 15 years for the findings to be partially adopted, despite several other high-quality studies replicating the findings. Similar resistance from the clinical community

has been encountered with trials of vertebroplasty for osteoporosis<sup>50</sup> and subacromial decompression for shoulder pain.<sup>13</sup> There are consistent features of the resistance and these include a belief by the surgical community that the patients in the trial do not represent the usual population undergoing the procedure. It is also suggested that the surgeons involved in the trial may not be sufficiently expert in the procedure. In other words, a feeling that the trial results 'do not apply to me and my practice' is commonplace. This sentiment is highlighted by the expressed views of 15 combined surgical associations of one European country. These associations have advised that, contrary to previous reports, the CSAW trial does not provide any new insights and there are no consequences from the CSAW study for this country's health system. The response in the UK was starkly different with NHS England moving to de-implement subacromial decompression surgery by placing it on a list of 'ineffective' treatments.<sup>173</sup>

The question then becomes 'How can the challenge of effective and timely change of policy and practice be improved?'. There are ways to facilitate, and ideally consideration of any impact should be included in the design phase and conduct of the trial. Most importantly, this should include key leaders in the patient groups, professional associations and clinical communities involved in delivering the investigated treatment. If the results are likely to have global impact then consideration should be given to involving international investigators. There should be 'buy-in' from patients and professionals. As soon as results are known, further discussions and the production of joint statements are necessary. If the implications are that the procedure will likely be performed less frequently then advice for patients about alternative treatment is essential.

### The policy-maker's perspective

Policy-makers consist of two broad groups: (1) those who issue guidance about how health-care interventions should be used and (2) those who commission and pay for services. In most health systems, those who make decisions about service provision attempt to maximise the health returns obtained for the investment [e.g. by maximising the quality-adjusted life-year (QALY) output of any health services provided]. Evidence of value from studies employing a placebo control and the value of any placebo effect itself may be viewed differently by each side.

Payers (e.g. commissioners in the English NHS and insurance companies in many European countries) tend to value a QALY gain, regardless of its origin. If a policy provides a net health gain for a reasonable price and is acceptable to patients and society, then the mechanism by which that gain occurs may not be considered important. The health-care system is a mechanism for turning money into QALYs, and exactly how that occurs may not be important.

Guideline generators see things differently. Producers of guidelines tend to pursue the understanding of how a health gain is generated. There can be unease when a gain occurs through a non-specific placebo mechanism, rather than the anatomical, physiological and psychological processes that the intervention's logic model presupposes. For interventions that may have a significant placebo effect, a guideline producer would like to see robust studies that explore that effect and enable them to separate out any placebo benefit. Therefore, the guideline producer tends to value more comparative studies with active control or placebos, whichever is clinically more appropriate.

There are potential impacts of establishing that an intervention has a significant placebo component contributing to the effect. First, there may be downgrading of any recommendation to use the procedure, as it has been shown not to 'work'. Second, the payer who may have previously willingly paid for the procedure now follows the downgraded recommendation and declines to fund an intervention that may be effective, albeit with a large placebo component (an unanticipated mechanism).

## The journal's perspective

The view expressed by journals may be best conveyed by the editorial accompanying the placebo surgery methods paper in *The Lancet*:<sup>174</sup>

*Writing in today's The Lancet, David Beard and colleagues review the role of placebo controls in surgical trials and present recommendations for their use. Over the past 10 years there has been increasing recognition of the importance of the placebo effect, particularly how strong this effect could be for a surgical procedure that involves high-intensity medical care, strong analgesia, and often physiotherapy. The growing use of placebo-controlled surgical trials to re-examine common surgical procedures that have a biologically convincing mechanism and a long history of use has led to a wave of unexpected results. Of surgical procedures examined with this rigorous method, half were proven to be no more effective than placebo.*

*The systematic debunking of many well established, definitive operations has become perhaps the biggest story in surgical research this decade. Common procedures such as vertebroplasty and subacromial decompression have been shown to be largely ineffective, but these procedures continue to be in common use. Challenging current practice is difficult in many areas of medicine, particularly where there are potential personal and commercial vested interests, including private practice. Stopping the use of a common but debunked surgical intervention will be especially tough because the alternative is not a newer or better intervention but often a continuation of the patient's current treatment course. For some of these procedures, where insurers or care commissioners have prevented surgeons from doing them, the discourse has often centred erroneously on rationing. The argument is not really about cost-effectiveness but rather that when robustly assessed, these procedures have been found to not be effective at all and still risk adverse effects.*

*Beard and colleagues discuss the need to plan for a negative result at the outset of a trial, anticipating the disruption that such a result produces, and creating processes to allow a transition of practice. The responsibility for doing this lies not only with surgical researchers, but also with the wider medical community. It is only by having the tenacious drive to question and critically assess with the most robust studies that we can leave behind ineffective procedures and concentrate on the many areas where surgery cures and heals.*

*Reprinted from The Lancet, vol. 395, Editorial. Gaining control: placebos in surgery trials, p. 756, Copyright (2020), with permission from Elsevier<sup>174</sup>*



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As part of the process of developing the ASPIRE guidelines, a 2-day workshop was held in St Anne's College (Oxford, UK) in December 2018. In addition to the applicants, the academic workshop participants were Dr Jonathan Pugh, Dr Felicity Bishop, Dr Sian Cousins, Professor Charles Weijer, Prof Richard Huxtable, Professor Jon Nicholl, Professor Pascal Probst, Professor Peter Brocklehurst, Dr Andrew Cook, Dr Katie Gillies, Professor Freddie Hamdy, Professor Ian Harris, Dr Naomi Lee, Professor Stefan Lohmander, Professor Amar Rangan, Professor Barney Reeves and Dr Sam Rowley.

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Ms Katie Chegwin was responsible for the administration and organisation of the workshop, editing of the manuscript and is thanked for her assistance.

Near-complete versions of the report were also sent to Professor Marion Campbell, Professor Jonathan Cook and Professor Manuela Ferreira for additional review, comment and edit.

## ASPIRE recommendation summary

A practical checklist that summarises the learning points from the ASPIRE guidelines and represents a minimum standard that researchers should attain and demonstrate when designing a placebo-controlled surgical trial is presented in *Box 1*.

### BOX 1 ASPIRE checklist for the design and conduct of placebo surgical controls in randomised trials

#### 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.



### BOX 1 ASPIRE checklist for the design and conduct of placebo surgical controls in randomised trials (*continued*)

#### Design

- Identify who the trial is designed to inform (and thus whether the inclusion of a no intervention arm is also desirable).
- Identify the essential 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 itself.
- Ensure balance in the information provided on both the index surgical procedure and the placebo surgical procedure.
- Consider use of enhanced processes (e.g. decision-aids) to facilitate patient understanding of the advantages and disadvantages for them of participating in a placebo surgical trial.
- Consider use of enhanced recruitment processes (e.g. 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 (e.g. 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 because of the trial findings.

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Reprinted from *The Lancet*, vol. 395, Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, *et al.*, Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines), pp. 828–38, Copyright (2020), with permission from Elsevier.<sup>12</sup>

## Example of using the guidelines

An example is given of how the guidelines may be useful in the development and conduct of a placebo-controlled surgical trial.

A researcher is considering a study to assess the efficacy of a new surgical treatment for knee pain in patients with osteoarthritis of the knee (prior to arthroplasty). The team wish to demonstrate fundamental efficacy for the treatment and are aware of the potential non-specific effects and placebo effects of undergoing a surgical treatment. Therefore, as one option, they consider a placebo surgical control design. They familiarise themselves by reading the background sections on placebo definitions, placebo effect and design in these NIHR/Medical Research Council (MRC) guidelines. If the study can be answered without a placebo surgical control, or the question does not involve fundamental efficacy (perhaps comparative effectiveness) or lack of efficacy is already evident from studies not using placebo (Dr Teemu V Karjalainen, personal communication), then no further placebo involvement is needed.

If placebo control remains an option, then researchers can check through the ASPIRE guidelines to assist their decision-making. An important aspect is justification for using a placebo control, as such designs are complex and have an ethics aspect (see *Chapter 6*). The team agree that the placebo and non-specific effects are potentially large for the new intervention and may need to be accounted for by a placebo control. Before confirming this design, other designs are considered for answering the set research question. One alternative for exploring efficacy is a two-armed study comparing the treatment against 'no treatment' (natural history). A further option is a three-armed study with both placebo and 'no treatment' controls. After considering the trial conduct and recruitment aspect of placebo designs and the ethics implications (see *Chapter 8*), it is felt that not offering any treatment would be inappropriate and unsuccessful for this particular trial. Therefore, a two-armed surgical intervention compared with placebo surgical intervention is decided.

The content of the placebo surgical intervention is then decided by breaking the surgical procedure down into component constituents, as per the DITTO framework. A decision on the level of fidelity of the intervention to the definitive surgery is made. This is contingent on the research question, the type of surgery and practicalities of the surgery.

The ethics of the trial and treatment are considered, and clear patient information leaflets/consent forms are designed on this basis, again with reference to the ASPIRE guidelines.

The conduct of the trial is designed using information and assistance highlighted in the ASPIRE guidelines. In particular, aspects of equipoise (patient and clinician) are explored. The trial is submitted for funding. Funding bodies may use the ASPIRE guidelines to check thoroughness and understanding of placebo control in surgery by the research team. The trial is funded (if appropriate) and delivered.

Interpretation of the results can be made with reference to recommendations provided in the ASPIRE guidelines. Change of practice resulting from placebo-controlled surgical trials can also be pre-empted by reference to this document.

Submitted manuscripts for journals can be checked for completeness and understanding by editors and reviewers using these guidelines.

## Further research priorities

- Evaluation of use of the ASPIRE guidelines in making decisions about the use of a placebo-controlled surgical trial.
- Use of the ASPIRE guidelines to assess the quality and comprehensiveness of pre-existing placebo-controlled surgical trials.

- Usability of the ASPIRE guidelines and evaluating their comprehensiveness.
- Further consideration of nomenclature in this area.
- Further work to establish when a placebo-controlled trial is warranted and necessary.

### Contributions of authors

**David J Beard** (<https://orcid.org/0000-0001-7884-6389>) led the development of the submission, chaired the workshop, and led production of the initial and final version of the manuscript.

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**Naomi Lee** (<https://orcid.org/0000-0003-0100-9659>) attended and presented a theme at the workshop, commented on the draft manuscript, and read and approved the final version.

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## Dissemination

The findings from the work have been presented in this report to the MRC/NIHR.

The findings were presented at the Society for Clinical Trials 2020 Annual Meeting [originally due to be in Baltimore, MD, USA (17–20 May 2020), but was converted to an online virtual conference on the same date because of the COVID-19 pandemic].

## Publications

Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, *et al.* Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). *Lancet* 2020;**395**:828–38.

Cousins S, Blencowe NS, Tsang C, Chalmers K, Mardanpour A, Carr AJ, *et al.* Optimizing the design of invasive placebo interventions in randomized controlled trials. *Br J Surg* 2020;**107**:1114–22.

Cousins S, Blencowe NS, Tsang C, Lorenc A, Chalmers K, Carr AJ, *et al.* Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol* 2020;**119**:109–16.

## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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# Appendix 1 Workshop agenda

**6 and 7 December 2018 at St Anne's College, 56 Woodstock Road, Oxford, OX2 6HS, UK**

*Medical Research Council/National Institute for Health Research state-of-the-art workshop on methods for placebo comparator group selection and use in surgical trials*

## Day 1: Thursday 6 December

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09.00	Registration: outside seminar room 11 Scene setting Session chairpersons: Cook and Beard
09.30	Welcome, introduction, overview and aims (10 minutes)
09.40	Tracey: The physiology of placebo
09.55	Bishop: The psychology of placebo
10.10	Beard: Definition of a 'surgical' placebo, sham or part treatment?
10.20	Campbell – Update on regulation requirements of placebo control trials
10.30	Discussion (all)
11.00	Refreshments Ethical considerations Session chairpersons: Campbell and Cuthbertson
11.30	Pugh: Overview introduction of ethical aspects
11.45	Huxtable: Ethical considerations for placebo surgical trials – part 1
12.00	Weijer: Ethical considerations for placebo surgical trials – part 2
12.15	Discussion (all)
12.45	Lunch Design of placebo-controlled trials in surgery Session chairpersons: Nicholl and Pinkney
13.30	Blencowe/Blazeby: Update of systematic review of placebo-controlled surgical RCTs: study rationale, mitigating risks and methods to design and optimise the placebo intervention
14.00	Probst: Is placebo intervention risky? And how to mitigate
14.10	Brocklehurst: The place of the funder for placebo control surgical trials
14.20	Discussion (all)
15.00	Refreshments Trial conduct: patients, personnel, recruitment Session chairpersons: Carr and Farrar-Hockley
15.20	Gillies: Patient information for placebo surgical trials: insights from evidence and practice
15.35	Brennan/Farrar-Hockley: What the patient hears/the patient perspectives

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15.50	Hamdy: Placebo trials, the surgeon perspective
16.00	Discussion (all)
16.30	Close of day

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## Day 2: Friday 7 December

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08.00	Breakfast: Dining Hall Placebo trials in action and lessons learnt Session chairpersons: Beard and Campbell
09.00	Buchbinder: Maximising recruitment – vertebroplasty and arthrographic joint distension studies
09.15	Lohmander: The content of placebo surgery – arthroscopic knee surgery
09.30	Cuthbertson: Importance of feasibility – lessons from KORAL
09.45	Cook J: Analysis plans, numbers, nuances and adjustments – lessons from CSAW
10.00	Harris: Spinal stenosis study SUCceSS – choosing the comparator and getting folk onsite
10.15	Discussion (all)
11.00	Refreshments Interpretation and changing practice Session chairpersons: Buchbinder and Rangan
11.30	Reeves: The statistical plan and potential result scenarios
11.45	Carr: Surgical community reception, changing practice
12.00	Cook A: The policymakers perspective
12.15	Discussion (all)
12.45	Lunch Planning and writing a guidance document Session chairpersons: Campbell, Cook, Beard and Blazeby
13.30	Lee: The Journal's perspective
13.40-15.30	<ul style="list-style-type: none"> <li>• Planned publications and outputs</li> <li>• Delphi work package</li> <li>• MRC/NIHR report: structure and contents</li> </ul> Discussion (all) and closing remarks
1.30	Close of meeting

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