Published in final edited form as:

Mov Disord. 2012 September 15; 27(11): 1461–1465. doi:10.1002/mds.25155.

Sham Surgery Controls in Parkinson Disease Clinical Trials: Views of Participants

Scott Y. H. Kim, MD, PhD^{1,2}, Raymond De Vries, PhD^{2,3}, Robert G. Holloway, MD, MPH^{4,5}, Renee Wilson, MA⁶, Sonali Parnami, MPH², H. Myra Kim, ScD⁷, Samuel Frank, MD⁸, and Karl Kieburtz, MD, MPH^{4,6,9}

¹Department of Psychiatry, University of Michigan, Ann Arbor, MI

²Center for Bioethics and Social Sciences in Medicine, University of Michigan, Ann Arbor, MI

³Department of Medical Education, University of Michigan, Ann Arbor, MI

⁴Department of Neurology, University of Rochester, Rochester, NY

⁵Department of Community and Preventive Medicine, University of Rochester, Rochester, NY

⁶Center for Human Experimental Therapeutics, University of Rochester, Rochester, NY

⁷Department of Biostatistics, University of Michigan, Ann Arbor, MI

⁸Department of Neurology, Boston University, Boston, MA

⁹Department of Environmental Medicine, University of Rochester, Rochester, NY

Abstract

Background—Sham surgery controls are increasingly used in neurosurgical clinical trials in Parkinson disease (PD), but remain controversial. We interviewed participants of such trials, specifically examining their understanding and attitudes regarding sham surgery.

Methods—We conducted semi-structured qualitative interviews with participants of three sham surgery controlled trials for PD, focusing on their understanding of sham design, their reactions to it, its impact on decision-making, and their understanding of post-trial availability of the experimental intervention and its impact on decisions to participate.

Corresponding author: Scott Y. H. Kim, MD, PhD, Center for Bioethics and Social Sciences in Medicine, University of Michigan, 300 North Ingalls Street, 7C27, Ann Arbor, MI 48109, USA, 734-615-8377, fax 734-936-8944, scottkim@med.umich.edu.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found at the end of this manuscript.

Author roles:

Scott Y.H. Kim, MD, PhD: Research project-study conception and design; obtaining funding; Statistical analysis-design, execution, interpretation and review; Manuscript preparation- writing of first draft and revisions. Raymond G. De Vries, MD: Research project-study conception and design; Statistical analysis- data analysis and interpretation; review and critique; Manuscript preparation- review and revisions. Robert G. Holloway, MD, MPH: Research project-study design and conception; obtaining funding; Statistical analysis-data interpretation; review and critique; Manuscript preparation- review and revisions. Renee M. Wilson, MA: Research project-organization and management; acquisition of data; Statistical analysis-data interpretation and analysis; review and critique; Manuscript preparation- writing of first draft; review and revisions. Sonali Parnami, MPH: Research project- acquisition of data; Statistical analysis- management of database; data interpretation and analysis; review and critique; Manuscript preparation- writing of first draft; review and revisions. H. Myra Kim, ScD: Research project- execution; Statistical analysis- design and execution; review and critique; Manuscript preparation- review and critique. Samuel A. Frank, MD: Research project- study design and conception; Statistical analysis- review and critique; Manuscript preparation- review and revisions. Karl Kieburtz, MD, MPH: Research project-study conception and design; obtaining funding; Statistical analysis- data interpretation; review and critique; Manuscript preparation- review and revisions.

Results—All subjects (N=90) understood the two-arm design; most (86%) described the procedural differences between the arms accurately. 92% referred to scientific or regulatory reasons as rationales for the sham control, with 62% specifically referring to the placebo effect. 91% said post-trial availability of the experimental intervention had a strong (48%) or some (43%) influence on their decision to participate but only 68% understood the conditions for post-trial availability.

Conclusions—Most subjects in sham surgery controlled PD trials comprehend the sham surgery design and its rationale. Although there is room for improvement, most subjects of sham surgery trials appear to be adequately informed.

Keywords

sham surgery; gene therapy; Parkinson disease; bioethics

Sham surgery controls are increasingly used in neurosurgical clinical trials of interventions for Parkinson disease (PD).^{1–3} Unlike a pill placebo, sham surgery is invasive, usually consisting of bilateral burr holes (full or partial) and with or without penetration of the dura. Despite their invasiveness, most PD clinical researchers in North America support sham controls because of the scientific advantages in controlling for placebo effects.⁴ A recent review noted that there have been six surgical interventions of PD that had initially shown promise in open label trials that later proved no more effective than placebo surgery.⁵ In five of six experimental therapies tested, the response to the active therapy was 50–70% less in the blinded trials compared to open trials; the open label studies also tended to underestimate the potential risks.

Yet sham surgery controls remain controversial. Some scientists reportedly consider sham brain surgery “an expensive, potentially dangerous and possibly unethical bit of biomedical theatrics.”⁶ In Europe and the UK, where sham controls are deemed less acceptable than in the U.S., a large clinical trial of a fetal cell transplant treatment is underway, without the use of sham controls.⁶ One prominent reason why sham controls have been deemed unacceptable is a concern that vulnerable, elderly patients with incurable and debilitating illnesses may be exploited in such research.⁷ In evaluating the ethics of this controversial topic, it is important to incorporate the perspective of those PD patients actually involved in such trials.

We interviewed persons who agreed to participate in sham controlled surgical trials for PD, examining their understanding and attitude toward sham surgery controls, as well as toward the availability of the experimental intervention to those in the sham arm after the trial, a usual part of sham controlled studies that has created controversies of its own as subjects have sought the experimental intervention even in negative trials.⁸

METHODS

Participants

Participants were recruited from three sham controlled intervention trials for PD. We recruited 31 of 56 (55%) enrollees at 5 sites from the ‘STEPS trial’¹ and 30 of 43 enrollees (70%) at 7 sites of the ‘CERE-120 trial’³; they were interviewed retrospectively, after their surgery (details of their recruitment can be found in an earlier report.⁹) In the ‘GAD study,’ sponsored by Neurologix, Inc.², we interviewed 29 of the 45 (64.4%) enrollees from 5 sites, of whom 24 were interviewed prospectively before surgery. All interviews were conducted via telephone and were recorded and transcribed. Interviewer notes were used for one interview because of technical difficulties in recording. The Institutional Review Boards of

the University of Rochester and the University of Michigan reviewed the study and deemed this study exempt from U.S. federal regulations.

Measures and Analysis

Conditional Probe Interview (CPI)—The CPI is a semi-structured qualitative interview guide designed to elicit how the subjects made their decisions about participation.¹⁰ This paper focuses on those questions in the CPI that specifically address the subjects' understanding and attitudes toward the sham placebo design (listed in Appendix 1). After all transcriptions were checked for accuracy, standard content analysis procedures were used, developing and refining codes in an iterative fashion, and resolving coding discrepancies through group discussion.¹⁰

RESULTS

Of the 90 subjects, most were white (n=88, 98%), male (n=64, 71%), married (n=66, 73%), and well-educated (n=52 with college degree or higher, 57%). Average time since PD diagnosis was 11.7 (SD 4.6) years.

Understanding sham surgery research design, rationale, and procedures

All subjects showed a basic understanding of the sham control design, i.e., that there were two arms in their study, a placebo and a treatment arm. When asked about the purpose of the control arm, the answers varied in specificity.

Whereas some merely said that the FDA requires it, others articulated the generic need (without specifically mentioning the placebo effect) for a comparison arm:

“I mean I’m not a world-renowned scientist or something, but I know basically that to confirm it to be a success, you have to have a control group.” (STEPS, S23)

Others specifically mentioned the need to control for the placebo effect in PD clinical trials:

“The placebo effect is extremely strong in Parkinson’s for some reason in some individuals. So, you’ve got to have a placebo group. The whole . . . All twelve of those people in the phase I study could have been affected by the placebo effect.” (CERE-120, S7)

Overall, 92% of subjects provided an answer that referred to the scientific or, less commonly, the regulatory rationale for the sham control arm.

86% of subjects described the procedural differences between the study intervention and the sham surgery groups accurately. These subjects correctly contrasted the treatment arm which involved injection with the study agent into the brain, with the placebo arm involving only burr holes (and a saline injection into the scalp for the GAD study). Approximately 77% of subjects stated that the study intervention arm has greater risks than the sham surgery arm.

Attitudes toward sham surgery design

Overall, half of the subjects reported that they had an initial negative reaction to finding out that there would be a sham surgery arm.

They mentioned being disappointed, concerned or apprehensive when they learned of the sham surgery design: “that part of it is really a turn-off, a real big one” (CERE-120, S18), “I had to think about that for a little bit” (CERE-120, S2), and “I was discouraged” (GAD, S15). Surprisingly, six subjects had a positive reaction after being informed that there would

be a sham surgery arm: “All good studies should be done that way” (STEPS, S12), “...the fact that there was a placebo and it was double-blind...it did make me more confident that... It’s a professional study as opposed to nonprofessional” (GAD, S5). Most of the subjects with an initial negative reaction who indicated the influence of this initial reaction on their decision (71% ,15 of 21) said it did not negatively influence their decision to participate.

When asked to comment on the invasive nature of the control condition, most of the enrollee comments (79%) expressed views to the effect that they understood the need for sham surgery, felt the risk was acceptable, trusted the researchers, or felt it was acceptable in light of the later offer of the study intervention. However, 14% of the comments from subjects expressed some residual negative sentiments about the sham arm.

Understanding and attitudes toward later offer of study intervention

All three clinical trials offered the subjects in the sham surgery arm the experimental intervention at the end of the study period, under the condition that the study intervention proved to be safe and effective. Although the majority of subjects understood the conditions under which the study intervention would be made available, a sizable minority (32% of enrollees) wrongly assumed that it would be offered without condition, were not sure of the conditions, or expressed themselves in a way that did not allow a clear determination of whether they understood the conditions.

The later offer of the experimental study intervention had a strong impact on the enrollees’ decision to participate, with nearly half (48%) saying that it was a necessary or strong reason for his/her decision to participate and an additional 43% saying it had some influence.

Finally, 89% of subjects (among whom data were available, 64 enrollees), said it would be better to be in the study intervention arm. Interestingly, four of the six subjects who had a positive reaction to the sham design still felt that the study intervention arm was the preferable arm to be in. For example, although GAD S24’s initial reaction to sham design was, “that was the best . . . a marvelous way of handling it,” he still preferred “the gene transfer....I would think that the genes have the best chance of doing something for me to help out.”

DISCUSSION

Unlike a pill placebo, placebo surgery in a randomized controlled trial is not benign. Although to date there appears not to have been serious adverse effects from sham surgeries,¹¹ an invasive control condition in studies involving elderly persons with incurable illnesses requires close ethical scrutiny. To inform this issue, we examined the level of understanding of participants of actual sham controlled trials regarding key design elements of a sham controlled clinical trial. There are several key findings. First, the subjects are overall well informed regarding the sham surgery design and its rationale. About two thirds of our subjects articulated the rationale for the sham condition with a fairly high degree of specificity (the need to control for placebo effects) and the rest of the subjects provided less specific but still accurate rationales for sham surgery. A large majority of enrollees (86%) also understood the differences in procedures between the two arms. The fact that nearly half (47%) of the subjects had an initial negative reaction to the sham design suggests that the subjects appreciated the implications of a sham control design—especially since most also understood that the study intervention arm is more risky than the sham arm. Further, even those few who had a positive reaction to the sham design provided a sound rationale for their opinion. On the other hand, there is room for improvement, as 14% of subjects did not adequately describe the difference in procedures between the sham arm and the intervention arm and 18% stated that the risks of the two arms were the same.

Second, the subjects' comments regarding the invasive nature of the sham surgery arm suggested that, even if they had a negative initial reaction, they accepted its rationale. Only about 14% of enrollees' comments (14 of 100 comments) reflected a residual negative sentiment. Of those, eight comments reflected the view that although the subjects saw a need for a comparison arm, they disagreed with sham surgery as the proper control. These subjects knowingly accepted the sham arm despite their objections, in order to participate in the trial. This raises the question of whether these subjects were therefore less (because they had to accept something they did not agree with) or more (because they might have made a knowing trade-off) "voluntary" in their decisions to participate. Third, the offer of post-trial availability of the study intervention is very important to those who enroll in sham controlled trials in PD. Almost half said it was either a necessary or strong condition for their participating, with another 43% citing it as having "some influence." However, a significant minority (32%) was either mistaken or unclear about the conditions for such an offer, and given its strong impact on decision-making, this is clearly an area in need of improvement. Finally, the results reinforce the need to carefully distinguish between subject motivation and subject understanding,^{10, 12} as clearly demonstrated by those subjects who recognized the need for the rigorous study design, all the while desiring to be in the intervention arm.

The study has limitations. First, the results are based on qualitative coding of narrative texts. Although we used methods to maximize reliability and reduce bias, such coding involves judgment, and others may have coded the texts differently. Second, the time of interviews varied, so that some subjects were interviewed prospectively while a majority were interviewed retrospectively, some several years after surgery. However, our sample included both prospective (n=24 enrollees) and retrospective interviews (n=66 enrollees), and the responses were similar in both groups. Third, missing data was a problem for a few of the follow-up probe questions, due to the nature of how we conducted the interviews—allowing the subjects to lead the discussion, and thereby sometimes not asking all of the probe questions. Fourth, because the informed consent process for these clinical trials was extensive, involving well-educated subjects, one should be cautious about generalizing these findings to other settings.

Most subjects in sham controlled PD trials achieve not only factual comprehension about the special features of a sham control design—as required by informed consent—but also achieve an appreciation of the scientific and regulatory rationale for the design that goes beyond the strict requirements of informed consent. They are also able to explain coherently their decision-making regarding research participation. But there is clearly room for improvement, especially regarding the conditions for post-trial availability of the study interventions. Overall, informed consent concerns regarding special features of sham controlled trials in PD, although needing some improvement, should not be seen as a special ethical barrier to such studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank the subjects who so generously gave their time and shared their experiences with them. They also wish to thank Ceregene, Inc. and Raymond T. Bartus, Ph.D., Executive Vice President and Chief Scientific Officer, for thoughtful comments on the study and access to the patients who were involved in their CERE-120 Phase 2 clinical study; Christine V. Sapan and Neurologix, Inc. in providing access to the patients involved in their GAD 2 clinical trial; and Titan Pharmaceuticals, Inc. for their cooperation.

Funding sources: This publication was made possible, in part, by the Michael J. Fox Foundation for Parkinson's Research (Rapid Response Innovation Award); the National Institute for Neurological Disorders and Stroke (R01-NS062770); and a CTSA award (UL1 RR024160) from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health.

Additional support to the authors comes from the following sources:

Consultancies: Hoffman-Roche (Dr. Scott Kim, DSMB member); American Academy of Neurology (Dr. Robert G. Holloway); Merz and Genzyme (Dr. Samuel A. Frank); Abbott, Biogen Idec, Boehringer Ingelheim, Ceregene, EMD Serono, Acorda, Biotie, Civitas, Clintrex, Cyapsus, Genzyme, Impax, Intec, Ipsen, Isis, Lilly, Linkmedicine, Lundbeck, Merz, Orion, Otsuka, Pharma2b, Phytopharm, Schering-Plough, Siena Biotech, Synosia, Solvay, Synagile, Teva, UCB Pharma, Xenoport, Novartis (Dr. Karl Kieburtz). Royalties: Oxford University Press (Dr. Scott Kim).

Employment: Milliman Guideline, Inc. (Dr. Robert G. Holloway). Payment for lectures: American Parkinson Disease Association (Dr. Samuel A. Frank). Expert testimony: Pfizer (Dr. Karl Kieburtz). Grants: Neurosearch and Medivation/Pfizer (Dr. Karl Kieburtz).

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Table 1

Understanding of Sham Control Rationale and Procedures.

	N=90 [*]
What is the purpose of having a sham surgery group?	
Need to control for placebo effect	55 (61.8)
To make study legitimate/rigorous (no specific mention of placebo effect)	25 (28.1)
Cannot determine from text if subject understands purpose of sham surgery	3 (3.4)
FDA requires it	2 (2.2)
Subject not sure	2 (2.2)
Other	2 (2.2)
Describe the difference in procedures between those who receive sham surgery and those who receive the [study intervention]	
Describes differences accurately	67 (85.9)
Does not describe differences accurately	4 (5.1)
Subject can't recall/not sure	6 (7.7)
Other	1 (1.3)
How are the risks faced by those in the [study intervention] group different from the risks faced by those in the sham surgery group?	
Those in [study intervention] group face greater risks	44 (77.2)
Those in sham surgery group face greater risks	-
No difference/ face same risks	10 (17.5)
Not sure	2 (3.5)
Other	1 (1.8)

* Numbers may not add to 90 for every question because of missing data for some of the questions.

Table 2Attitudes Toward Sham Surgery Controls. (N=90^{*})

What was your initial reaction to finding out there would be a sham surgery group?	
Negative reaction (disappointed, concerned, surprised, etc.)	42 (47.2)
Neutral reaction (not surprised or concerned, etc.)	41 (46.1)
Positive reaction (strengthens study, makes study more rigorous, etc.)	6 (6.7)
What influence did this initial reaction have on your decision, if any?	
Negative influence on decision/made subject more hesitant regarding participation	7 (15.6)
No negative influence on decision/neutral influence	35 (77.8)
Positive influence on decision	3 (6.7)
Usually placebos are risk-free (like taking a sugar pill), but sham surgery placebos involve a neurosurgical procedure. What do you think about the fact that sham surgery involves an invasive procedure?[#]	
Understood need for control group, so accepted this	42 (42.0)
Risks of sham surgery seemed acceptable	22 (22.0)
Understood need for control group, but disagreed with inclusion of sham surgery	8 (8.0)
Trusted researchers and so accepted this/deferred to researchers	11 (11.0)
Understood and accepted need for control group, but still has some negative feelings concerning invasiveness	6 (6.0)
Acceptable in light of later offer of [study intervention]	4 (4.0)
Risks of sham surgery seemed unacceptable	-
Other	7 (7.0)

[#] For this question numbers refer to comments, not subjects, and exceed the total number of subjects because some subjects made more than one comment.

^{*} Numbers may not add to 90 for every question because of missing data for some of the questions.

Table 3

Understanding and Attitudes Toward Later Offer of Study Intervention.

	(N=90) *
How are researchers going to decide if the [study intervention] will be offered later to those who get the sham surgery initially?	
If the intervention is determined to be potentially beneficial and safe	60 (68.2)
Automatically offered/ no preconditions	13 (14.8)
Not sure what conditions must exist	10 (11.4)
Can't determine if subject understands conditions	5 (5.7)
Please explain what influence [the post-trial offer of study intervention] had on your decision to participate, if any.	
Necessary or strong condition for participating	37 (48.1)
Some influence but not necessary	33 (42.9)
Didn't influence decision	7 (9.1)
Other	-
Do you think it would be better to be in the [study intervention] group or the sham surgery group?	
Active treatment group	66 (89.2)
Placebo group	3 (4.1)
Tried not to think about it	1 (1.4)
Other	4 (5.4)
Why [would that arm be better to be in]?#	
Motivated by desire for direct personal benefit	33 (41.3)
Didn't want to wait a year to receive [study intervention]	18 (22.5)
Didn't want to go through surgery twice	12 (15.0)
Each option has advantages	6 (7.5)
Wanted to wait and see what happened to subjects who received [study intervention] before subject received it	2 (2.5)
Didn't want to be influenced by expectations, so tried not to think about this	1 (1.3)
Other	8 (10.0)

For this question numbers refer to comments, not subjects, and exceed the total number of subjects because some subjects made more than one comment.

* Numbers may not add to 90 for every question because of missing data for some of the questions.