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Are Therapeutic Motivation and Having One's Own Doctor as Researcher Sources of Therapeutic Misconception?

Scott Y H Kim, MD, PhD[a,b], **Raymond De Vries, PhD**[b,c], **Sonali Parnami, MPH**[b], **Renee Wilson, MA**[d], **H Myra Kim, ScD**[e], **Samuel Frank, MD**[f], **Robert G Holloway, MD, MPH**[g,h], and **Karl Kieburtz, MD, MPH**[d,g,i]

[a]Department of Bioethics, National Institutes of Health, Bethesda, MD, USA

[b]Center for Bioethics and Social Sciences in Medicine, University of Michigan, Ann Arbor, MI, USA

[c]Department of Medical Education, University of Michigan, Ann Arbor, MI, USA

[d]Center for Human Experimental Therapeutics, University of Rochester, Rochester, NY, USA

[e]Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA

[f]Department of Neurology, Boston University, Boston, MA, USA

[g]Department of Neurology, University of Rochester, Rochester, NY, USA

[h]Department of Community and Preventive Medicine, University of Rochester, Rochester, NY, USA

[i]Department of Environmental Medicine, University of Rochester, Rochester, NY, USA

Abstract

Background—Desire for improvement in one's illness and having one's own doctor functioning as a researcher are thought to promote therapeutic misconception (TM), a phenomenon in which research subjects are said to conflate research with treatment.

Purpose—To examine whether subjects' therapeutic motivation and own doctor functioning as researcher are associated with TM.

Methods—We interviewed 90 persons with advanced Parkinson Disease (PD) enrolled or intending to enroll in sham surgery controlled neurosurgical trials, using qualitative interviews. Subjects were compared by motivation (primarily therapeutic versus primarily altruistic or dually motivated by altruistic and therapeutic motivation) and by doctor status (own doctor as site investigator versus not) on the following: understanding of purpose of study; understanding of

Corresponding author: Scott Kim, MD, PhD, Department of Bioethics, National Institutes of Health, 10 Center Drive, 1C118, Bethesda, MD, 20892-1156, USA. T 301.435.8706. F 301.496.0760. scott.kim@nih.gov.

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CONFLICT OF INTEREST STATEMENT

The Author(s) declare that there is no conflict of interest.

research procedures; perception of chance of direct benefit; and recollection and perceptions concerning the risks.

Results—60% had primarily therapeutic motivation and 44% had their own doctor as the site investigator, but neither were generally associated with increased TM responses. Overall level of understanding of purpose and procedures of research were high. Subjects responded with generally high estimates of probability of direct benefit but their rationales were personal and complex. The therapeutic-motivation group was more sensitive to risks. Five (5.6%) subjects provided incorrect answers to the question about purpose of research and yet showed excellent understanding of research procedures.

Conclusions—In persons with PD involved in sham surgery clinical trials, being primarily motivated by desire for direct benefit to one's illness or having one's own doctor as the site investigator were not associated with greater TM responses.

INTRODUCTION

One of the most prominent constructs used to examine the adequacy of informed consent is the concept of therapeutic misconception (TM), a phenomenon in which research subjects are said to conflate research with treatment.[1] This may manifest in subjects' misunderstanding the purpose of research, failing to understand that research procedures are not individualized to them, and harboring false beliefs about the risks and benefits of participation. The prevalence of TM is reported to be high,[2–5] and some authors refer to the "ubiquity" of TM.[6] In terms of causes of TM, there are two factors that are often mentioned as likely sources: the research subject's motivation for direct personal benefit[1, 4] and the involvement of the subject's own physician as the researcher.[1, 7]

Despite some claims of high prevalence of TM-related phenomena that are based on analysis of very few closed-ended questions,[4, 5, 8] TM does not have a widely accepted definition and lacks an accepted operationalization for research.[9] Our approach has been to use a mixed methods framework to examine TM-related phenomena by attempting to understand how research subjects make their research participation decisions.[10–12] Our subjects are persons with advanced Parkinson's disease involved in sham surgery trials. This is a particularly good setting to study TM because of the seriousness of the illness, the lack of disease-altering or curing treatments for PD, and the nature of the intervention (neurosurgery) that is very rarely an experimental procedure—all of these factors should in theory promote a therapeutic mindset in the subjects.

We report here the relationship between, on the one hand, the two potential sources of TM (subject's motivation for direct personal benefit and the involvement of subject's own physician as the researcher) and, on the other, the most often discussed loci of TM-related phenomena: the subjects' understanding of the purpose of research; their understanding of the extent to which the procedures would be individualized to their needs; their beliefs and expectations concerning the chance of direct benefit; and their recollection and perceptions concerning the risks involved in the research.

METHODS

Participants

Participants were 90 individuals from three sham surgery controlled intervention trials for PD. The participants were asked by the parent study staff if they were willing to be contacted by our study team for this interview study. The subjects who agreed to be contacted were then recruited and interviewed by phone. In the 'GAD study,' participants were individuals considering enrollment in a study evaluating glutamic acid decarboxylase gene transfer in subjects with advanced Parkinson's Disease, sponsored by Neurologix, Inc. [13] Subjects were randomized at a 1:1 ratio to receive either injections of the study agent or sham surgery placebo, which involved partial thickness burr holes with injection of saline under the skin. The trial assessed 66 individuals for eligibility across seven sites. We recruited from 5 of the 7 sites and conducted interviews with 29 of 45 (64.4%) subjects evaluated for enrollment at those sites. Although our goal was to interview everyone prior to surgery, 5 subjects were interviewed after their surgery due to scheduling difficulties. Five additional subjects were found to be ineligible following screening and 1 subject ultimately declined participation after screening; however, their interviews were conducted at a time when they were actively considering participation in the trial. Thus, they are included in this report.

The subjects from the second (STEPS trial) and third trials (CERE-120 trial) were interviewed retrospectively. The STEPS trial tested human retinal pigmented epithelial cells which secrete dopamine.[14] Sham surgery involved partial thickness burr holes. The trial enrolled 71 subjects at 10 sites. We recruited from five sites, interviewing 55% (31/56) of enrollees at those sites. The CERE-120 trial tested the gene for neurotrophic factor neurturin.[15] Sham surgery involved partial thickness burr holes. We recruited from seven of the nine study sites, interviewing 70% (30/43) of enrollees. Due to sponsor requests, the time point of interviews differed between these latter two trials. CERE-120 enrollees were approached for interviews approximately one month after surgery. Twenty-six (86.7%) enrollee interviews took place between one to nine months after their surgery. STEPS enrollees were approached after the blind in the trial had been broken. Thus, for the STEPS trial, seven (22.6%) interviews occurred less than two years post-surgery, ten (32.3%) interviews between two to four years after surgery and 14 (45.2%) occurred greater than four years post-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.

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Measures

Conditional Probe Interview (CPI)—The CPI is a semi-structured qualitative interview guide designed to elicit how the subjects made their decisions about participation.[16] It places a strong emphasis on allowing the subject to follow his/her own narrative in eliciting a chronological description of how the subject came to make his/her decision. The

instructions emphasize that the interview is designed to be "qualitative and subject oriented, so the interview should remain flexible enough to allow the subject to speak openly and share information that is important to him/her." More detailed description of the CPI can be found elsewhere.[16] This paper focuses on those questions in the CPI that specifically address motivation, MD status, and TM-related phenomena.

Demographic and clinical background information—Basic demographic information (age, gender, education, race and ethnicity, marital status, employment status) and information on the subject's PD status were collected (number of years since diagnosis).

Analysis

After all transcriptions were checked for accuracy, two research assistants read through the transcripts and developed a provisional coding scheme by adapting the coding framework used in a previous study.[16] These codes were further refined in meetings involving two of the investigators (SK and RDV). The two assistants then independently coded each transcript using the coding scheme. Any coding discrepancies were discussed until a consensus was reached; if the two coders could not reach a consensus, the discrepancies were brought to a weekly meeting with the two investigators and resolved by discussion. Through this iterative process the team ensured the coding scheme was open to change and refinement and allowed the team to capture new and unanticipated themes. To prevent drift in coding, 10% of the transcripts were also coded independently by two investigators (SK and RDV).

The analysis was then organized around responses to the following question about motivation: "What is your main reason for participating in the [study name]?" (hereafter referred to as the motivation question) and a question about whether one's own neurologist was also the site investigator: "Is your regular doctor (the person who treated you before the study) also the [site investigator]?" (doctor status question). We divided the subjects into those who stated only direct personal benefit motivation versus those who stated only altruistic motivation or both personal benefit and altruistic motivations. This was done because having an altruistic motivation (even if in addition to a therapeutic motivation) suggests that the subject understands that at least one purpose of research is to benefit others and thus persons expressing such a motivation (even if they also express a therapeutic motivation) may be distinct from those who mention only therapeutic motivation.

We examined the differences in the distribution of various measures by motivation and by doctor status using cross tabulations with variables of primary interest (e.g., understanding purpose of study, study design, etc.) using Fisher's exact tests.

RESULTS

The subjects' motivations for participation in their clinical trials are shown in Table 1. Sixty percent responded only with personal benefit as their motivation for participation; the remainder expressed altruistic or dual motivation. Almost half (44.3%) of subjects reported that their regular neurologist was also the site investigator. Among subjects with own doctor as site investigator, half (51%) mentioned only direct personal benefit as their motivation,

compared with 68% of those with site investigators who were not their own doctors (Fisher's exact test, p=0.19). The subjects' characteristics according to their motivation and whether their own doctor (own doctor versus other) was the site investigator revealed no significant differences (Table 2).

Understanding of Purpose of Research

Five subjects (9.3%) in the direct personal benefit motivation group stated that the clinical trial is primarily intended to help the study participants, whereas none of the altruism/dual motivation group gave that response; none of these 5 subjects were from the group with their own doctors as site investigators. (We separately examined the understanding of research procedures and design in these five subjects; see below). Also, although we asked the subjects to name the "primary" purpose, some subjects resisted expressing a priority and said that the purpose was "both" to help future patients and to help the participants (or to increase knowledge). (Table 3)

Understanding of Research Procedures and Design

Overall, large majorities correctly answered questions regarding method of arm assignment, randomization probabilities, purpose of sham surgery arm, and the difference in procedures between the two arms (Table 4).

There were no significant differences by motivation or by doctor status. Of note, when asked about the purpose of the sham surgery arm, 68% (36/53) of subjects with only direct personal benefit motivation versus 54% (19/35) of altruism/dual motivation subjects specifically mentioned the need to control for the placebo effect, although the difference was not significant (p=0.08).

We examined whether the 5 subjects (from Table 3) who incorrectly said that the purpose of the clinical trial is primarily to benefit the participants also lacked understanding of study procedures. Despite their incorrect answer to the purpose question, all five subjects correctly stated the purpose of sham arm (4 specifically mentioning the placebo effect) and described the differences between two arms accurately. Only one person gave an incorrect probability of placebo assignment ("I think it was 1 in 8…") and one subject was "unsure" of method of arm assignment. Thus, 18 of 20 understanding questions (5 subjects x 4 questions) were answered correctly.

Perception of and Attitudes toward Potential Benefits & Risks

In regard to perception of likelihood of personal benefits, subjects generally gave an optimistic answer with fewer than a quarter of the subjects saying there was very low or modest chance of benefit, with no significant difference by motivation or by doctor status (Table 5).

The subjects' statements regarding likelihood of direct personal benefit were probed with follow up questions (Table 5). When asked about the basis for the belief concerning the chance of benefit, a variety of answers were given. The most common response referred to information connected to the phase 1 study (whether disclosed by the study or found on their

own from other sources). When asked if their belief regarding chance for direct personal benefit was based on something that was disclosed to them, most subjects replied in the negative. However, greater proportion of direct personal benefit motivation subjects than altruism/dual motivation subjects said it was [25% (13/53) vs. 6% (2/34), p=0.04], while the doctor status variable was not associated with the response.

When the subjects were asked about what the researchers or the informed consent form stated regarding chance of benefit, persons in the direct personal motivation group were more likely to say that researchers were negative about likelihood of direct benefit (16% vs 7% in the altruism/dual motivation group) but also that researchers were positive about direct benefit (21% vs 3% in the altruism/dual motivation group), whereas persons in the altruism/dual motivation group were more likely to say that researchers did not give specific or general indication regarding direct personal benefit (79% vs 52% in the direct personal benefit group). These results however were not statistically significant (Fisher's exact test, p=0.08). (Table 5)

In terms of risks, majority of the subjects (approximately 58% of the entire group) recalled risks associated with both the surgery and the experimental treatment (i.e., gene insertion or cell transplant), and this did not vary significantly by motivation or doctor status. (Table 6)

But a sizable minority (37%) recalled only risks of surgery or only risks of the experimental treatment. In terms of perception of probability of harm, a large majority (83%) of subjects responded that there was no, very low, or modest chance of experiencing adverse events. If subjects are compared by no/very low chance of risk versus all other responses, it appears that a higher proportion of the altruism/dual motivation group perceived low probability of risk than the direct personal benefit group (82% vs. 60% responding no/very low chance, p=0.03) and a higher proportion of the own doctor group perceived low probability of risk (81% vs. 60%, p=0.06). (Table 6)

DISCUSSION

Research participants' motivation for direct personal benefit [1, 4] and the involvement of their own doctors as researchers are perhaps the two most discussed potential sources of the therapeutic misconception.[1, 7] In our study, whether one had primarily a personal benefit motivation versus an altruistic or dual motivation was not associated with TM related phenomena. The two groups' understanding of purpose of research were similar. Although 5 (9.3%) in the personal benefit group incorrectly stated that the study was primarily intended to help those participating, those five subjects' specific understanding of arm assignment, randomization probability, rationale for sham arm, and difference in procedures between two arms was excellent, with only one instance of an incorrect answer and one "not sure" answer (out of 20 opportunities, i.e., 5 subjects x 4 questions). The direct personal benefit group and the altruism/dual motivation group showed no differences in understanding of various research design elements, in perception of direct benefit, and in recollection of research risks. Both groups were also quite optimistic in their replies to likelihood of personal benefit but the overwhelming majority in both groups said this was not based on what they were told by the researchers or the informed consent form; instead, the

participants cited as bases for their views of potential benefits a variety of personal interpretations and reasons.

The altruism/dual motivation group was *more* likely to perceive no or very low chance of risk (82% vs. 60% in direct personal benefit group). Thus, being motivated solely by desire for therapeutic benefit does not seem to lower or dampen perception of risk. In fact, it may be that therapeutic motivation as part of an overall regard for one's welfare may, rather than blinding one to the dangers of research (out of desperation), make someone more likely to pay attention to the risks of research as a matter of guarding or promoting one's own welfare.

What was the effect of having one's own doctor as the site investigator? One might expect persons whose own doctors were also the site investigators to have more of a therapeutic motivation, since they would have been more likely to see the research participation as receiving treatment from their own doctor. This was not the case. Instead, although the difference (51% of own doctor group had primarily therapeutic motivation versus 68% of those whose site PI was not their own doctor) was not statistically significant, the direction of the effect was opposite of expected. None of the 5 subjects who stated that the research was primarily intended to help the subjects of the study were in the own doctor group.

Further, the doctor status variable was not associated with differences in understanding of procedures or in perceptions and expectations of benefits and recollection of risks. The own doctor group had a higher proportion (81% vs. 60%) of subjects who said there was no or very low chance of adverse events.

These results regarding the doctor status are generally not consistent with the traditional TM interpretation which says that having one's own doctor as the site investigator will blur the line between research and treatment, leading to TM. Instead, it appears that those who do *not* have their own doctor as the site investigator (i.e., those who seek out research opportunities of their own initiative) are more likely to be concerned about potential direct benefit from research (and perhaps more concerned about risks as well, as a matter of an overall concern for their own welfare). In contrast, when patients are recruited by their own doctors—patients who may not have been actively "looking for research"—there may be a greater prevalence of altruistic motivation (although in this small sample study, the difference was not statistically significant). They may also be less concerned about risks, perhaps, we speculate, due to a greater trust in the researcher who is their own doctor.

We highlight three ethical implications of our findings. First, our results reinforce the need to distinguish between motivation and understanding in the ethical assessment of informed consent. Consistent with previous studies, [4, 16, 17] we saw that research participants understand the purpose of research and its various elements regardless of their motivation for participation. As others have noted, it is important not to assume that being motivated by a desire for benefit implies a faulty understanding of research [17, 18]—just as one can rationally buy a lottery ticket desiring to win, all the while understanding that a lottery's purpose is not to enrich the buyer of tickets, but rather to raise funds.

Second, the traditional TM framework makes empirical assumptions that may not be warranted. For example, it focuses on the potential that therapeutic motivation will blind subjects' understanding of research purpose, design, benefits, and risks. But this ignores the self-protective function of self-interest which may in fact enhance understanding (for example, understanding the scientific rationale for the sham design) or *heighten* sensitivity to risks.

In fact, based on our results, some may even ask if it is those with altruistic motivation who need special protections, if their motivation leads to decreased sensitivity to risks. Our sense from the data is that there is not a need for special protections. Both the personal benefit group and the dual/altruism group had good understanding of the purpose and design of their clinical trials, and the two groups did not differ on their recollection of research risks. It is also arguable as to which group is "more accurate" regarding their perception of likelihood of adverse events. That is, "very low" chance and "modest" chance could imply similar numerical probabilities for different people and we do not have an objectively "correct" answer to the perception of risk question. However, the potential divergence on perception of risks based on motivation for research participation does suggest that in enrolling subjects into clinical research, we should not assume altruistically motivated subjects are immune to potential misperceptions. Perhaps learning of a subject's altruism should alert the person obtaining informed consent to especially focus on the risks and burdens of participation.

Third, another unexpected finding of this study raises questions about how we assess subjects' understanding of purpose of research—the jumping off point of all discussions about the therapeutic misconception.[9] Our study revealed unexpected complexity on this issue. Even when asked specifically "Is the primary goal to benefit the subjects participating in the study, or future PD patients?" some insisted on endorsing *both* purposes—the correctness of which is unsettled even among experts in research ethics.[9] Curiously, the five people who clearly stated the wrong answer showed nearly perfect understanding of all of the dimensions of research design having to do with lack of individualized treatment in research; this casts considerable doubt on whether we should interpret their "incorrect" responses as an indication that they truly believe that research is being conducted primarily as a form of treatment for them (as would be interpreted by standard TM view).

This study has several limitations. First, the sample size was quite modest, and for the qualitative questions, we were able to conduct only post-hoc statistical tests. However, a highly powered comparison of groups (which generally requires large samples) within sham surgery trials in PD is quite unlikely given the usual small sample sizes of such studies, and our results which combined several such studies may represent the limit of what is feasible. Second, qualitative research involves interpretive judgments in development of coding schemes and in the coding itself. Third, sham surgery trials in PD are a highly specialized type of research and any generalizations must be made with caution. Finally, in combining subject data from 3 different clinical trials, we interviewed subjects (due to sponsor requests) at various time points from the initial point of informed consent for their trials, with long lags in some cases.

In conclusion, we found that therapeutic motivation for entering sham surgery trials is very common and having one's own doctor as the researcher is common. These factors did not specially increase the TM-related phenomena and overall understanding of the purpose of research and of the research procedures was high. Although most subjects gave overly optimistic responses about potential benefits, their explanations present a complicated picture, as has been shown in other studies.[5, 17] We also saw an alternative role that therapeutic motivation may play: rather than leading people to false understandings and inaccurate assessment of risks and benefits, therapeutic motivation may indicate a "self-interested" decision-maker who is *more* rather than less likely to pay attention to factors pertaining to their welfare and rights. Finally, our results show that eliciting subjects' understanding of purpose of research is more complicated than is commonly assumed by methods that use one or two closed ended questions to assess it. In future research, such assessments may need specific validation to ensure that intended phenomena are being measured.

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Table 1

Motivation for participation (N = 90)

Response	N (%)	Sample quote
Direct personal benefit	54 (60.0)	"My biggest motivation? I guess my biggest motivation is I would like to get better." (S7)
Altruistic motivation	7 (7.8)	"No, I just . . . . I just felt I should do something to help the next guy down the road." (S19)
Dual motivation (both direct personal benefit and altruistic motivation)	28 (31.1)	"Well, an improvement in my condition….And, you know, to help further the research in Parkinson's." (S3)
Other[a]	1 (1.1)	Subject stressed entering study mainly because her husband wanted her to.

[a]This subject was not included in subsequent analyses by motivation.

Table 2

Comparison of subject characteristics by motivation and by doctor status.

	Motivation			Doctor Status		
Responses	**Direct personal benefit N = 54**	**Altruism/dual N = 35**	**P Value[b]**	**Own doctor N = 39**	**Other N = 49**	**P Value[b]**
Age (years; mean (SD))	59.9 (7.4)	58.9 (7.4)	.54	60.6 (6.4)	58.6 (8.0)	.21
Female (N (%))	14 (25.9)	11 (31.4)	.63	9 (23.1)	15 (30.6)	.48
Married (N (%))	39 (72.2)	26 (74.3)	1.0	32 (82.1)	32 (65.3)	.10
Race (N (%))			.64			.69
White	53 (98.1)	34 (97.1)		38 (97.4)	48 (98.0)	
Black	0 (0)	1 (2.9)		1 (2.6)	0 (0)	
Asian	1 (1.9)	0 (0)		0 (0)	1 (2.0)	
Education (N (%))			.70			.67
High school or less	12 (22.3)	10 (28.6)		9 (23.1)	13 (26.5)	
Some college	8 (14.8)	7 (20.0)		8 (20.5)	7 (14.3)	
College degree	25 (46.3)	12 (34.3)		14 (35.9)	22 (44.9)	
Post college	9 (16.7)	6 (17.1)		8 (20.5)	7 (14.3)	
Years since PD diagnosis (mean/SD)	12.3 (4.4)	10.5 (4.6)	.07	11.7 (5.0)	11.8 (4.3)	.92

[a] Two subjects were missing doctor status data and were not included in analyses.

[b] Two-group t-test for continuous variables and Fisher's exact test for categorical variables. Abbreviations: SD: standard deviation; PD: Parkinson's Disease

Table 3

Comparison of subjects' understanding of purpose of research by motivation and doctor status.

	Motivation		Doctor Status	
Responses (N (%))	**Direct personal benefit N= 54**	**Altruism/dual N= 35**	**Own doctor N= 39**	**Other N= 49**
Is the primary goal to benefit the subjects participating in the study, or future PD patients?[a]				
1. Primarily intended to help subjects participating in study	5 (9.3)	0 (0)	0 (0)	5 (10.2)
2. Primarily intended to help future PD patients	28 (51.9)	20 (57.1)	25 (64.1)	24 (49.0)
3. Primarily intended to advance science/gain knowledge	6 (11.1)	1 (2.9)	3 (7.7)	3 (6.1)
4. Primarily intended to benefit the sponsor	1 (1.9)	0 (0)	0 (0)	1 (2.0)
Both 1 and 2	10 (18.5)	12 (34.3)	9 (23.1)	12 (24.5)
Both 2 and 3	2 (3.7)	2 (5.7)	1 (2.6)	3 (6.1)
Other	2 (3.7)	0 (0)	1 (2.6)	1 (2.0)

[a] Fisher's exact test (primarily intended to help subjects vs. all other responses): p=0.14 for direct personal benefit vs. altruism/dual; p=0.05 for own doctor vs. other.

Table 4

Comparison of subjects' understanding of research procedures and design, by motivation and doctor status.

	Motivation		Doctor Status	
Responses (N (%))	**Direct personal benefit N= 54[a]**	**Altruism/dual N= 35[a]**	**Own doctor N= 39[a]**	**Other N= 49[a]**
How is it decided who will receive the experimental treatment vs. sham surgery?				
Random assignment	39 (75.0)	29 (82.9)	31 (81.6)	35 (74.5)
Subject mentions some method other than random assignment	4 (7.7)	3 (8.6)	2 (5.3)	5 (10.6)
Subject not sure	9 (17.3)	3 (8.6)	5 (13.2)	7 (14.9)
What were the chances of a subject being assigned to the sham surgery group?				
Correct answer	43 (82.7)	30 (90.9)	33 (86.8)	39 (84.8)
Incorrect answer	4 (7.7)	2 (6.1)	2 (5.3)	4 (8.7)
Subject not sure	5 (9.6)	1 (3.0)	3 (7.9)	3 (6.5)
What is the purpose of having a sham surgery group? sham condition? Why do researchers need to have a				
Mentions or describes need to control for placebo effect	36 (67.9)	19 (54.3)	23 (60.5)	30 (61.2)
Mentions to make study legitimate/rigorous (no mention or description of placebo effect)	10 (18.9)	14 (40.0)	10 (26.3)	15 (30.6)
Mentions that FDA requires it	1 (1.9)	1 (2.9)	1 (2.6)	1 (2.0)
Can't determine from text if subject understands purpose of sham surgery (response unclear)	2 (3.8)	1 (2.9)	1 (2.6)	2 (4.1)
Subject not sure	2 (3.8)	0 (0)	1 (2.6)	1 (2.0)
Other	2 (3.8)	0 (0)	2 (5.3)	0 (0)
Describe the difference in procedures between those who receive sham surgery and those who receive the experimental intervention.				
Correct answer (describes difference between two arms accurately)	42 (89.4)	25 (80.6)	25 (80.6)	40 (88.9)
Incorrect answer	2 (4.3)	2 (6.5)	2 (6.5)	2 (4.4)
Not sure	3 (6.4)	3 (9.7)	3 (9.7)	3 (6.7)
Other	0 (0)	1 (3.2)	1 (3.2)	0 (0)

[a] Denominator varies because of missing data for some questions.

Fisher's exact tests did not show differences in the responses for any of the four questions for understanding of research procedures by motivation or by doctor status.

Table 5

Comparison of subjects' perception of potential direct benefit and reported bases for that perception, by motivation and doctor status.

	Motivation		Doctor Status	
Responses (N (%))	**Direct personal benefit N= 54[a]**	**Altruism/dual N= 35[a]**	**Own doctor N= 39[a]**	**Other N= 49[a]**
Realistically, what do you think the chances are of your PD improving (or slowing down)?				
No chance at all	0 (0)	0 (0)	0 (0)	0 (0)
Very low chance	1 (1.9)	1 (2.9)	0 (0)	2 (4.1)
Modest chance	11 (20.4)	9 (25.7)	9 (23.1)	11 (22.4)
Good chance	19 (35.2)	8 (22.9)	12 (30.8)	15 (30.6)
Very good chance	19 (35.2)	12 (34.3)	14 (35.9)	16 (32.7)
Gives quantitative answer greater than50%	2 (3.7)	3 (8.6)	3 (7.7)	2 (4.1)
Tried not to think about it or go in with expectations	1 (1.9)	2 (5.7)	1 (2.6)	2 (4.1)
Other	1 (1.9)	0 (0)	0 (0)	1 (2.0)
What is the basis for your belief concerning the chance of benefit? [b]				
Information about Phase 1 results and/or Phase I related reasons (e.g. through researchers, discussion w/Phase 1 subject, or own research)	37 (40.2)	14 (24.6)	21 (33.3)	28 (33.3)
Subject's own confidence in the science behind the procedure or some scientific aspects of the study	12 (13.0)	8 (14.0)	7 (11.1)	13 (15.5)
Reputation of/ confidence/ trust in research team; Trust in the research process in general	9 (9.8)	8 (14.0)	10 (15.9)	6 (7.1)
Information gathered by the subjects on their own	12 (13.0)	9 (15.8)	6 (9.5)	15 (17.9)
Chance benefit not stated explicitly by researchers or ICF, but inferred based on what researchers said	3 (3.3)	3 (5.3)	2 (3.2)	4 (4.8)
Based on fact that sponsor's invested lots of time and/or money on the study	4 (4.3)	1 (1.8)	3 (4.8)	2 (2.4)
Gut feeling, intuition, optimism	8 (8.7)	7 (12.3)	8 (12.7)	7 (8.3)
Other	7 (7.6)	7 (12.3)	6 (9.5)	9 (10.7)
Is this belief [chance for direct personal benefit] based on something the researchers said or did or on what you read in the informed consent? [c]				
Yes	13 (24.5)	2 (5.9)	7 (18.4)	7 (14.6)
No	39 (73.6)	29 (85.3)	27 (71.1)	41 (85.4)
Can't recall/not sure	1 (1.9)	3 (8.8)	4 (10.5)	0 (0)
Do you recall what the researchers told you/what the informed consent stated, in regards to your chance for benefit?[d]				
Researchers were negative about likelihood of direct personal benefit or downplayed likelihood of benefit	7 (15.9)	2 (6.9)	5 (15.2)	4 (10.5)
Researchers were positive about likelihood of direct personal benefit	9 (20.5)	1 (3.4)	5 (15.2)	5 (13.2)

	Motivation		Doctor Status	
Responses (N (%))	**Direct personal benefit N= 54[a]**	**Altruism/dual N= 35[a]**	**Own doctor N= 39[a]**	**Other N= 49[a]**
Researchers didn't give any specific or general indication of probability of direct personal benefit	23 (52.3)	23 (79.3)	19 (57.6)	26 (68.4)
Can't recall	5 (11.4)	3 (10.3)	4 (12.1)	3 (7.9)

[a] Denominator varies because of missing data for some questions.

[b] For this question numbers refer to comments, not subjects; some subjects made more than one comment.

[c] Fisher's exact test (yes vs. all other responses): direct personal benefit vs. altruism/dual, p=0.04; own doctor vs. other, p=0.77.

[d] Fisher's exact test (2x4): direct personal benefit vs. altruism/dual, p=0.08; own doctor vs. other, p=0.81.

Table 6

Comparison of recollection and perception of risks, by motivation and doctor status.

	Motivation		Doctor Status	
Responses (N/%)	**Direct personal benefit N= 54[a]**	**Altruism/dual N= 35 [a]**	**Own doctor N= 39 [a]**	**Other N= 49 [a]**
What do you recall about the main risks of the surgery and [the study intervention]?[b]				
No, does not identify at least one risk of the procedure.	2 (3.7)	3 (8.6)	1 (2.6)	4 (8.2)
Identifies at least one risk for BOTH surgery and [study intervention].	32 (59.3)	20 (57.1)	22 (56.4)	30 (61.2)
Identifies presence of risks for SURGERY ONLY	17 (31.5)	8 (22.9)	14 (35.9)	11 (22.4)
Identifies presence of risks for [study intervention] ONLY	3 (5.6)	4 (11.4)	2 (5.1)	4 (8.2)
Realistically, what do you think the chances are of your experiencing one or more adverse events?[c]				
No chance at all	0 (0)	1 (2.9)	0 (0)	1 (2.1)
Very low chance	31 (59.6)	27 (79.4)	30 (81.1)	27 (57.4)
Modest chance	12 (23.1)	2 (5.9)	5 (13.5)	9 (19.1)
Good chance	0 (0)	0 (0)	0 (0)	0 (0)
Very good chance	0 (0)	1 (2.9)	0 (0)	1 (2.1)
Tried not to think about it	4 (7.7)	1 (2.9)	0 (0)	4 (8.5)
Other	5 (9.6)	2 (5.9)	2 (5.4)	5 (10.6)

[a] Denominator varies because of missing data for some questions.

[b] Fisher's exact test (identifies risks in both surgery and experimental treatment vs. all other responses): direct personal benefit vs. altruism/dual, p=1.0; own doctor vs other, p=0.67.

[c] Fisher's exact test (no/very low chance vs. all other responses): direct personal benefit vs. altruism/dual, p=0.03; own doctor vs. other, p=0.06.