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Sham Surgery Trial Controls: Perspectives of Patients and Their Relatives

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Abstract

THIS STUDY REPORTS ON QUALITATIVE research conducted in the UK with people with Parkinson's Disease and their relatives on the subject of "sham surgery." It explores attitudes toward sham surgery and reasoning about hypothetical participation in a sham-controlled trial. Results showed that attitudes toward sham surgery may not necessarily predict trial participation behavior. A small majority of interviewees deemed sham surgery ethically acceptable with certain provisos, but hypothetical participation was driven primarily by disease severity and a lack of standard treatment options, with a preference for receiving the real surgery over sham. Ethical implications for patient equipoise and the autonomy of patients' research participation decisions are discussed.

Keywords

sham surgery; Parkinson's Disease; research ethics; placebo; control groups; autonomy

IN 1999, NEUROSURGICAL RESEARCHERS IN THE United States published their intention to conduct a trial of a fetal cell transplant (FCT) technique to treat patients with severe Parkinson's Disease (PD) (Freeman et al., 1999). The trial would use a "sham surgery" control group. For the patients randomized to the control group, participation would involve two sham operations; each involving general anaesthesia, the fitting of a stereotactic frame to the skull with metal pins, an MRI scan, a burr hole drilled partway into the skull (but not penetrating the brain), and follow-up immunosuppressant drugs. This announcement precipitated heated debate over the ethics of using such sham controls.

The study went ahead nevertheless (see Olanow et al., 2003), following as it did a similar trial investigating FCT in which the control group involved local rather than general anaesthesia and no immunosuppression, but which still required the fitting of a stereotactic frame, scans, and a partial hole drilled into the skull (Freed et al., 2001). A number of other sham surgery–controlled trials for severe PD have also been conducted relatively recently (Watts et al., 2001; Marks Jr. et al., 2010; LeWitt et al.; 2011; Gross et al., 2011), all involving some level of active control intervention.

Proponents of sham surgery have argued that a rigorous scientific method involving a placebo control is necessary for testing experimental procedures since results may otherwise be compromised by placebo response (Freeman et al., 1999; Gillett, 2001; Albin, 2002). Sham-controlled trials have been conducted in the past showing that procedures evaluated in comparison to sham have proven no more effective than placebo (e.g., Cobb et al., 1959;

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Thomsen et al., 1981). Such procedures have subsequently dropped out of use. The ethical argument in favor of sham controls in surgery is thus that they may prevent ineffective procedures from becoming wide-spread and hence performed for no valid reason upon a large number of patients. It is also argued that those in the sham group may receive benefits such as the reward of altruism, receive standard medical treatment at no cost, and avoidance of the risks of the real surgery should it prove unsafe or ineffective (Freeman et al., 1999), as well as the placebo effect itself (Stock, 2003).

Opponents of sham surgery, however, provide a number of ethical arguments against the practice. First, the benefits listed above are collateral ones, rather than directly related to the intervention being tested. The National Bioethics Advisory Commission (2001) advises that these are not taken into consideration when weighing the risks and benefits of trial participation. An offer of real treatment subsequent to the completion of the trial may also act as an undue inducement to take part in a trial if it causes patients to overlook the associated risks of participation (Edwards, 2006). The risks of sham surgery are also admittedly “non-trivial” (Freeman et al., 1999) and hence above minimal risk, leading commentators to argue that sham surgery simply fails a test of non-maleficence (Macklin, 1999; Clark, 2002).

Proponents of sham surgery have argued that patients’ decision-making autonomy should be respected, and thus participation in trials involving more than minimal risk should be permitted so long as patients are fully informed of all risks and can make a competent and voluntary decision. Opponents, however, argue that the autonomy of patients may be compromised (Dekkers & Boer, 2001; Macklin, 1999; Clark, 2002). First, they may labor under the “therapeutic misconception” that the research is designed to benefit them, or is likely to benefit them, when in fact there is no guarantee that it will (Lidz & Appelbaum, 2002). More importantly, in a patient group with a serious, degenerative illness, patients’ participation decisions may potentially lack autonomy as a result of fear and desperation caused by a lack of treatment options. The possibility that a patient in such a position will agree to participation in any trial offering them hope may leave them vulnerable to exploitation.

The arguments are persuasive on both sides and lead to something of an ethical impasse. As a consequence, it has been argued that the voices of stakeholders in the issue should be heard (Leeds, 2003; Cohen et al., 2007), including patients, the public, and surgeons. Although little empirical research exists on the topic, the views of neurosurgery researchers in North America have been explored in two surveys (Kim et al., 2005; Prehn et al., 2006). In both, sham surgery was not merely supported but viewed as superior to open label trials on the utilitarian grounds that it will obtain the most accurate results regarding experimental treatments.

Frank et al. (2007) presented PD patients and patients with other conditions with a hypothetical trial involving a sham surgery trial arm to test a new gene transfer protocol. The study found that the groups held similar views about sham surgery but that patients with PD were more cautious about participation.

Cohen et al. (2010) report a survey by the Parkinson’s Disease Pipeline, a patient advocacy group in the United States, which showed that only 17% of respondents would volunteer for a trial involving sham surgery. Only 23% agreed that information gained using sham surgery was worth the risk to those in the sham group. The survey authors hypothesize that, based on open comments received, patients, when they do agree, may do so because they lack treatment options and are desperate.

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The findings above show that there are two aspects to exploring stakeholders' attitudes to sham surgery: first, whether or not they believe sham surgery is ethically acceptable and, second, whether or not they would participate in such a trial, independently of their opinion of it. This distinction is important for two reasons. First, a mere survey of opinions may fall afoul of the "is-ought" distinction; that is, one cannot conclude what *ought* to be the case merely from statements about what *is* the case (Hume, 2000 [1740]). Second, since one of the questions arising from the literature is whether decisions to participate are sufficiently autonomous or not, investigation of the reasoning behind participation decisions may provide deeper insight into what motivates a patient to take part in a sham-controlled trial—which is a different question from whether or not they approve of the method.

The qualitative research study reported here is an attempt to provide further insight into the ethics of sham surgery by generating empirical data with regard to the perspective of patients in the UK, consonant with a call by Kim et al. (2005) for data from outside North America. In line with the distinction made above between attitudes toward sham surgery and participation behavior, the specific goal of the qualitative study reported here is not only to investigate attitudes of patients and their relatives toward sham surgery, but also to explore what reasons may determine decisions to accept or decline participation in a trial involving sham surgery, and the ethical implications of such reasoning. Since the research reported here concerns beliefs and reasoning about sham surgery, adoption of a naturalistic paradigm and a qualitative methodology seemed most appropriate. Qualitative methods are well suited for investigating abstract concepts such as meanings and values (Bowling, 1997). This fits with a level of consensus that has been reached in bioethics regarding the utility of qualitative methods for the purpose of empirical ethical inquiry (Haimes, 2002; Ives, 2008).

Method

A qualitative, semi-structured interview guide was used (see Boxes 1 and 2 in online supplementary material at http://dx.doi.org/10.1525/jer.2012.7.3.15). The interview guide consisted of: a definition of the placebo effect and an explanation of why a placebo-controlled research trial is used; a vignette describing aspects of a placebo-controlled surgical trial for PD; and a list of questions. Readability calculations were performed for all documents and were within Plain English guidelines.

The objectives of the interview were fairly specific and set in advance in order to address issues specific to sham surgery, but questions were open-ended and the style of the interview conversational, with opportunities given for participants to expand upon topics or introduce new ones not covered by the interview guide.

The interview guide was designed to explore interviewees' attitudes toward the concept of sham surgery and their thoughts on participation in a sham-controlled surgical trial for PD. Questions reflected the key ethical arguments identified in the literature: the importance of rigor in research, research participants' best interests, and the issue of autonomy. Neutrality of questioning (such that the questionnaire did not appear either in support of or against sham surgery) was assessed by asking two independent colleagues to review the interview guide for bias.

Two interviewers were used to reduce interviewer bias. The first interviewer was the main study investigator, who provided training for the second interviewer. Key literature was provided to the second interviewer in order to give background information on the concept of and ethical debate regarding sham surgery. A "procedure sheet" was developed to guide the interview encounter as a whole and to assist with standardization of approach across

interviews. Meetings were held to discuss the interview guide and to review how the first few interviews proceeded in practice.

Recruitment and Sampling

The study received approval from the local research ethics committee (REC) attached to the hospital through which participants were recruited. After discussion with the REC, inclusion criteria for patients were set as follows: any age, both genders, and a minimum of two years since diagnosis of PD. Exclusion criteria were as follows: anyone currently undergoing or very recently having undergone surgery, since the ethics committee did not want any extra burden put upon the patient at such a time; major cognitive problems; and significant depression. Key to the decision to include relatives in the study was respect for the normative force of their opinions. As with many other chronic or incurable illnesses, family members are often involved in key ways and on a regular basis, giving them insight into the condition and a personal stake in the issue of how PD research is conducted. Day-to-day contact with the person with PD was an inclusion criterion for relatives.

As required by the REC, invitation letters were handed out in person by a PD nurse specialist at a weekly movement disorder clinic at a hospital neurology department. The letters were written from one neurology consultant with the approval of all doctors whose patients attended the clinic.

Eighty invitation letters were sent out over a period of several months (forty for patients, each including a separate invitation letter to a carer or relative). The response rate was 22/80 or 27.5%. Twelve interviews were conducted, five of which were single interviews with patients and seven of which were conducted jointly with relatives (in one case with two relatives present). Twenty individuals were interviewed in total. One relative's participation was declined on grounds that she did not have day-to-day experience of living with her relative with PD. One person with PD dropped out just before interview due to time constraints and ill health in the family.

People who returned a reply slip were telephoned by the investigator, given further details and a chance to ask questions, and then enrolled into the study if they wished to proceed. Consent forms were signed at the outset of each interview following a further chance to ask questions. Convenience sampling was employed, but an even range across participant age, sex, and time since diagnosis was achieved. Participants' disease severity ranged from mild to moderately severe, as self-rated. Participant demographics are presented in Table 1, while interview type (one-to-one or joint interview) and type of relationship between joint interviewees are presented in Table 2.

Procedure

Participants received the vignette and questionnaire in advance by post in order to give them more time to read, understand, and reflect on the relatively complex issue of sham surgery before the interview itself.

Interviews all took place in respondents' homes. The series of interviews was conducted over a six-month period. The interviews took between twenty minutes and an hour. It was emphasized to participants that there were no "right" or "wrong" answers to the questions; the exercise was to elicit their thoughts and opinions. All participants agreed to be tape recorded. Field notes were made directly after interviews to record additional impressions; for example, interview dynamics and participants' understanding of the interview guide. Audio-recorded data were transcribed and rendered anonymous. Paper and electronic data were kept under secure arrangements in line with the relevant data protection requirements.

Data Analysis

An iterative analysis process began as transcripts became available. The analysis method adopted was framework analysis, a method originally developed for applied policy research. It differs from "basic" or "theoretical" research due to a requirement to meet specific information needs and the potential for actionable outcomes (Ritchie & Spencer, 1994). This analytic approach matches well with the purpose of this research, which sought specific information about attitudes and decision-making relating to sham surgery. This study focused on two particular objectives that Ritchie and Spencer outline for applied policy research. The first was contextual: to find out what attitudes were held about sham surgery as described in the interview and what participation decisions interviewees might make. The second was diagnostic: to explore the reasoning underlying the opinions and decisions expressed by participants.

The five key stages of framework analysis are: familiarization; identifying a thematic framework; indexing; charting; and mapping and interpretation. Familiarization involved immersion in the data: reading all interview transcripts and notes several times to gain an appreciation of the depth and range of responses to questions. Key points and recurrent themes were noted. A thematic framework reflects the key issues, concepts, and themes by which the data would be examined. In keeping with Ritchie and Spencer's own description of the analysis method, this was initially based upon a priori issues in the interview guide, but also included issues emerging from respondents themselves. Transcripts were then marked throughout with short text "labels" relating to the index domains and subdomains. This allows patterns and connections to emerge. Subsequent versions of the thematic framework were developed as these connections emerged. Charting involved sorting the indexed sections of the transcripts into the appropriate themes but with the data for each theme remaining in interview order for ease of reference. Mapping and interpretation activities depend on the aim of the study: in this case it involved mapping the range and nature of attitudes to sham surgery and of reasoning regarding hypothetical participation in a sham-controlled trial; it also involved an attempt to specify associations between themes and to provide explanations for the findings in the data.

The transcripts were given to a second rater to perform an independent initial thematic framework development and indexing of the transcripts. Results showed agreement on key themes but with some differences in how themes and subthemes were ordered. These differences were resolved through discussion.

Results

Key aspects of the data analysis are reported below and are organized according to the key questions asked in the interview guide. Verbatim quotes from interviewees are presented to illustrate points.

Reasoning about Hypothetical Participation in a Sham-Controlled Trial

DISEASE SEVERITY—Most People with Parkinson's (PWP) who were interviewed stated that at the present time they did not feel their PD was severe enough to undergo an operation, whether within a trial or not. This likely reflects the restrictions of the recruitment process. However, when asked to hypothesize about the scenario presented (which stated that the trial was for people who had severe PD), a majority of interviewees indicated that they would be more likely to agree to take part (or agree with their relative with PD taking part) if their PD were at a more advanced stage.

> It would be something we'd talk about, I think, and if I was bad enough, if my condition was chronically bad, then probably we'd go for it, depending on my

> condition at the time…. The severity would be the major concern. If I'm desperate for a solution to the problem… [PWP, Interview 12]

It is important to establish that interviewees were not simply talking about severity as a minimum criterion for entering a trial, in much the same way as the trial doctors would assess their eligibility for trial entry. From some interviewees' responses, it does seem that disease severity was sufficient reason, as well as simply being a necessary criterion, for agreeing to trial entry, seemingly whether or not there was a sham surgery group.

> Yes, because of the tremor and the pain that goes along with that, I think, I would be desperate to see if I could stop the tremor whatever way possible. [PWP, Interview 9]

Most people thought that someone with PD would be more likely to take part the worse their condition was. Furthermore, some people's responses indicate that agreement to trial participation may actually become a "forced choice" when disease severity affects quality of life to an unacceptable degree.

> If you didn't like going to the dentist but had a really bad toothache, you'd do whatever it takes to make you feel better. I'd think it would be the same. [PWP, Interview 3]

However, in contrast to the majority, one interviewee stated that she would be less likely to take part the more severe her Parkinson's was, because she would have enough difficulty coping with the regular tasks of life without adding the inconveniences of a research trial. As a consequence, she stated:

> I think I was more prepared to be experimental when I had it first than I am now. Even though it's worse now than it was then. [PWP, Interview 10]

Severity cannot, therefore, be assumed to promote trial participation in all instances. Another participant stated that disease severity would not make any difference to her personally; she believed it was better to try and fight the disease as early on as possible, given the inevitability of its progress.

ALTRUISM AND ATTITUDE TO RESEARCH—People's attitude toward research in general was another potential influence on participation. One interviewee espoused particularly strong support for research in general. When asked if she had any reservations about the sham surgery group, she replied:

> No, because it is research and without research people wouldn't—I wouldn't—have got the treatment I'm getting now. So somebody had to take the risk somewhere along the line. But only if I was severe I would take the chance, yes. [PWP, Interview 6]

Although the appropriate disease severity was a necessary condition for participation, this interviewee's hypothetical decision to participate seemed largely due to a global positive regard for research and gratitude to others who had participated in research before her. Her narrative thus also appeared to provide an example of an altruistic approach to trial participation.

GENERAL ATTITUDES TO SURGERY AND THE MEDICAL ENVIRONMENT—Another related participation decision dimension was interviewees' perceptions of the risks of the hospital environment in general, the risks of surgery in general, and the likely risks of brain surgery in particular. Two people specifically said that they disliked the thought of an operation at all, with one of these interviewees particularly put off by the concept of the sham surgery group:

> I think at the moment with the situation I'm in, definitely no…the thought of having an operation anyway would horrify me, let alone a fifty-fifty chance of not even having any benefit from it. [PWP, Interview 3]

> I wouldn't like to go in for any operation…. No, not with drilling holes in heads and things like that. [PWP, Interview 4]

> One relative also said that he considered hospitals a risky place to be because of the risk of iatrogenic illness.

INDIVIDUAL DIFFERENCES IN ATTITUDE TO OPPORTUNITY AND RISK-TAKING—Two interviewees consciously attributed their hypothetical participation decision to their own personal tendencies toward or against risk-taking in general. One interviewee expressed his general positive attitude toward new opportunities:

> Well, I'm a great believer in trying things as long as the chances of it going wrong are not too high. You don't want to end up worse than you started…. I'd have to discuss it with the family, I think. My first reaction would be I'd be for it. [PWP, Interview 2]

In contrast, the interviewee who had stated she was less likely to take part the more severe her Parkinson's was, was clearly more risk-averse in nature and stated later on in her interview that she was not the sort of person who participated in trials:

> I had a chance of going into one [a research trial] once and I turned it down because I said I wasn't of the stuff that guinea pigs were made. [PWP, Interview 10]

Another interviewee clearly had a strong belief in availing oneself of any opportunity that arose. Throughout the interview she spoke with genuine emotion about the suffering of people she had encountered in the later stages of Parkinson's Disease. Her answers seemed strongly motivated by a desire to see such people's quality of life improved by any means possible. She thus prioritized the opportunity for benefit over the risk of harm.

> Life is precious. If you don't take the chance and see what happens if it doesn't work at least you've taken the chance and done it. [PWP, Interview 5]

Reasoning about Trial Group Preference

This aspect of the interview revealed information about potential patient equipoise or the lack of it.

FOCUS ON ACCESS TO POTENTIAL BENEFITS OF THE REAL PROCEDURE—Four interviewees clearly saw no benefit to being in the sham surgery group and thus their decision on group preference was easy. For example:

> Well, no point having a pretend one. If they're going to do anything, I might as well have the real thing…. What's the point of going through all that if you're not going to have the proper thing? [PWP, Interview 2]

One interviewee with PD noted the considerable burden of having to go through two operations rather than one if he were allocated to the sham group first (and if the real operation proved beneficial). It was clear that, for another interviewee, the placebo group's existence was off-putting and the desire to avoid this had to be weighed against the desire to access the real trial intervention:

> Well, initially I thought I don't know if I'd want to go ahead with it if I was in the pretend group, because I'm really volunteering because I want to get in the real

> thing and therefore I wouldn't be too happy just being in the pretend thing. [PWP, Interview 8]

In contrast, of the two interviewees who thought the sham surgery group was preferable, one said:

> Right now I'm interested in my welfare and if I were in the placebo group and something terrible happened with the real stuff, I would avoid that…and the fact that you can always go in later and do it again if it works well… [PWP, Interview 1]

This is an example of the sham group being chosen because it offers the ability to avoid the unknown risks of the real surgery, but the opportunity to obtain the benefits of the real surgery (if still only available through the trial), once proven.

INDECISION, EQUIPOISE, AND GENUINE INDIFFERENCE—In contrast with the relative ease with which some interviewees made their decision, others found it more difficult. Describing the decision as "difficult" or "tricky", some interviewees appeared to be engaged in an active cognitive process of weighing the various risks, inconveniences, and benefits of each trial group. This shows that, although a majority of interviewees did prefer the real treatment group, a number clearly did not discount the risks of the real group, nor consider the sham group to be without some perceived advantage. It is important to note, however, that the interviewees were weighing the choice between the real treatment and a sham surgery which is followed by a guaranteed offer of the real surgery if it proves successful. This is a different equipoise consideration to weighing the real surgery against sham in the absence of such an offer.

> This is very difficult because part of you thinks, well obviously you'd want to be in the group that is having the real op because you want to become better, but the fear of whether or not it would work or not, would you prefer to be in the group that didn't and then see what happened and then have the opportunity to have it done after? So it's really difficult to sort of make a decision. It's hard, isn't it? [PWP, Interview 7]

In contrast to most, one interviewee did not seem to be operating within the realms of concepts such as equipoise or self-interest at all, and refused to contemplate the issue of trial group preference, stating that she was happy to leave it entirely to fate. Her rationale for this appeared to be her belief in the importance of the research enterprise as a whole and the basic need for people to participate in trials.

DISEASE SEVERITY—Disease severity was also implicated in hypothetical trial group preference by three interviewees, as it was in the decision to take part or not in the trial.

> I'd want to be in the real group because if my symptoms were bad enough that I was prepared to have a brain operation then I'd want the real thing… [PWP, Interview 11]

AGE, DISEASE SEVERITY, AND DELAY—A few interviewees discussed the time span between having a sham operation and then receiving the real one if it proved successful. Perceptions of the importance of this time gap varied, possibly in relation to age, possibly in relation to disease severity, two factors which are themselves likely to be related. For one relative the gap did not seem overly long in relation to the benefits of the information that could be gleaned in the intervening period. This may have been because his wife's PD was not very far advanced and the couple were at the younger end of the age range of the

interviewees in the study. Risk avoidance was thus prioritized over speed of access to the real operation.

> I think if there was only a year difference I would want her in the placebo side of it. Because in the long life of Parkinson's that we're going to have to live with, a year may be not a very long time to wait to see if it works. [Relative, Interview 7]

In contrast, for another person the gap between the sham and real procedures was clearly viewed as a disadvantage. For him, this potential delay caused by languishing in the sham arm was far more significant.

> I'd want to be in the real group because if my symptoms were bad enough that I was prepared to have a brain operation then I'd want the real thing…. I wouldn't want to wait another eighteen months…. I'd reinforce that I wouldn't want to go through all the stresses when I was badly handicapped and have no chance of benefiting from it…and it depends on your age as well, and being in my late sixties another eighteen months will be a large part of what's left of my life. I would guess (laughter). [PWP, Interview 11]

In summary, age as well as disease severity (both of which are obviously correlated) may influence a person's perspective on waiting to get the real treatment after the sham one.

Reactions to Hypothetical Allocation to Sham Surgery Trial Group

NEGATIVE REACTIONS—A majority of people said they would feel some disappointment or upset about finding out they had been allocated to the sham surgery group. Some people expressed outright unhappiness:

> Based on my feelings about having the damn thing anyway, I'd be a bit annoyed I should think. I mean I suppose what's the point? Personally. [PWP, Interview 2]

Reasons that people gave for their disappointment were: having to go through the operative procedures again; having all the stress of sham surgery and no possibility of benefiting; the time wasted between the sham operation and the real operation; and the lack of purpose in being in the sham group (they did not acknowledge or value any possible placebo effect or the chance to avoid the potential risks of the real operation, even when asked). One person said:

> Well, it depends how unpleasant the operation was. If it was unpleasant you'd think: "God, I've got to go through that again now," and I don't think you'd be that pleased about it, would you? [PWP, Interview 3]

Three participants, however, were not upset about hypothetically being allocated to the sham surgery group (or having their relative allocated to the sham group). They gave the following reasons: avoiding the potential risks of the real operation; still having a chance to subsequently have the real operation; having a chance to see if the real operation worked before actually undergoing it; gaining potential benefit from the placebo effect; and making an important contribution to research by participating, regardless of trial group allocation.

RESPONSIBILITY FOR DECISION-MAKING—Some interviewees stated that they were personally responsible for making the decision to take part, having understood what the trial would involve and having made a free decision.

> Well, you've gone in for a trial and I've already agreed that I know there's a fifty-fifty chance and I already know that there's a sham there. Obviously you'd be disappointed but you'd have to expect a fifty-fifty either way you go…won't you, really? [PWP, Interview 9]

This appeared to temper some people's disappointment and assist with acceptance of hypothetical randomization to the sham group.

CONSIDERATION OF RESEARCHERS' MOTIVES AND GOALS—One particular interviewee commented upon researchers and doctors at a number of stages during the interview. When asked how she would feel if she had been allocated to a sham group, she responded:

> No, because of what I said before about wanting to…it's only helping me, I mean, you know, it's… the doctors might get rich and famous but I think ultimately it's for the benefit of the patient… [PWP, Interview 1]

In contrast, however, comments about researchers were not limited to just positive ones. Another interviewee voiced her reservations about the relationship between researcher and participant, and the status of the patient in a sham-controlled trial:

> But this is the only way they're going to be able to find out. So, sorry, patient but we need you…you take on the semblance of something in a petri dish, rather than a person. [PWP, Interview 10]

Attitudes to Sham Surgery

This theme concerns itself with the final key question in the interview of whether interviewees agreed or disagreed with the concept of sham surgery control groups.

AGREEMENT—A majority of interviewees (n=13) agreed with the existence of the sham surgery group as described in the interview, although in some cases agreement was subject to certain provisos and assumptions. Reasons given for agreeing with the trial design were: being supportive of research in general, and agreeing with the methodological rationale behind the trial design.

PRO-RESEARCH ATTITUDE—Some people agreed with the trial on general grounds that research of any kind was valuable and necessary in order for treatments to be discovered and refined for the future. One interviewee, for example, acknowledged self-interest in supporting trials and wanting an operation to be available for her when she needed it later in the progression of her disease. Another interviewee focused on the potential benefit of research to future generations of her own family.

AGREEING WITH THE METHODOLOGICAL REASONS FOR USING A PLACEBO GROUP—A number of interviewees accepted the rationale behind the design of the trial.

> Yeah, the basic theory behind it I agree with and, you know, I think it is a way of finding out whether the operations are going to work and whether they're worth doing or not. [PWP, Interview 7]

CONDITIONS OF AGREEMENT—Rather than accepting the trial design outright, however, some interviewees stipulated conditions of agreement. These provisos reflect some of the issues which are debated within the ethical literature on sham surgery.

Information and Understanding: A condition that one interviewee gave was that potential participants should be absolutely clear on all possible outcomes from the trial. This is a requirement of informed consent and is related to a participant's ability to make an autonomous decision.

Support: Another interviewee suggested that perhaps counseling should be available to aid with decision-making.

Methodological Provisos: Some interviewees agreed with the use of a sham surgery controls, but their decision was based upon the assumption that a sham design is actually the only or best way of getting accurate results.

> I don't disagree with it. Because as I said, they need to know what works and what don't work, don't they? And if this is their best method of trying to find out what works and what don't work, then um I'd have to go with it. [PWP, Interview 9]

Ambivalence: Some people still agreed in the end with the trial but had stronger reservations, going so far as to question the assumptions built into the trial design about needing a sham group and the actual strength of the placebo effect of surgery. The necessity of this particular methodology is of course debated in the ethical literature (e.g., Dekkers & Boer, 2001) as has been placebo effect size (Hróbjartsson & Gøtzsche, 2001).

> The inference is that the operation we're talking about now would, if it was beneficial, the benefits would be quite small, otherwise you don't need a placebo group. If it was a good operation and the results gave big improvements then I don't see why you'd need a placebo group in that case. [PWP, Interview 11]

Another participant's narrative was clearly ambivalent towards the sham design:

> Initially I disagreed with it really. I thought no that's not fair because they should just ask for volunteers to do this and also I wasn't convinced that the placebo effect did apply in these operations…that's how I felt initially and then I thought well maybe there is a point in that there are days when I feel really good and I think I'm on the same drugs as I was yesterday and I still feel better today and so there is an effect because some days you think they work and other days they don't work, so it's in your mind as well so…. So I think as long as it's made clear that there is this chance I think it's fair enough to go ahead with it. [PWP, Interview 8]

His concerns obviously remained, however, as he discussed whether there were alternative ways to design the trial so that those who did not want sham surgery could avoid it.

Disagreement

Those who disagreed with the idea of the sham surgery were in a minority (n=6). One main reason stated for disagreeing with the placebo control group was a belief that people would be disappointed or upset if they ended up in the sham surgery group. The second reason given was that it was unfair for people to be in the sham surgery group: first, because they would have to wait for the real surgery and, second, because the placebo surgery could not offer the same potential benefits.

> Relative: I don't believe in, not honestly, I don't honestly believe in the pretend group…I think it's upsetting for people.
>
> PWP: Yeah that's what put me off in the beginning when we were talking about it. [PWP and Relative, Interview 5]

Discussion

This research builds on previous empirical work by providing in-depth analysis of the reasoning behind hypothetical participation decisions, indications regarding the likely presence or absence of patient equipoise, and overall attitude to sham surgery among patients with PD and their relatives.

Attitudes to Sham Surgery

Overall, a small majority of interviewees were sympathetic to the concept of sham surgery. This appeared to be linked in part to a supportive attitude toward the research enterprise in general. This gives rise to a hypothesis that sham surgery as a specific method partially gains acceptance among some patients and relatives due to its status as research *per se*, rather than purely on its own specific merits. This does not mean that patients are not cognizant of the risks they face in a given research trial, nor did interviewees espouse absolute trust in researchers, but the finding may have a relationship to literature on the profound trust which patients place in the research enterprise (see, e.g., Kass et al., 1996; Dixon-Woods et al., 2007). Some participants' agreement with sham surgery, however, was conditional upon the proviso of its methodological necessity. Trust is involved again here since, unless a patient is an expert in clinical trial methodology, they can only trust that the methodology is necessary.

Disagreement with the concept of sham surgery was evident in a minority of accounts. Key concerns were: a sense of the unfairness of a sham operation, with its burdens but lack of direct benefit; the possible distress caused by allocation to sham; and the delay in receiving the real operation. This could be interpreted as interviewees judging the ratio of harm/risk to potential benefit of sham surgery as unacceptable.

Participation and Trial Group Preferences

In contrast to the small majority of somewhat favorable attitudes to sham surgery, a majority of interviewees stated that they would not personally want to receive (or have their relative receive) sham surgery, but would instead prefer to receive the real treatment. These interviewees' decisions were apparently driven by a desire to access the potential benefits of a new intervention. This suggests a lack of hypothetical patient equipoise, this being defined as a situation in which a patient would rationally accept randomization (Lilford, 2001). Participants who had disagreed with sham surgery altogether discussed the burdens of having an operation with no direct benefit, and of having to undergo an additional operation after some delay. Conversely, a minority saw benefits to the sham group such as: the placebo effect, the chance to avoid the risks of the real treatment, and the advantage of receiving the real treatment after it had been tested the first time round. Only one interviewee could not decide between the hypothetical trial groups and hence appeared to be in genuine equipoise. While theoretical and clinical equipoise are the concepts usually used in determining whether randomization is in a patient's best interests, Veatch (2002) argues that clinicians are only morally justified in entering a patient into a trial if the *patient* has no preference for a particular treatment option. While the precise role of patient equipoise may be debated, the data presented here indicate the potential for problems if one wishes only to recruit patients in equipoise into a sham-controlled PD surgical trial under the conditions described in this research. The data from this study also support Creel et al.'s (2005) suggestion that patients may move further from hypothetical equipoise the more serious their condition, as they seek the potential benefit which is only available from the real operation.

Autonomy

Where an experimental procedure is only available within a trial, it may become an inducement to participate even in the absence of patient equipoise (Edwards, 2006). While it is reassuring that some interviewees did not appear to consider the sham group of concern, and a minority even preferred allocation to such a group, it is worrying that a different minority of interviewees did disagree with the idea of sham surgery and/or were unwilling to undergo it but nonetheless stated that they would take part in such a trial in order to access the experimental treatment. The key variable appearing to influence participation decisions

in these cases was, in fact, not attitude to sham surgery but disease severity and the desperation it might create when no established, effective treatment exists. Agreeing to participate in a sham-controlled surgical trial should not therefore automatically be taken to mean that a participant finds the use of a sham group ethically acceptable. These findings support Cohen et al.'s (2010) hypothesis that agreement to participation may relate to desperation and lack of treatment options. It also tallies with other empirical research into other conditions which links desperation to decisions to take part in any research opportunity offered, because the research trial is seen by the patient as their only hope for improvement (Kass et al., 1996; Karlawish et al., 2001; Scanlan & Kerridge, 2009). This supports the potential transferability of the research findings to other illness conditions.

There are implications in this data for the autonomy of research participation decisions. Valid consent requires a decision to be informed, competent and voluntary in the sense that another person has not unduly influenced the decision in any way. Olsaretti (1998), however, believes that the current definition of voluntariness should in fact be correctly referred to as freedom. She defines a voluntary decision as one in which more than one of the available options in a situation is perceived as acceptable to the person deciding, in terms of their well-being. If participation in a sham-controlled trial is the only option perceived as acceptable by a desperate person who nonetheless disapproves of the sham group, their decision to participate may not be voluntary in the sense meant by Olsaretti, and hence may not be maximally autonomous.

Some interviewees, however, specifically stated that they were personally responsible for any decision to take part and hence for potentially receiving their nonpreferred trial treatment; in other words, they felt their decision to participate was made freely. This sense of ownership of their decision mitigated their disappointment at being hypothetically allocated to the sham surgery group. This data clashes with a conclusion that participation decisions may be a "forced choice," but this conflict may be reconciled by the use of Olsaretti's definition of voluntariness, in which the option to participate may be the only acceptable option. Hence, a *nonvoluntary* choice may be made, but it is still *freely* chosen by the deciding individual in the sense that no other person unduly influenced the decision. Such a decision has implications for autonomous decision-making even if it does not have implications for the elements of informed consent as they stand (Swift, 2011).

A particular concern with certain sham surgery trials is that patients are being invited to undergo higher than minimal risks in the sham group without any chance for direct benefit. With regard to autonomy, the concern therefore is that patients whose decision to participate is less than maximally autonomous may be vulnerable to exploitation—exploitation being defined as a situation in which an individual receives an unfair share of the risks and benefits of a transaction (Wertheimer, 1996). This was precisely the complaint of the minority of participants who disagreed with the concept of sham surgery: that it was unfair.

In summary, while opinion was divided among interviewees on the ethical acceptability of sham surgery, the data reported here indicate that the voluntariness (in the sense meant by Olsaretti) of patients' research participation decisions may not necessarily be relied upon where the twin factors of (a) lack of standard or effective treatment and (b) restriction of an experimental treatment to trial pertain. Under these conditions, some patients may choose to participate in a sham-controlled trial despite disagreeing with the sham surgery in question or despite a lack of patient equipoise. The possibility of upset and disappointment from sham group allocation also provides cause for concern regarding the potential emotional well-being and psychological best interests of some patients who undergo sham surgery, although data indicate that distress may be mitigated by a supportive attitude toward research and the belief that one made a free decision to participate.

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Best Practices and educational implications

From the point of view of autonomous decision-making about a trial with an ethically contentious method, the data reported here suggest that researchers who wish to enroll patients into trials involving a sham group may wish to establish not only whether the patient fulfills the criteria for informed consent but also whether the patient approves of the concept of sham surgery and, additionally, whether they feel they have any acceptable alternative other than to say yes to participation. Although it is not presently obligatory to ask, the answers to these questions may give a better determination of the autonomous nature of a patient's decision to participate than mere reliance on informed consent procedures. Since the effect of desperation on autonomy may not be amenable to change at the recruitment stage of such a trial, however, it may be especially important that the risks to which researchers are asking participants to expose themselves in sham-controlled trials are carefully assessed both at the trial design stage and at the ethics committee stage, in order to protect the best interests of those participants who feel there is little real choice but to participate in a trial once it is offered, despite the risks or their own lack of equipoise.

In addition, when patients' support for research is based upon provisos such as the necessity for sham surgery in the face of lack of methodological alternatives to it, researchers should ensure that the assumptions patients hold are correct lest patient trust be undermined.

Research Agenda

Methodological Issues

There are a number of methodological limitations to this small—but hopefully nonetheless interesting—empirical study which should be considered, both in relation to this study's findings and with regard to future empirical research on the ethics of sham surgery control groups.

1. Hypothetical Vignettes—First, interviewees' responses are based on the hypothetical vignette given. The study-specific nature of the findings reported here is therefore recognized. While attempting to remain faithful to the key aspects of the PD sham trials conducted, the vignette was relatively simple. It is acknowledged, therefore, that more detailed description of risks and other factors such as hospitalization, follow-up appointments, and a specified time delay between sham and real surgery might impact upon willingness to participate in a sham surgical trial. The vignette may also have differed in certain respects to any individual actual trial, in the same way that real sham-controlled trials have differed from one another.

The use of hypothetical vignettes does, however, allow for the standard presentation of information and the ability to avoid some social desirability responses (Gould, 1996). Their simplicity also allows participants the flexibility to define the vignette situation in their own terms (Barter & Renold, 1999). Future research utilizing a slightly different hypothetical vignette would provide interesting data for comparison. Research into the views, reasoning, and decision-making processes of patients who have been invited into a real sham-controlled trial would also be of great interest.

2. Study Participants—This was a small, exploratory study, and the author was prohibited from interviewing patients falling into the exclusion criteria. A further limitation of this study sample is also that interviewees were a self-selected group as defined by their decision to respond to the invitation to take part in the study. No data is available about people who declined to take part since, as a nonclinical researcher, REC rules did not allow the author access to this data.

Although qualitative studies often do not aim at generalization to a larger population, it would be of interest to know if results could be replicated in a larger study or with different subject groups. For example, not all interviewees in this study were at a disease stage at which they would personally consider surgery for their condition. A range of disease severity among interviewees did allow for exploration of potential differences in attitude to receiving sham surgery caused by varying disease severity; for example, the finding that one interviewee who had the disease more severely wished to gain quicker access to the real surgery, in comparison to an interviewee whose wife had the condition less severely. Nevertheless, it would be informative to see if results would be replicated in a study conducted with individuals whose condition were at a stage at which they would consider surgery or individuals who have even undergone brain surgery.

3. Single versus Joint Interviews—There are methodological issues regarding the conduct of both single and joint interviews, and of analyzing the data from both types of interview together. Arksey (1996) provides a useful discussion of such issues. Two key concerns regarding interviewing individuals together in a joint interview are that one respondent may dominate the other or that friction or disagreement may be provoked between the interviewees. This was reflected upon in post-interview field notes and during the analysis stage. Relatives' preferences were often closely aligned with the relevant patients' opinions (patients having been asked each question first), but this could have been coincidental, could reflect couples sharing similar social attitudes, or could show a supportive or respectful attitude towards the ill person's viewpoint. Mild disagreements did manifest between patients and relatives in some interviews but these were managed good-naturedly and were interpreted as showing that these joint interviewees at least were not overshadowed by one another. The relatively nonpersonal and hypothetical nature of the interview topic may have helped to avoid any personal tensions. Advantages of joint interviews, meanwhile, include the following: (i) the opportunity for generating additional richness of data through shared and dissimilar understandings and attitudes; (ii) provision of more complete data if one interviewee can help with the memory lapses or errors of the other; (iii) the social "balance of power" may be shifted from interviewer to interviewees, encouraging them to speak more assertively; and (iv) in the case of interviews with people who have disabling conditions, co-interviewees may be able to assist with physical or cognitive issues that arise.

A concern regarding the amalgamation of the single interview data and the joint interview data at the *analysis* stage, however, is that the data might be considered qualitatively different depending on whether it is a sole or a shared reconstruction of events. Furthermore, the presence of an additional interviewee may change or limit what another interviewee says. These potential qualitative differences are acknowledged, but the key point to consider is how far these issues might affect the analysis presented here.

First, the possibility of "joint construction" of opinions on sham surgery was already introduced in one-to-one interviews in any case by the decision to send interview guides to participants in advance, during which time they may have discussed the topic with others. This was in order to encourage what was seen as the greater advantage overall of giving participants a chance to familiarize themselves with, and reflect upon, the concept of sham surgery, thus possibly providing more nuanced or richer responses to questions during the interview. Second, joint interviewees were both asked each interview question in turn, such that separate answers were obtained, rather than simply a single "joint" reply. On the issue of response bias, "contamination" caused by another interviewee's presence may be more likely the more sensitive or personal the interview topic (see, e.g., Taylor & de Vocht, 2011), whereas the topic of this research was, as stated above, of a hypothetical and less personal nature and hence potentially less methodologically problematic in this regard.

Bearing in mind the above considerations, it was judged appropriate to analyze and report the data from single and joint interviews together. Although no statistical comparisons can be carried out upon such a small sample of interviews, a retrospective separate examination of the single and joint interview data (made simple by using the abstracted data from the "charting" stage of the framework analysis method) revealed no major differences with regard to the key interview questions. Future research, however, may wish to consider the methodological complexities of using both single and joint interview data.

On a related matter, no particular differences in opinion or reasoning were noted between male and female interviewees.

4. Bias—Bias caused by interviewer personal characteristics or interview style can never be ruled out, but such bias may be less likely in a semi-structured interview, as was used, than an in-depth and more variable interview. Two interviewers were also used, in an attempt to avoid potential bias being introduced throughout by one particular interviewer. With regard to this specific study, a social response bias toward sham surgery among interviewees cannot be ruled out by the fact that interviewees may have been aware that they were themselves being interviewed by researchers, albeit not researchers conducting clinical trials. Since some patients and relatives were interviewed together, however, this was thought to offer a more favorable "power balance" between interviewer and interviewees and thus reduce the likelihood of such a bias.

Theoretical Issues

Moving on from methodological considerations, there is much scope for further exploration, of a theoretical or an empirical nature, into the nature of the relationships between restricted experimental treatments and voluntariness of research participation, serious physical illness, desperation, and patient equipoise. In particular, since "Discussion" above generates a hypothesis that disease severity and lack of treatment options may have an effect on autonomous decision-making through a concept of voluntariness which is not incorporated within the traditional definition of informed consent, this concept in particular might be explored further to provide a richer account of the nature of autonomous decision-making by patients invited into research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author's Biographical Sketch

Teresa Swift has a PhD in medical research ethics, having investigated the ethical implications of sham surgery in Parkinson's Disease for her doctoral thesis. Prior to this she worked as a healthcare researcher for five years, conducting qualitative research into chronic illness in fields such as rheumatology, rehabilitation medicine, and gynecology.

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Table 1

Participant Demographics

Participant	Sex		Age Range	Disease Duration (yrs)
Patients	Male	7	54-72 (median: 67)	2.5-18 (median: 14)
	Female	5	44-64 (median: 63)	3-20 (median: 10)
Relatives	Male	2	47-60 (median: 53.5)	–
	Female	6	34-71 (median: 58)	–
	TOTAL	**20**		

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Table 2

Interview and Relationship Types.

	Patients		Relatives		
Joint interviews	Male	4	Wife/partner	4	
	Female	3	Husband/partner	2	
			Daughter	2	
One-to-one interviews	Male	2	–		
	Female	3	–		
Total		12		8	20

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