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The Ethics of Sham Surgery on Research Subjects with Cognitivie Impairments that Affect Decision-Making Capacity

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Abstract

Populations recruited to participate in sham surgery clinical trials sometimes include patients with cognitive impairments that affect decision-making capacity. In this commentary we examine arguments for and against including these patients in sham surgery clinical trials. We argue that patients with cognitive impairments that affect decision-making capacity should not be excluded from a sham surgery clinical trial if there are scientific reasons for including them in the study and basic ethical requirements for clinical research are met.

Keywords

sham surgery; ethics; clinical trials; vulnerable populations; decision-making capacity

Using a placebo control group in surgical randomized controlled trials (RCTs), otherwise known as sham surgery, has been ethically controversial since Beecher described this method in 1961.[1–8] Sham surgery has been used to study treatments for a variety of conditions, including Parkinson's disease[9], osteoarthritis[10], compression fractures[11], and treatment-resistant depression[12]. The main ethical argument for sham procedures in surgical RCTs is that they are required for sound research design in some cases, especially when primary outcomes are subjective. Sham surgery can also control for report bias of patients who know that they are receiving an invasive intervention and for the placebo effect, both of which can affect treatment outcomes and produce false positive results.[1,5,6,8] Some studies have proven that treatments thought to be effective, based on clinical experience and RCTs without placebo controls, are actually no better than sham surgical treatments.[10]

Opponents of sham surgery argue that it is scientifically unnecessary because the placebo effect and report bias are small. They also argue that sham surgery is unethical because it imposes excessive risks on subjects in the control group; is incompatible with the doctrine of clinical equipoise, because subjects in the control group do not receive an effective treatment even though one is available; and it violates informed consent requirements, because subjects often do not understand they may not receive an effective medical treatment.[2–4,7] Proponents of

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sham surgery have countered these ethical objections to sham surgery by arguing that risks to subjects in the control group are not excessive and can be minimized; sham surgery does not violate clinical equipoise because the effectiveness of the standard treatment is in doubt; and the subjects can understand that they may not receive an effective treatment.[5,6]

In this commentary, we will assume that sham surgery can be justified when the ethical requirements for clinical research are met, such as scientific validity, risk minimization, and informed consent.[13] Instead of revisiting old debates concerning sham surgery, we will explore an ethical issue that has received scant attention: protecting subjects with cognitive impairments that may affect decision-making capacity who may participate in sham surgery RCTs. This is an important concern for investigators and institutional review boards (IRBs), because some of the populations recruited into sham surgery studies may include people with cognitive impairments that affect decision-making capacity (DMC). Twenty to forty percent of patients with Parkinson's disease develop dementia in the later stages, which can involve short-term memory loss, difficulty with abstract thinking, delusions, paranoia, hallucinations, and mood disturbances.[14] Stroke patients also experience a variety of cognitive impairments, including dementia and language difficulties.[15] Investigators in protocols that involve sham surgery on patients with Parkinson's disease, stroke, or other neurological disorders are likely to encounter prospective subjects who have compromised DMC. In the future, patients with other conditions that affect decision-making, such as Alzheimer's disease or age-related cognitive decline, may be invited to participate in sham surgery RCTs. Moreover, because justifications of sham surgery have recommended that investigators take additional measures to document consent, such as requiring subjects to write in their charts that they understand that they might receive fake surgery, it is important to consider the ethics of sham surgery involving a population of patients who may have difficulties with decision-making.[5]

Enrolling people with cognitive impairments that may affect DMC in research raises ethical issues, because people with these deficits are vulnerable subjects who may not be able to provide adequate informed consent or protect their own interests.[16] Though there is a general consensus that clinical investigators have ethical obligations to provide extra protections for people with cognitive impairments that affect DMC, there is little agreement on what this means or legal or policy guidance on this topic. The U.S. federal research regulations and the Belmont Report require that investigators provide additional safeguards for vulnerable subjects who participate in research, but they do not include any rules that specifically address people with cognitive impairments.[16–18]

Several widely influential documents provide advice on protecting subjects with cognitive impairments that affect DMC, though they are not legally binding on U.S. investigators. The World Medical Association's Helsinki Declaration states that research should be conducted on subjects with a physical or mental condition that prevents them from giving consent only if the physical or mental condition is a necessary characteristic of the population.[19] The Council for the International Organization of Medical Sciences (CIOMS) International Ethical Guidelines for Research Involving Human Subjects recommend that people who cannot provide adequate informed consent due to mental or behavioral disorders should participate in a study only if the research cannot be conducted equally well on subjects who have no problems providing consent, and the research addresses health needs relevant to people with those particular mental or behavioral disorders.[20] The Guidelines also recommend that subjects provide consent to the extent that they are capable, and if they cannot provide consent, that consent be obtained from a legally authorized representative.[20] The National Bioethics Advisory Commission (NBAC)'s report on protecting people with mental disorders in research recommends that people with mental disorders that affect DMC should be excluded from clinical trials if the research can be conducted equally well on other subjects. The report also recommends that subjects' refusals to participate in research should always be heeded, and that

for studies involving more than minimal risk, an independent qualified professional should assess the subject's capacity to consent.[21]

In thinking about protecting people with cognitive impairments that affect DMC who may be invited to participate in studies involving sham surgery, the first question to ask is whether these people should ever be included in this research. The Helsinki Declaration, CIOMS Guidelines, and NBAC report all agree that subjects with cognitive impairments that compromise decision-making should not be included in a study if the research can be conducted equally well without including those subjects. The ethical rationale for this requirement is to protect vulnerable subjects and to ensure that patients who cannot make decisions for themselves receive appropriate clinical care. For example, subjects with compromised DMC can be excluded from a sham surgery clinical trial on the effectiveness of an arthroscopic procedure for treating arthritis of the knee without compromising the scientific value of the study, because a person's mental abilities have little relevance to this disease or its treatment with surgical procedures. However, excluding subjects with compromised DMC from a sham surgery clinical trial to treat late-stage Parkinson's disease might compromise the scientific value of the study because a large percentage of people in the later stages of Parkinson's disease have dementia, and it may be important to determine whether the intervention can improve this condition.

Even those who accept sham surgery as a legitimate clinical research method might argue that people with cognitive impairments that may affect DMC should never be included in sham surgery studies, because the risks of sham surgery are substantial and the benefits are questionable. The risks of sham surgery RCTs include the risks of the procedure itself as well as risks related to anesthesia, infection, and surgical complications.[9] People in the control group will undergo these risks with no compensating benefits.[4,22] Because the benefit/risk ratio of sham surgery research can be so unfavorable to subjects, the DMC of those who participate in research should be unquestionable and well-documented, according to this objection. For their own protection, people with impairments that may affect DMC should be excluded from sham surgery protocols, even if there are sound scientific reasons for including them.

While we recognize the importance of taking additional measures to protect people with cognitive impairments that may affect DMC, we think this objection goes too far because it would exclude people from potentially beneficial studies. Moreover, it would preclude developing rigorous generalizable knowledge about the benefits of surgical interventions for those conditions that are prevalently associated with cognitive impairment.

If one decides to include research subjects with cognitive impairments that may affect DMC in a sham surgery protocol, then the next question to ask is what types of additional protections need to be implemented. One of the most important safeguards for protecting subjects with cognitive impairments is to use reliable procedures for assessing DMC. DMC is not an all-or-nothing trait: people have different levels of DMC, ranging from full DMC, to diminished DMC, to no decision-making abilities whatsoever.[16] DMC also is context-specific: a person can be capable of making one type of decision, such as deciding what to eat for dinner, but not another, such as choosing medical care.[16] Clinicians have developed a number of different instruments for assessing DMC, which we do not have space to explore in depth here.[23] Some of the key factors that affect a person's level of DMC are memory, problem-solving abilities, attention, intellectual ability, attention, and emotional balance.[16] Although instruments can help clinicians assess decision-making abilities, determining a person's level of DMC is an evaluative judgment that cannot be reduced to the application of simple formulas.[23]

Once DMC has been assessed, investigators must determine whether subjects are capable providing informed consent for the study. The level of DMC required to make a decision to participate in a research study should vary according to the complexity of the study, the uncertainty of the benefits, and the risks of the procedures or interventions.[16] Because sham surgery trials usually involve a high degree of complexity, uncertainty, and risk, only subjects with full (or nearly full) DMC should be allowed to provide unassisted consent for participation in these studies. Subjects with diminished DMC may participate with some assistance in the consent process, and those with minimal or no DMC should only participate if proxy consent from a legally authorized representative is obtained and the subject assents.[16,21]

In most studies involving subjects with cognitive impairments that may affect DMC, members of the research team assess decision-making abilities when they enroll research subjects and initiate informed consent discussions. Because clinical trials with sham surgery control groups often involve considerable uncertainty and risk, and members of the research team may have financial or professional interests that could bias their judgment when evaluating a prospective subject's decision-making abilities, DMC assessment by a professional independent of the research is an important step for protecting human subjects in these studies. Though independent DMC assessment cannot prevent investigators from falsifying enrollment criteria or committing other types of misconduct, it can provide an additional layer of protection for human subjects.[16,21]

Using an advance directive is another strategy for protecting subjects with cognitive impairments that affect DMC. Someone who expects that his or her cognitive abilities will decline during the course of the study should use an advance directive to assign a legally authorized representative to make choices related to study participation, if necessary.[16] Advance directives could also be useful for people who have not yet enrolled in a research study but who may in the future. A person with sound decision-making abilities could complete an advance directive when someone learns that he/she has a condition that may cause cognitive abilities to decline, such as Parkinson's disease. The person could use the document to express his/her wishes concerning research participation and also specify the general risk level that he/she is prepared to accept. Legally authorized representatives could rely on the advance directive to make choices for the person, if necessary.[18]

To conclude, patients with cognitive impairments that may affect DMC should not be prevented from participating in sham surgery RCTs, if there are scientific reasons for including them in these studies and basic ethical requirements for clinical research, such as risk minimization, justifiable benefit/risk ratio, informed consent, and additional protections for vulnerable subjects, are met.

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