History

Reconsidering the ethics of sham interventions in an era of emerging technologies

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Background. *Our aim was to ethically evaluate the arguments in favor and against sham interventions, as presented in literature. Two developments underscore the need to reconsider the ethics of sham interventions. First, the number of clinical trials investigating interventions in the field of regenerative medicine are increasing, in which the choice for a placebo requires an invasive intervention. Second, the increased awareness of the lack of systematic research in surgery stresses the need to discuss the necessity and acceptability of sham-controlled clinical trials.*
Methods. *A systematic search in Medline was performed, of which 104 articles were considered relevant.*
Results. *Arguments in favor of a sham controlled design are that it increases the scientific validity and the benefits to society while at the same time the risks and harm can be acceptable. Arguments against sham controls include that they pose unacceptable risks to participants, present difficulties with informed consent, that the use of deceptive tactics is unethical, and that the feasibility of such controls is compromised because of a lack of public support.*
Conclusion. *None of the published literature fully rejects sham interventions, and many regard sham interventions acceptable provided the conditions of scientific necessity, reasonable risks, and valid informed consent are fulfilled. Further debate should no longer address whether a sham control is ethically acceptable but rather when these conditions are fulfilled. (Surgery 2015;157:801-10.)*

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An important ethical challenge in the design of clinical trials is the decision whether a control group is necessary and, if so, whether this control group should receive placebo, standard of care, or no intervention. A placebo group can allow blinding of participants and investigators. Placebos for other types of procedures than pills are called sham interventions, which can range from (minimal) invasive operative procedures to other interventions such as radiotherapy.[1,2] In this article we concentrate on the ethics of invasive sham procedures, also known as placebo surgery, ie, procedures that are

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characterized by a physical change of bodily tissue through manual or robotic operation and thereby inherently imply physical harm and/or risks.

A range of invasive sham interventions have been used in clinical trials, including investigating the efficacy of arthroscopy,[3] vertebroplasty,[4,5] subcutaneous placed stimulators,[6] open operative neurectomy in the abdominal wall,[7] intracoronary infusions with a cell intervention,[8] intravitreal injections,[9] and, recently, meniscectomy.[10] The debate about the ethics of sham interventions emerged more than 10 years ago in response to 2 fetal stem cells trials for Parkinson's disease.[11,12] These trials evoked debate, due to the high risks to the control group, because the control group received drill holes without the introduction of stem cells.

Two developments in contemporary medicine underscore the need to reconsider the ethics of sham interventions. First, more clinical trials investigating innovative approaches in regenerative medicine are being proposed and conducted, including randomized controlled trials (RCTs) with a sham intervention as a control group.[13-15] Such research studies in regenerative medicine encompass (stem) cell-based interventions, gene transfer, use of biomaterials, or a combination of these, often aimed at reversal of organ failure and degenerative disorders.[16] Insertion of these novel interventions is performed via surgery or injection(s) in the (systemic) circulation, target tissue, or organ.[15,17]

Second, increasing attention is being paid to the negative consequences of poor quality or even lack of clinical research for operative procedures,[18-21] leading to a lack of evidence-based practice in several fields of surgery.[22] This awareness is fuelled by clinical trials, such as the use of a certain bone cement for vertebroplasties, that appear to have been researched insufficiently and led to unnecessary harm and even death to patients and public concern.[23] Because an RCT is often assumed to provide the greatest level of evidence in surgery, it is expected that the need of conducting double-blinded trials will also increase, although an RCT is not appropriate for all types of interventions.[24,25] Because currently neither the Food and Drug Administration nor the European Medicines Agency provides clear guidance on when the use of sham interventions is acceptable, it is important to reflect on the scholarly literature. Our work aims to ethically evaluate the key arguments in favor and against sham procedures as they appear in the literature. We will end with suggestions about how to move the debate forward.

METHODS

On July 21, 2014, a search in the electronic database of Medline was performed using the key words "ethically," "ethical," "ethics," "morality," "moral," and "morally" in combination with the key words "placebo surgery," "placebo intervention," "surgical placebo," "sham surgery," "sham intervention," "sham procedure," "sham," and "sham-controlled." The inclusion and exclusion criteria were defined before the literature search by discussion among all authors. S.N. screened the title and abstract of studies in accordance with our inclusion and exclusion criteria. The selected articles were crosschecked to identify relevant studies missed by the initial search. In total, 104 articles were included (the Fig). S.N. collected the provided arguments in the papers and recorded them in an argumentative scheme. After that, the type of arguments were clustered in sets and separated in arguments in favor and against sham controls. Some (review) articles referred to arguments put forward in other work; in this paper, only the original article is referred to.

ARGUMENTS IN FAVOR OF ACCEPTABILITY OF SHAM CONTROLS

The use of a sham control increases scientific validity. The first argument to include a sham procedure is that it increases the scientific validity of an RCT.[2,26-28] A comparison of the experimental intervention with a sham intervention allows the ability to blind the patient and/or investigator and thereby, discern between specific effects of the intervention and other, nonspecific effects such as reporting bias, and performance bias (eg, difference in care based on the allocated arm).[2,28-31] Furthermore, a blinded study prevents the lack of adherence to the allocated arm.[32] Including a placebo in surgery trials is considered to be especially important because placebo effects and distorted participant reporting appear to be greater in surgical trials than in pharmacologic trials.[27,28,30,33-39] Factors such as need for hospitalization, the involved rituals in surgery, pain management, ancillary treatment, greater stress, and the disease recognition that surgical patients receive, can heighten the effects of placebo.[34,35,40,41] Correcting for and even recognizing placebo effects becomes more important as surgery is moving toward an increased use of subjective (or soft) outcome measures, such as quality of life, which are prone to be influenced by placebo effects.[38,39,42-44] In contrast, in the past, operative procedures were mainly life-saving operations, in which the response to an intervention is more dramatic and thereby, less likely to be biased.[38]

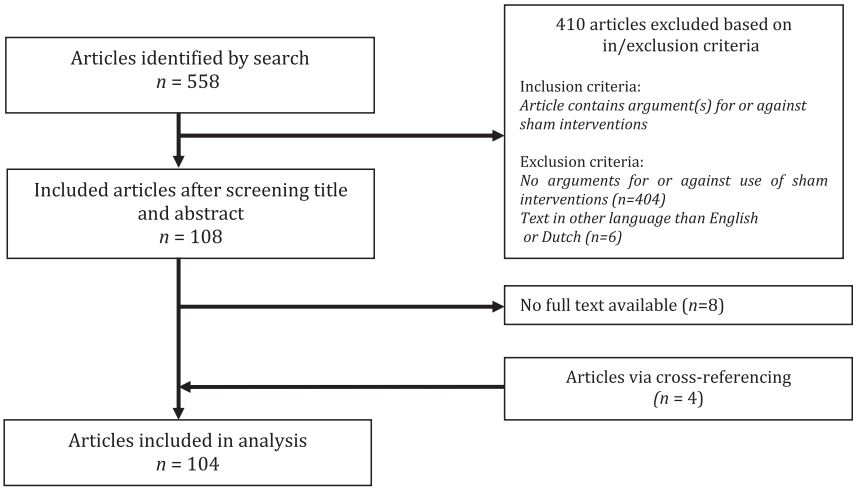

Fig. Flowchart of the systematic search conducted on July 21, 2014 on MEDLINE.

The use of a sham control increases benefits to future patients and society. A second argument in favor of sham-controlled clinical trials is the increased likelihood of benefits to future patients and society, because inclusion of a sham group leads to knowledge that will prevent the introduction of insufficiently proven, potentially risky interventions in clinical practice.[2,35,38,45] and thereby prevent unnecessary and often expensive costs to the health care system.[2,13,28] Numerous examples of surgical interventions exist that have been applied in clinical practice, but only later have appeared to be ineffective after the conduct of sham-controlled studies.[27,28,38,44,46-49] Because invasive interventions are costly and may potentially cause harm, this argument provides reasons to ensure that such interventions are tested with rigorous scientific scrutiny.[38,48]

The risks and harms of a sham control can be acceptable. A third argument for using sham interventions is that the risks and harms to the research participant in the sham group can be considered acceptable. A sham intervention involves inherent risks and harms because of its invasiveness, in contrast to placebo pills. Different conditions are put forward under which the risks of sham interventions are acceptable.

The predominant line of reasoning in much of the literature is that the risks and harms are acceptable when a favorable risk-benefit balance is achieved. Because it is argued that a sham intervention cannot provide individual benefits to participants, the risks and harm of a sham control to the study participants need to be weighed with the potential benefits of the trial to science and society.[38,44,50-53] An analogy is drawn between sham interventions and other interventions in research that are not compensated by potential individual benefit but are justified by the expected benefits for science and society.[2,28,33,34,38,44,54] Examples include diagnostic studies (eg, muscle biopsies, bronchoscopies), studies involving healthy volunteers, phase 1 studies, or studies aimed at understanding pathophysiology.[2] Some authors argue that in the risk-benefit ratio, the individual benefits caused by the placebo effects of the sham intervention also should be included.[1,27,38,55-59]

Second, some maintain that an additional requirement to the first condition should be that the risks must be minimized. Risk minimization means that measures are taken to decrease the inherent risks for the sham group, for example, by using a less-risky anesthetic or using only superficial, less-invasive approaches, while at the same time ensuring a valid research design.[28,41,60] Furthermore, some state that when no alternative design is suitable to acquire reliable and valid evidence and poses less risks, the risks are minimized.[2,28,34]

An additional condition that a few authors mention is that the risks of the sham intervention arm should not exceed a risk threshold. To determine this threshold, the risks should be compared with the risks of study interventions aimed at pathophysiology[28] or with the risks of procedures with diagnostic or therapeutic intent in clinical practice.[38] It is argued that sham interventions will probably not exceed a risk threshold, because in general, the morbidity of operative interventions is decreasing[38] and use of minimally invasive procedures will not exceed this limit.[2] Empirically, a recent systematic review has shown

that the risks of adverse effects associated with placebos in surgery trials are small.[61]

ARGUMENTS AGAINST THE ACCEPTABILITY OF A SHAM CONTROL

A sham control often is unnecessary for scientific validity. The first argument against the acceptability of a sham intervention is that it does not per se increase the scientific validity of a trial. Correcting for placebo effects might be unnecessary, because the extent of placebo effects often is exaggerated.[60] Furthermore, sometimes sham-controlled studies are conducted when relevant results also could have been obtained by using the standard of care or no intervention as a comparison, although the results could thereafter still require a sham intervention to confirm efficacy.[30,62] Others criticize the simplistic way in which sham-controlled trials are performed currently, because the different components of an operative procedure are not tested separately.[51] A more complex trial design with various arms is required to truly determine what causes the effect of an intervention.

A sham control does not increase benefits to society. A second argument is that the comparison of an intervention with a sham procedure does not show whether the interventions will be an advantage to the current clinical practice, because sham procedures will not be implemented in clinical practice. It is more useful to perform trials without sham controls to show whether the intervention is superior or inferior compared with usual practice.[51,52,63-65] Because sham procedures are not always necessary scientifically, public money will be spent unnecessarily, because surgical trials are expensive.[65]

Risks and harm to a sham control group are unacceptable. A third argument is that the risks of sham interventions are not acceptable. Four different reasons are provided. First, it has been argued that the lack of chance of potential therapeutic benefits fails to be consistent with the duty of physicians to act in the best interest of participants, which is inconsistent with the Declaration of Helsinki.[27,60,63,66] In contrast, other authors maintain that this argument conflates the ethical principles of research with the principles of clinical practice, because the goal is not to provide medical treatment to participants.[28]

Second, it is argued that risks in these trials are unacceptable, because risks are often not minimized. One author poses the argument that risks are not minimized when individuals are exposed to risks without any potential individual benefits.[67]

Third, others argue that sham interventions violate the standard of minimal risk (according to the US Federal regulations for Human Subject Research), ie, that the risk are not greater than one encounters in daily life or during routine physical or psychological tests/examinations.[27,67,68] In contrast, proponents of sham controls state that in general, this is not an appropriate argument for clinical research with competent adults.[28]

Fourth, risks are considered not reasonable in relation to the expected benefits for society, for which most authors use the example of the trial with fetal stem cells for Parkinson disease.[66,67] Some authors have stated that reaching a proportionality between risks for the participants and the benefits to society offers little guidance for decision making and may lead to the risk of exploitation of participants for the sake of scientific knowledge.[62] While some authors acknowledge that benefits for the sham group could occur, these benefits should not be taken into account in the risk-benefit ratio, because the placebo is used to control for placebo effects and not to assess therapeutic activity.[2,27,67]

Difficulties in obtaining valid informed consent. A fourth objection to use a sham control is that adequate informed consent is more difficult to obtain in sham-controlled trials, because of the inherent risks and a high deviation from the standard of care.[33] Some authors have suggested that participants in these trials have a greater risk of not really appreciating or understanding all the potential implications of a sham control; many participants may have the misunderstanding that the purpose of research consists of providing medical care, instead of gaining scientific knowledge (also known as the therapeutic misconception).[67-69] Some authors have hypothesized that participants may actually think that an invasive intervention will not be performed if it does not have any potential benefits, especially if a surgeon is to perform such an invasive intervention.[38] Furthermore, it is suggested that a substantial misestimation of risks and benefits by the participants could occur. *Gaining valid informed consent is possible.*[67]

These aspects, however, are not necessarily contra arguments, but can be used to stress that informed consent procedures need more safeguards. These safeguards could ensure that the implications of participating in a sham-controlled trial is explained sufficiently.[2] Others state that often it might even be unreasonable to assume there are specific difficulties in obtaining a valid informed consent in sham-controlled clinical trials.[28]

Moral discomfort for investigator and participant. A fifth argument is the possibility of moral discomfort raised by the possibility of active deception, both for the investigator performing the procedure and the participant. Sometimes the investigator (who can be the treating surgeon) performing the procedure is aware of the participant's allocated arm and has to pretend to provide the "real" intervention. Hence, the investigator has to actively mislead the participant by pretending to perform the procedure, which could raise moral discomfort to the investigator, especially when having to continue the potentially misleading dialogue after the intervention.[34,46,54,67,70] If the participant is not sufficiently informed of these deceptive strategies, this approach violates the principle of respect for persons, and their autonomous decision-making.[71] Furthermore, some also maintain that participants will become patients when involved in these types of trials because of the creation of a wound. If harm to a participant occurs, the investigator (often a surgeon) is likely to be regarded as the direct cause of the adverse event, raising the moral stress of the investigator.[46,72]

Active deception is not a priori unethical. Potential moral stress from the need for misleading dialogue from the investigator, however, can be relieved if the investigator performing the procedure and the one who does follow up and outcome assessment are separated.[34] In addition, it should be taken into account that sham interventions are part of clinical research and not medical practice, even if the investigator is a surgeon. Furthermore, violation of the autonomy of participants can be prevented if a research participant is clearly informed beforehand of the chance of being in the sham control group.[54]

Lack of support by public and researchers. Another potential objection to the use of sham interventions is the aversion of both the public and investigators toward sham interventions, which influences the feasibility of performing sham-controlled trials.[73] Some state that empirical research indicates that some patients are unwilling to participate in placebo trials,[27] whereas others argue that patients' views are lacking in the debate.[74]

Counter argument: sufficient support exists. Currently, there are mixed opinions, because many patients are willing to participate in these trials.[27,41,75-77] Furthermore, empirical research has shown support for sham interventions by investigators, both surgeons and anesthetists.[27,70,78,79] Others propose that more studies need to be conducted that explore the attitudes toward sham controls,[73] and the public should be educated about the need of a sham control.[60,67,80] The resistance toward a sham intervention might also be mitigated by using different linguistics, by at least avoiding the negative word "sham."[81]

DISCUSSION

Six sets of arguments appeared from the literature: scientific validity, benefits to society, the risks and harms, informed consent, the use of deceptive tactics, and feasibility. We noted 4 patterns concerning the arguments for and against the ethical acceptability of sham procedures (Table).

First, it appears that in comparison with other clinical research, no *significantly different* arguments are provided, even though sham interventions have a unique combination of specifics: the exposure of participants to "positive harm" without a chance of individual benefits, and the need for active deception. Sham interventions do not only involve a chance of harm of omission because of the withholding of a treatment (if an established effective intervention exists) such as in oral placebos but also a degree of harm and risks because the bodily integrity is affected by definition, also called "positive harm."[2,60] This concept, however, is not different ethically from the positive harm without direct potential benefits for the participants in other clinical research, such as phase 1 trials, especially when these involve first-in-class drugs.[82-84] First-in-class drugs are drugs with a novel mechanism of action in comparison with existing drugs.[83] Furthermore, active deception occurs in other types of clinical trials, which is considered acceptable when the participants are informed beforehand of the possibility of being exposed to deceptive tactics, so the participant can consent to its use.[85] Furthermore, in (oral) placebo controlled trials, similar concerns have been raised regarding the extent to which this approach actually increases the scientific validity, particularly when a standard of care is available.[86,87] Nevertheless, ethical guidelines show considerable agreement that placebo-controlled trials are necessary scientifically and valuable for society in certain instances, and it is likely that these situations are comparable with sham interventions.[88-90] Therefore, it may be inappropriate to treat sham-controlled trials as a categorically different type of clinical research.

Second, although no difference in kind exists, the combination of specific features of sham interventions leads to a *difference in degree* in comparison with other research. For example, because of the inherent risks and harms involved and the involvement of deceptive tactics, the informed consent procedure is more likely to be complex and needs a specific type of attention.

Table. Arguments in favor and against the ethical acceptability of sham interventions

Arguments in favor	*Arguments against*
A sham intervention increases scientific validity	A sham intervention is often unnecessary for increasing scientific validity
A sham intervention increases benefits to future patients and society	A sham intervention does not always increase benefits to society
Risks and harm of a sham intervention can be acceptable	Risks and harm of a sham intervention are unacceptable
Gaining valid informed consent is possible	Difficulties are present in obtaining a valid informed consent
Active deception is not a priori unethical	Moral discomfort for investigator and participant can occur, mainly from active deception
Sufficient support by public and researchers exists	There is a lack of trust and support by public and researchers

Third, although we presented the arguments "in favor" and "against" the use of a sham intervention group, the 2 extreme positions, which range from "sham interventions are always acceptable" to "sham interventions are never acceptable," are rarely, if ever, defended. Moreover, almost no author fully condemns sham interventions. To begin with, the main arguments against sham interventions are provoked because of the risks and/or harm of a sham intervention, but these arguments were directed primarily at the fetal stem cell trials for Parkinson disease.[67,68] Although these trials were considered morally problematic because of the high risks involved and the alternative scientific designs, this argument does not imply that sham-controlled trials always involve unreasonable risks.

Furthermore, although some critics doubt the need of sham procedures to increase scientific validity and, subsequently to increase benefits to science and society, these critics usually argue that a sham control is used more often than scientifically necessary. Furthermore, they suggest that also pragmatic trials, in which the intervention is compared with the standard of care, are important, because these types of trials ensure information about the effectiveness in daily clinical practice.[91] Hence, hardly any disagreement exists that sham interventions are scientifically necessary in certain instances. The argument of substantial benefit to future patients and society is not a separate argument but determined by the scientific validity; if a sham intervention increases the scientific validity, it also increases the benefits to science and society. Besides, the argument of the aversion of the public is mainly an argument of emotion, which (alone) is often not a strong enough argument to consider the practice unacceptable. In addition, it is reasonable that there is potential moral stress for investigators and participants because of the need of deceptive tactics, but many of the authors also showed ways to lessen the moral stress, also because sometimes the investigator can be blinded. Finally, the argument of the difficulties in obtaining valid consent is not a strong argument because measures can be taken to find out whether the participant has understood the information sufficiently.

Fourth, it appears that most regard sham interventions as *conditionally acceptable*. These conditions consist of: scientific necessity, reasonable risks (in terms of a proportional risk-benefit ratio), and valid informed consent. To ensure a valid informed consent, information about the chance for deception should also be provided, also called "authorized deception."[69] Regarding the assessment of the conditions of scientific necessity and reasonable risk and/or harm, various criteria in literature are presented.

We conclude that sham-controlled trials should not be treated as a categorically different type of clinical research but rather as different in degree. Further debate should no longer address whether a sham control is ethically acceptable, but rather when the conditions are fulfilled. Particularly attention should be paid to *when a sham intervention is scientifically necessary* and *when risk and harm are reasonable*.

The question when a sham intervention is necessary scientifically should be addressed by clear methodologic criteria. Although placebo-controlled trials often are regarded as trials that ensure the greatest level of scientific validity, one should avoid the belief that placebos or sham interventions are considered a *goal*, instead of *means* to blind participants (and investigators) to prevent certain types of bias. If blinding a patient and/or the investigator is considered scientifically

necessary,[92] one should assure that the blinding is maintained during the trial to prevent bias as much as possible[93] and also to ensure that this is reported adequately to achieve comparability of trials in systematic reviews.

Nevertheless, even in double-blind RCTs, biases can still occur, for example, different investigators can elicit different placebo responses.[94] Furthermore, one should remain aware that double-blind RCTs often assure precision and generality, but realism is not always achieved, because the setting of a trial does not necessarily reflect the situation in clinical practice.[95] Furthermore, an RCT might not be feasible for several reasons; when a long follow-up time is required to assess intervention effects, when only a small number of patients are available, or because of patient preferences.[25,96-99] In these situations, cohort or case control studies, based on registries, might be more appropriate.[24]

An important criterion to determine the reasonableness of risks of a sham procedure is to consider whether the risks and/or harm (not only physical, but also psychological) are proportional to the benefits to science and society.[84,100] Aspects that determine the societal benefits are the seriousness and prevalence of the disease.[101,102] Assessing whether the risks are proportional to societal benefits is challenging because societal benefits are "often vague, indeterminate and uncertain."[103] Several frameworks have been developed to assist researchers and institutional research boards (IRBs) in assessing the risk-benefit balance, such as the "net risk test"[104,105] or addressing this challenge via decision theory.[106] Assessing the reasonableness of risks and benefits is a task for both the researchers and the IRBs, but the IRBs should make the final decision, before the potential participants are given information about the risks and potential societal benefits.[107] Hence, only sham-controlled trials with reasonable risks should be proposed to participants, instead of leaving the participants to determine the reasonableness of risks. In addition, some sham procedures will not lead to any substantive risk and harm, because these sham interventions involve only a minimally invasive intervention such as an intravenous or intra-articular injection. For other more invasive sham interventions, the risks of the sham procedure should be minimized by withholding a part of the intervention and, if possible, without deblinding.

Another aspect that should always be considered is whether a standard of care exists. Even if a sham procedure might be scientifically necessary and its risks might be proportionate to the benefits, withholding the standard of care could be viewed as unacceptable. Withholding the standard of care is acceptable, however, when this would not add any risk of serious or irreversible harm to the participants.[88,90]

In this paper we have ethically evaluated the arguments in favor and against sham interventions as they appear in the literature. We conclude that none of the published papers on this topic fully reject sham interventions, and many regard sham interventions acceptable provided the conditions of scientific necessity, reasonable risks, and a valid informed consent (including authorized deception) are fulfilled. We suggest that further debate should no longer address *whether* a sham intervention is ethically acceptable but rather *when* these conditions are fulfilled. In particular, the issue about when a sham intervention is necessary scientifically and when the risks and harm are reasonable should receive further interdisciplinary discussion.

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