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Randomised placebo-controlled trials of surgery: ethical analysis and guidelines

Julian Savulescu,[1] Karolina Wartolowska,[2] Andy Carr[2]

[1]Faculty of Philosophy, Oxford Uehiro Centre for Practical Ethics, Oxford, UK
[2]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK

Correspondence to
Professor Julian Savulescu, Faculty of Philosophy, Oxford Uehiro Centre for Practical Ethics, Suite 8, Littlegate House, 16/17 St Ebbe's St, Oxford OX1 1PT, UK; Julian.savulescu@philosophy.ox.ac.uk

Julian Savulescu and Karolina Wartolowska are joint first authors.

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ABSTRACT

Use of a placebo control in surgical trials is a divisive issue. We argue that, in principle, placebo controls for surgery are necessary in the same way as for medicine. However, there are important differences between these types of trial, which both increase justification and limit application of surgical studies. We propose that surgical randomised placebo-controlled trials are ethical if certain conditions are fulfilled: (1) the presence of equipoise, defined as a lack of unbiased evidence for efficacy of an intervention; (2) clinically important research question; (3) the risk to patients is minimised and reasonable; (4) there is uncertainty about treatment allocation rather than deception; (5) there is preliminary evidence for efficacy, which justifies a placebo-controlled design; and (6) ideally, the placebo procedure should have some direct benefit to the patient, for example, as a diagnostic tool. Placebo-controlled trials in surgery will most often be justified when surgery is performed to improve function or relieve symptoms and when objective outcomes are not available, while the risk of mortality or significant morbidity is low. In line with medical placebo-controlled trials, the surgical trial (1) should be sufficiently powered and (2) standardised so that its results are valid, (3) consent should be valid, (4) the standard treatment or rescue medication should be provided if possible, and (5) after the trial, the patients should be told which treatment they received and there should be provision for post-trial care if the study may result in long-term negative effects. We comment and contrast our guidelines with those of the American Medical Association.

BACKGROUND

The number of surgical procedures is rising. They are less risky because of advances in anaesthesia and infection control; they are also less invasive due to technological progress. Consequently, the indications for surgical interventions have extended from being limited to life-saving procedures to being offered to improve function, pain and quality of life. Therefore, the primary outcome measures for many currently used surgical procedures are not objective, like mortality, but instead they rely on patients' subjective report. When the evidence for efficacy is based only on subjective measures in open-label studies, it is difficult to establish whether the improvement is a result of the surgery or a consequence of non-specific factors and bias. As Cobb wrote in 1959, "after observing some of the dramatic results afforded by only minor bilateral thoracic skin incisions, one seriously questions how much of the reported clinical improvement after thoracotomy is actually dependent upon the patients' psychologic [*sic*] reaction to surgery rather than an enhancement of coronary-artery blood flow or other physiologic [*sic*] alteration".[1]

Surgical placebo-controlled trials (SPTs) are still very uncommon,[2] although it has been over 70 years since Beecher advocated that all surgical interventions should be controlled and that "a valid design of surgical activity is most important when principal change to be produced by a surgical procedure is subjective".[3] One of the reasons for low number of SPTs is that including a placebo arm in surgical randomised controlled trials (RCTs) raises strong ethical concerns and not all ethicists recognise the scientific and ethical justifications for placebo-controlled trials.[4 5] London and Kadane[6] suggested that surgical placebo should not be used because of its invasiveness and associated risks. Polgar and Ng[7] argued that a placebo arm does not improve the study's validity or clinical decision-making, and comparative trials should be used instead. Macklin[8] was concerned that placebo control may deprive patients of effective treatment, may undermine the patient–doctor trust and argued that such trials are unethical unless the placebo procedure could be recommended for therapeutic purposes only.

We propose that SPTs are necessary and ethical as long as certain conditions are fulfilled. The aim of this paper is to provide guidelines for use of surgical placebo and to clarify what conditions have to be fulfilled so that these trials are ethical.

DEFINITIONS

In this paper, 'surgery' is defined as any interventional procedure that changes the anatomy and requires a skin incision or use of endoscopic techniques. This includes invasive percutaneous procedures such as ablation and vertebroplasty but excludes stimulation, modulation, dental procedures and interventions using invasive delivery of pharmacological substances.

We use the term 'placebo' to refer to a surgical placebo, a sham surgery or an imitation procedure intended to mimic the active intervention. The true 'placebo effect' is the clinical or behavioural improvement related specifically to placebo manipulation.[9] It is not a result of placebo itself, but of the context in which placebo is administered, as well as patient's anticipation of benefit, their previous experience with treatment and their interactions with the health professionals.[10] A placebo procedure has no therapeutic effect and it 'does' nothing to directly improve anatomy or physiology; its function is to mimic the surgery, so that the expectations and 'meaning of treatment' are comparable between the surgical and the

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placebo arm, and bias is minimised. While placebo refers to positive change, the term 'nocebo' is used to describe a negative result, reported as deterioration or side effects. The magnitude of placebo effect, that is, the difference between the improvement in the placebo arm and the improvement in the non-treatment arm, has not yet been measured for surgical RCTs because of paucity of trials with both placebo and non-interventional groups. A meta-analysis of clinical trials, not specifically surgical, has demonstrated that the 'true placebo effect' is generally small.[11]

The 'placebo response' refers to the overall magnitude of change in the placebo arm, including the 'true placebo effect' and other improvement related to non-specific factors (natural history of disease, fluctuations in symptom severity, non-specific effects of taking part in a trial such as patients' reaction to being observed and assessed or to additional contact with clinicians), but not related to the investigated critical surgical element (the part of surgical procedure that is believed to be responsible for the clinical effect). Interestingly, interactions with clinicians were reported as the most powerful of the non-specific effects and this is important in surgery that involves connection with the surgeon.[12] Compared with many pharmaceutical trials, the magnitude of placebo response in surgical trials with subjective outcomes is moderate to large[13] with pain outcomes being particularly susceptible to bias and the placebo/nocebo effect.[11]

It is important to remember that the placebo response contributes to the magnitude of improvement in the active arm. Many SPTs demonstrated a large improvement in both arms, surgical and placebo, while showing little or no difference between the arms.[2 13] This means that a large proportion of improvement observed in surgical trials with subjective outcomes may be related to non-specific factors rather than the critical surgical element.

AN EXAMPLE: PATIENTS WITH CHRONIC PAIN DUE TO SHOULDER IMPINGEMENT WHO PARTICIPATED IN THE CAN SHOULDER ARTHROSCOPY WORK? TRIAL

Shoulder pain is a common condition in the general population, with prevalence in the UK of about 14%. It is associated with high socioeconomic burden because it limits patients' ability to work and to perform everyday tasks. Standard therapy is arthroscopic subacromial decompression, though there is little evidence to support its effectiveness. In light of this, the Can Shoulder Arthroscopy Work? (CSAW) trial was devised. CSAW is a three-group parallel design RCT assessing the clinical and cost-effectiveness of arthroscopic subacromial decompression for shoulder pain. This trial was initiated because, although subacromial decompression is frequently performed, the evidence of effectiveness of this procedure is limited and there is an equipoise whether removal of a bony spur on the acromion of the scapula relieves shoulder pain. In this trial, patients were randomised either to arthroscopic surgery with spur removal (active arm), diagnostic arthroscopy only (placebo arm) or active monitoring with specialist reassessment (control arm). The patients were told that arthroscopy only did not include the critical element of the standard procedure. The risks associated with both these procedures were fully explained. Importantly, the placebo intervention (arthroscopy only) in this trial had direct clinical benefits as patients with alternative diagnosis were removed from the trial and received appropriate treatment. The study is described in more detail in the protocol.[14] The trial is still ongoing, and first results will be available at the end of 2016.

WHY ARE SPTS SCIENTIFICALLY NECESSARY?

The reason why scientific evaluation of medical interventions is necessary is because (1) ineffective interventions expose patients to the risk of side effects with insufficient prospect of benefit; thus, they can directly harm the patient; and (2) ineffective interventions have an opportunity cost to both society and patients of 'crowding out' the employment or development of effective interventions under the false impression they are doing good.

These justifications apply with even greater force to surgical interventions. While medical interventions may merely be useless, surgery by its very nature always involves some harm by way of skin incision, invasion of the body, risk of infection, perforation, hernia, etc. Ineffective surgery will not merely be useless; it will be harmful.

Another difference between surgery and medicine is that typically the side effects last longer. As soon as a pill is stopped, its effects generally stop (though of course side effects, such as death, can be permanent). In the case of surgery, side effects typically last longer, like wound infection, contracture, adhesion, hernia, etc. This means that a greater degree of certainty is necessary that the benefits outweigh the risks.

The double-blind randomised placebo-controlled trial has become the gold standard in medicine, providing the highest level of evidence for the effectiveness of new interventions, such as pharmaceuticals. The reason for this is that it controls for the placebo effect and reduces bias. It is important to recognise that the same justifications as for medical placebo-controlled trials apply to SPTs.

The following section summarises the reasons why SPTs are necessary and other ways in which they differ from medical placebo-controlled trials (see also Box 1).

Placebo arm helps to distinguish between the true treatment efficacy and the effect of placebo and non-specific factors

Placebo control allows surgeons to estimate the improvement directly related to the crucial surgical element. Demonstrating the true efficacy is particularly important when the only available outcomes depend on patients' subjective rating and no objective outcomes such as laboratory tests, mortality or even

Box 1 Arguments for surgical placebo-controlled trials —what a placebo control adds to a blinded randomised controlled trials?

Placebo control

- Demonstrates true efficacy and helps to identify effective treatments
- Controls for placebo and nocebo effect and bias
- Helps to estimate the magnitude of the effect caused by non-specific factors
- Demonstrates the risk-to-benefit ratio of the procedure when the critical surgical element is omitted
- Substitutes 'doing nothing' scenario when efficacy of a well-established procedure is tested when actually doing nothing is not acceptable
- Discontinuing the ineffective surgical procedures saves patients from potentially harmful but no-beneficial interventions and helps to allocate funding to truly effective procedures

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clinician-assessed measures exist. If a critical surgical element is demonstrated to be ineffective, is should not be performed or there should be a change in indications for this procedure as was the case with vertebroplasty or arthroscopic surgery for knee osteoarthritis.[15 16]

Placebo control arms for bias

A placebo arm controls for the placebo or nocebo effect, but even more importantly, it protects from various forms of bias such as report bias, assessment bias or attrition bias. Interestingly, in SPTs with a placebo arm, drop-out is very low and is similar in both arms, which supports the importance of blinding.[17] Because surgery involves arguably greater trust and expectations than medical therapy, there is a greater potential for bias and placebo effect.

Placebo arm provides a comparator for a risk-to-benefit assessment

In surgery, the risk-to-benefit profile may be less clear because of larger surgical risks; therefore, placebo-controlled trials may be necessary to prove superior efficacy or a better risk–benefit ratio of surgery versus placebo. For a treatment to be clinically indicated, it must not only be effective, but the expected benefits must outweigh the risks and the overall 'expected utility' must be greater than the expected utility of alternatives. Therefore, placebo-controlled trials of apparently efficacious surgical procedures are justified where it is not clear whether the benefits outweigh the risks.

In public healthcare, it is important to have an accurate estimate of treatment effect in order to perform cost-effectiveness analysis and allocate finite healthcare resources justly. This typically involves allocating them to bring about the most benefit. However, any account of resource allocation and justice requires accurate information on the net magnitude of the effect of the intervention. Because significant risks are prevalent in surgery, it is also important to objectively evaluate both benefits and harms.

An active comparator or a waiting list is not a substitute for a placebo arm

A trial in which the surgery is compared with a pharmacological treatment or a waiting list may be considered more ethical than an SPT. However, it has several flaws. First, it is not possible to blind patients because they know whether they have received an interventional procedure. Second, the true placebo effect in surgical and pharmacological trials is likely to be different. Therefore, trials comparing surgery to a pharmacological treatment introduce additional bias while they do not control for it because they cannot demonstrate what proportion of the effect is truly related to the critical surgical element.[18] Such trials cannot determine the mechanism behind efficacy, that is, they might only show that surgery is a better placebo than a medical treatment.[26] Finally, comparing a placebo group with a non-treatment group is effectively comparing patients who know they might have not received an active treatment with patients who definitely know they did not receive any treatment. Patients in the non-treatment group are likely to show a nocebo response related to the fact that their treatment expectations were not met.

ARE SPTS ETHICAL? SURGICAL PLACEBO AND ETHICAL CODES

The Declaration of Helsinki is the most influential document governing ethical conduct of medical research. It recognises that.

Although the Declaration of Helsinki does not specifically deal with surgical placebo it states that placebo-controlled trials can be used when there is no proven treatment or a placebo-controlled trial is the most appropriate design "for compelling and scientifically sound methodological reasons", and the placebo arm will not result in "additional risks of serious or irreversible harm as a result of not receiving the best proven intervention" (paragraph 33). The Declaration of Helsinki recognises the fact that medical procedures involve risk (paragraph 16); however, it states that "medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects" and the "[new knowledge] can never take precedence over the rights and interest of individual research subjects", which means that the societal benefits are not a sufficient justification for a trial (paragraph 8). If the risks outweigh the benefits, the study must be stopped (paragraph 18). While the Declaration of Helsinki does not explicitly consider SPTs, similar principles apply.

The American Medical Association (AMA) made an attempt to formulate guidance regarding specifically placebo controls in surgery. The AMA guidelines include similar conditions as the Declaration of Helsinki. They permit use of placebo to test efficacy of new or existing surgical procedures, except when the innovative intervention is only a slight modification of an existing one. They highlight the importance of informed consent and recommend including standard non-surgical treatment as a part of RCT design.[20] These guidelines were adopted as the AMA's ethics policy and are now incorporated in the AMA's Code of Medical Ethics.

There has been extensive discussion of placebo controls and ethics of research in medicine.[4 5 19 21–23] The principle adopted by the World Medical Association is "in general it is ethically unacceptable to conduct placebo controlled trials if a proven therapy is available for the condition under investigation" (http://www.wma.net/en/40news/20archives/2001/2001_01/).

There are two qualifications that need to be made. First, 'proof' is best interpreted as a high level of confidence, which is often statistical in nature. What level of confidence is taken as 'proof' is a value judgement that is determined by a number of factors.[24] From the perspective of the patient's interests, the patient's expected loss (the probability of the loss multiplied by its magnitude) should be reasonably small. Thus, where a patient has a condition that might cause death or serious morbidity and a new intervention has the prospect of preventing that, from the patient's perspective, it is reasonable to accept lower levels of confidence of efficacy (assuming a low rate of serious side effects).

Let us assume that the risk of the new treatment killing you is 0.01% but there is a 10% chance of the underlying condition killing you (in fact, the chance of the condition killing you is irrelevant as long as there is some chance). How confident do you have to be that the treatment will save your life for it to be better for you to take than not take it? The answer is anything >0.01%, that is, >1/10 000. At that point, it is lowering your odds of dying.

The moral of the story is that if the risk of serious side effects is low, then the chance a treatment is efficacious can be low for it to be justified from the patient's perspective (the issue of distributive justice and resource allocation is a separate issue). Thus, it is rational to take statins, provided that the side effects are low. (At best, they probably lower the chance of a fatal event by about 1%.) The chance that any individual will have his or

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her life saved by a statin is incredibly low, but because the alternative is death, it is rational to take them.

Where the risk of serious side effects of a treatment is small, and the condition the person suffers from is serious, even very low levels of confidence would make it rational to accept the treatment. The balance between risks and benefits occurs when the expected utility of the treatment equals the expected utility of not taking it; in this example, if there is a 1/10 000 chance the treatment works. As the risk of side effects increases, or as the severity of the underlying condition decreases, the level of confidence should rise. Thus paradoxically, in the case of life-enhancing surgery for increase in function or reduction of symptoms, higher levels of confidence of efficacy are required than for interventions into life-threatening conditions. That is, there is a stronger incentive for placebo-controlled trials of surgery in these conditions.

There is another factor that is relevant to SPTs. The kind of position articulated by the World Medical Association has been developed in the context of drug trials, such as azathioprine for the prevention of transmission of HIV, or other trials of drugs where the major end points are mortality or significant morbidity. Patients should not be placed on placebo when delaying therapy could have serious outcomes, such as death. However, in the case of many surgeries performed to improve quality of life or relieve pain or discomfort, such as treatment of shoulder pain, delay in definitive treatment is less catastrophic. Where the effects of delay of definitive treatment are reversible, there is a stronger licence to use placebo. Although a placebo-controlled trial might delay definitive treatment and expose the patient to a second anaesthetic, not conducting such trials might expose patients to anaesthetics for no benefit and might even exacerbate their symptoms. Paragraph 33 relevantly states that "the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention".

CRITERIA THAT SHOULD BE FULFILLED TO MAKE AN SPT ETHICAL

We suggest that there are several criteria that should be fulfilled when a placebo-controlled surgical RCT is being considered (Box 2). We have argued that SPTs are appropriate for two broad classes of condition: (1) conditions that impair function or cause symptoms (such as pain). The AMA guidance states that SPTs should be used "only when it is known that the disease being studied is associated with symptoms that are susceptible to placebo effects; that is, can be significantly influenced by psychological factors". While we concur the subjectivity of outcome is an important target of SPTs, it is not the only target. (2) The condition that patient suffers will not significantly deteriorate during the duration of the trial. That is, there is no significant cost to delaying intervention. Thus if one is not sure if X is better or worse than doing nothing for condition Z and if X is better than Y, and condition Z will not deteriorate during an SPT, it is reasonable to do a PST of X and an SPT of Y, given that if one is superior patients from the other group can later access it. If one might die or suffer serious avoidable morbidity during a trial as a result of receiving placebo, then one can accept lower levels of confidence in an intervention's efficacy before administering it outside of a placebo-controlled trial.

Equipoise

While the AMA recommendations do not refer to the concept of equipoise, there is a need for equipoise in the surgical community, that is, uncertainty either regarding the efficacy of the investigated procedure or the lack of unbiased evidence for efficacy of the intervention. There are three likely scenarios: (1) no effective treatment exists and a new treatment is being proposed, which has shown encouraging results during preclinical trials; (2) there are serious doubts about superiority of one treatment over another or conflicting evidence about efficacy from earlier trials or animal research; or (3) clinical experience does not match published reports (see Box 3).

Only when there is an equipoise is it fair to decide about patients' treatment by randomly assigning them to each procedure.[6] Genuine uncertainty about efficacy also facilitates recruiting patients as well as the trial team.[25] If there is a true or justified equipoise, the requirement of the Declaration of Helsinki that all patients receive the best proven available treatment is not violated because there is no 'best proven treatment' available and Macklin's[8] argument that placebo control denies patients 'the best proven treatment' does not apply. As we have

Box 2 What criteria have to be fulfilled for an surgical placebo-controlled trial be ethical?

Essential criteria (*condicio sine qua non*):

- The presence of equipoise, that is, lack of unbiased evidence for efficacy of an intervention
- Some preliminary evidence that the procedure results in a significant improvement and that there may be a placebo/nocebo effect or bias
- The risks are minimised and unnecessary harms are avoided as much as possible
- No deception
- The research question is clinically important and will potentially result in a significant difference to clinical practice

Box 3 Examples of surgical equipoise

- The trial on arthroscopic treatment for knee osteoarthritis[56] was performed because open-label studies demonstrated that debridement and lavage result in better outcomes than no treatment, and although it was a standard procedure, there was no evidence that its effect is anything more than a placebo effect.[57]
- The rationale for the study on abdominal pain was that there was no agreement in the clinical community whether adhesions are the actual cause of pain. Adhesiolysis was not an accepted procedure and there was conflicting evidence about its efficacy as not all studies demonstrated an effect.[36]
- The trial on the internal mammary arteries ligation was undertaken because the clinical experience did not correspond to results of clinical and animal studies.[1]
- In the trials for Parkinson's disease, the rationale for transplantation of dopaminergic neurons was slightly different. There was no effective therapy. The results of preclinical studies were encouraging as they demonstrated that implanted fetal dopaminergic neurons could survive and release dopamine and that fetal nigral transplantation may result in clinically meaningful improvement.[52 53]

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argued, there are few surgical treatments for functional or symptomatic treatment that have been proven to work using scientific methods. There are levels of confidence in efficacy, but such confidence is the appropriate object of scientific analysis if the benefits to the patient and society are sufficient and risks are reasonable.

In some cases, there is sufficient evidence that one treatment is superior to others, yet clinical equipoise persists, and placebo-controlled trials are conducted denying patients proven therapy because of failure to systematically review evidence[26] or other factors. This is unethical. However, this is not true or justified equipoise. Whether equipoise is justified turns on weighing all the evidence through systematic review, reasoning on the basis of animal studies and clinical experience, and using other lines of inferential reasoning.

Miller and Joffe[27] criticised the concept of equipoise as being imprecise and based on expert opinion, and not all surgeons or members of the trial team may equally believe that there is a state of equipoise. In response, Young *et al*[28] have suggested measuring both individual and community equipoise. We however suggest that equipoise must be rationally justified on the basis of evidence. (For a procedure of rational justification, see ref. 29).

How we should determine whether equipoise truly exists is, however, a deep question involving philosophical questions of knowledge and rational belief, epistemic confidence, etc. Some have even argued that equipoise rarely exists in clinical research or is rapidly disrupted during a trial well before the trial is terminated but that nonetheless placebo-controlled trials can be justified on the basis of the interests of future patients or distributive justice concerns[24] What is most important for our present purposes is that these issues pertain to *all* placebo-controlled research, not merely SPTs. Patients given potentially life-saving medical interventions can die as a result of placebo-controlled pharmaceutical trials.[24]

Preliminary evidence for efficacy of the procedure

An SPT is not acceptable when there is no preliminary evidence for efficacy of the investigated procedure, such as preclinical data or results from an open-label trial.[7] An SPT should not be undertaken as a proof of concept. The placebo control design is particularly useful when there is some evidence that the intervention results in a significant improvement but there is also doubt whether this effect is directly caused by the critical surgical element.[11 30] If there are objective outcomes and the risk of bias is low,[31] then an RCT without a placebo control may also provide reliable answers.

Minimising risks to patients in the placebo arm

Surgical trials always involve some risks because of invasiveness of surgery and need for analgesia or anaesthesia. The risks of adverse events in the surgical trial, especially in the placebo arm, should be minimised as much as possible and unnecessary harm should be avoided. The principle of non-maleficence states that the placebo arm should not expose patients to serious and irreversible harm.[21] However, in surgical trials where avoiding risk of any serious harm may not be possible, acceptable risk should be phrased in relative terms. There is a need for contextualised judgement.[32] The ethical considerations whether the risks are excessive should be discussed in the context of other trials in similar patient population, a standard treatment or the natural history of disease. In the published SPTs, serious harms in the placebo arm were rare and less often associated with serious harms. The adverse events in these trials were often related to the severity of the investigated condition rather than the intervention.[2] Problems with anaesthesia, infections and excessive blood loss, which were the main ethical concerns,[33] were not mentioned as major adverse events in published trials.[2]

One objection to SPTs compared with pharmacological placebo-controlled trials is that surgery inherently involves risks, such as postoperative pain, wound infection, incisional hernia, etc; thus, a placebo surgery exposes that patient to risks with no prospect of benefit, in a way that a pharmaceutical trial does not. However, the risks must be reasonable[24] and not disproportionate to the benefits. Where the risks are minimal (such as arthroscopic surgery), SPTs may be reasonable but they are not recommended if there is the significant risk of serious and irreversible adverse events, and only minimal benefits. It is important to remember that ineffective surgery will be harmful, so those entering an SPT may be spared the risks of ineffective additional surgery (the critical element), provided there is justified equipoise.

Avoiding deception

Neither patients nor surgeons approve of deception.[34 35] Patients must know, understand and consent to the fact that they are participating in a placebo-controlled trial.

Potential significant change to clinical practice

A trial should result in a substantial improvement of the health of future patients, be likely to change clinical practice and result in cost saving or waste avoidance. This is related to the AMA's guidelines that "a placebo control is not justified when testing the effectiveness of an innovative surgical technique that represents only a minor modification of an existing, accepted surgical procedure".

Benefits to the patients in the placebo group

In SPTs, the placebo intervention may provide a direct diagnostic benefit for the participants, for example, to confirm the primary diagnosis or to revise it. In an adhesiolysis trial,[36] if during a diagnostic laparoscopy a patient was diagnosed with pathology other than an adhesion, they were withdrawn from the trial and received an appropriate treatment.

Taking part in a trial may be also beneficial to trial participants in an indirect way because patients in a trial tend to do better than patients in standard care.[37] For example, patients who are in the placebo arm of a trial report less pain[38] and patients with cancer have a higher survival rate.[39] An improvement in the placebo arm was reported in most of the published SPTs.[2] This may be related to the fact that trial participants get more care, attention and support while they are in the trial.[37] It is controversial whether the possible placebo effect, that is, the perceived improvement attributable to placebo intervention, is enough to treat it as a benefit that counterbalances the risks; however, minimising the placebo effect does not seem like a valid goal either.[40]

Patients may value the altruistic aspect of participating in an RCT as the knowledge gained from the study would benefit future patients. They are willing to take part in clinical trials to help discover new treatment for themselves and other patients with the same condition because they feel they are contributing to advances in treating the disease affecting them as individuals.[20]

RCTs provide the highest level of clinical evidence and have huge benefits for science and future patients. Whether the clinical utility and 'societal importance' outweighs the risks of placebo and delayed treatment is an ethical dilemma. Miller,[5]

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Horng and Miller[4] as well as Tenery[20] whose ethical guidelines have been incorporated by the AMA suggested that "the risks in the trial are compensated by the substantial knowledge that might be gained from it research". However, this argument is not acceptable in the light of the Declaration of Helsinki, which forbids sacrificing the interests of an individual patient in the interest of society (paragraph 8).

ISSUES THAT NEED TO BE ADDRESSED WHILE PLANNING AN SPT

SPTs are in many ways similar to any other clinical RCT. Issues such as informed consent, therapeutic misconception, deception and provision for long-term consequences are similar for pharmacological and surgical trials. There are, however, several elements that make surgical trials different and that need to be taken into consideration while planning and running an SPT.

Patients' recruitment

Recruitment in RCTs, in general, is challenging but surgical trials are particularly difficult to recruit into because many patients fail to fulfil the inclusion/exclusion criteria.[41] It is unethical to perform a trial that is not powered to answer the research question. Therefore, before beginning an SPT, it is important to confirm that the trial will be able to access a sufficiently large population of potential participants so that it will be possible to recruit the necessary number of patients in a reasonable period of time. Some of the published SPTs were underpowered because of the authors' assumption that it is more ethical to recruit fewer patients.[17]

It is also important to ascertain that the potential participants are willing to be randomised into the proposed trial. Rogers *et al*[33] recommended undertaking a structured consultation. However, experience from the CSAW trial suggests that a survey among potential patients may be sufficient.[14] Patients are willing to take part in SPTs[42 43] and acceptability of placebo depends on how risky patients perceive it.[44] There has been very little research on how patients conceptualise placebos and what is their attitude towards placebo-controlled trials.[45] A recent survey[46] demonstrated that patients have limited knowledge about placebo and they conceptualise placebo as inert. Patients prefer an unblinded design[47] but they may simply prefer a design they understand.

Informed consent

The requirement to obtain fully informed consent and respect patients' autonomy are particularly important in the context of SPTs. Consent to placebo surgery must be valid, that is, freely given by a competent patient informed of the risks and benefits of the proposed trial and its alternatives. Patients who participated in an SPT must understand the rationale and the design of such a trial.[48] However, it is important to ascertain that there is no 'therapeutic misconception', that is, that patients understand the differences between the standard treatment and a trial, the uncertainty principle of the trial, randomisation process or placebo control.[49] The authors of the policy adopted by the AMA[20] recommended explaining the differences between the surgery and the placebo procedure, especially the essential procedures that will or will not be performed, and the risks involved with each of them. They have also suggested using extended consent formula and adding a neutral third party to provide the information or obtain the consent or an external monitor to oversee the consent process as safeguards during the informed consent process. Rogers *et al*[33] suggested using educational materials before seeking consent to ensure understanding.

Standardisation of the intervention and timing of the trial

Standardisation and timing is particularly important in the context of surgery. A surgical intervention involves many different procedures, and it may differ slightly between hospitals and surgeons. It is important that the investigated intervention and the additional procedures are standardised as much as possible. Therefore, the timing is very important. A trial should not be initiated too early in the development of the procedure so that the procedure does not change during the trial and surgeons have mastered the skills necessary to perform it. On the other hand, testing a well-established procedure may lead to problems with recruitment and reluctance of the surgical community to accept the results of the trial. For example, in the study on vertebroplasty for osteoporotic vertebral fractures by Kallmes *et al*,[50] only 30% of eligible patients entered the trial. In another vertebroplasty trial performed around the same time, only 17% of eligible patients were randomised.[51]

Attitudes of surgeons and non-surgical staff towards placebo

Surgeons are generally not opposed to placebo, recognise that some surgical interventions may have a placebo component and they support use of placebo control in surgical trials as long as it does not involve deception.[35] Therefore, equipoise is important so that the surgeons and other clinical staff accept the placebo trial. Rogers *et al*[33] suggested introducing governance measures; however, if there is equipoise, this should not be necessary and review by an ethics committee should suffice.

What needs to be recognised is that the elements of agency and causality are different in surgical and in medical trials. Pharmacological trials investigate drugs invented, produced and provided by pharmacological corporation rather than the doctor administering the drug; therefore, they are impersonal. Surgical treatment is personally performed by a surgeon (or a surgical team) who has a direct influence on the procedure and its outcome. As for causality, surgery is a one-off event and, in theory, it should be easy to link the outcome or complication to the surgery; however, surgical procedures are usually complex and involve many different procedures. It may be difficult to identify the crucial surgical manoeuvre or to find an imitation procedure without any therapeutic effect.

Minimising the risks to trial participants and providing standard treatment

In SPTs, apart from adverse events, which are the result of the trial interventions, that is, consequences of 'doing something', there may be also potential harms in the placebo arm related to 'doing nothing', for example, lack of improvement as a result of withholding the treatment.[5] The majority of published trials have offered some form of standard or rescue medication or intervention. Therefore, there was rarely a risk of harm due to lack of treatment. In surgical trials, medical treatment and lifestyle modifications may be offered to patients in both arms as a part of the study, especially if the investigated condition is severe. For example, in the trials on tissue transplantation in Parkinson's disease, participants continued their L-DOPA medication.[52 53]

Also, any additional procedures should be safe and, if they are not necessary for medical reasons, additional interventions should be avoided. For example, in one of the Parkinson's disease trials the procedures in the placebo arm involved general anaesthesia and burr holes as well as positron emission tomography (PET) scans and antibiotics.[52] In comparison, in the trial on the patent foramen ovale closure the placebo group patients

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did not receive heparin, which is associated with potentially serious side effects, because they did not undergo the surgical procedure that required it.[54]

Provisions after trial's completion

After finishing the trial, patients should be informed which group they were randomised to.[4] There should be also provisions for long-term consequences of the trial, for example, in the Parkinson's disease trial patients in the surgical arm developed severe dyskinesias as a result of tissue transplantation.[52]

Offering the active treatment after unblinding is controversial in surgery. If treatment is shown to be effective, it should be offered as suggested by the Declaration of Helsinki in relation to medical trials (paragraph 34). Some trials offered the surgery at the end of the trial either when the patients in the placebo group did not achieve improvement[36 50] or without such a caveat.[55] If the trial's null hypothesis is that the effect of surgery is the same as the effect of a placebo intervention, a design in which patients receive the treatment after the trial undermines the validity of this hypothesis. Offering one treatment after the trial at the outset as a part of trial design suggests that we believe that this treatment is indeed better, which means that there is no true equipoise. Any such offer at the outset should be conditional on proof of efficacy.

However, patients tend to prefer the surgical treatment even if it has not proven to be effective, for example, in the trial of fetal dopamine neurons transplantation as a treatment for Parkinson's disease, patients opted for the active treatment, although the study did not demonstrate that surgery is better than placebo,[53] and for some of them, the availability of the active treatment had an influence on their decision to take part in the trial. Respect for autonomy may require offering such an option even if not proven to be effective.

CONCLUSIONS

Placebo-controlled trials help to identify truly effective procedures and to stop non-effective ones, therefore improving clinical practice, reducing unnecessary risk to patients and optimising allocation of resources. While surgical and medical placebo-controlled trials share many similar features, there are several factors that make SPTs different. Surgery is inherently risky, and many of its adverse effects are temporally extended. Thus, it is important to justify undertaking it. Surgery involves trust and personal contact with the surgeon, making a placebo effect and bias in evaluation more likely. SPTs are necessary when surgery is performed for improvement of function or relief of symptoms, especially when the trial's outcomes are subjective. A placebo control helps to minimise and control for bias and therefore to estimate the magnitude of the effect related to the critical surgical element. SPTs can be conducted ethically as long as there is equipoise, the research question is clinically important, the risks are acceptable and there is no deception.

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