

**Patient-Subject Perspective on
RCTs with Sham Surgery Control:
Early Results of an Interview Study**

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Worrisome vs. Ideal?

SUBJECT A

It didn't take long for me to decide that it was really the best thing for me. . . There aren't too many other things I can try out there, you know, and I need to try something.

SUBJECT B

...I feel an obligation to the Parkinson's community that I need to do what I can do to improve the lot of the people. You know, I'm not a Washington person. I'm not a lobbyist. I can't do those things, but I can do studies.

Therapeutic Misconception: Various Definitions

Some define it narrowly: Conflating research and treatment.

- “...inaccurately attributes a primacy of therapeutic intent and individualized care typically seen in ordinary clinical settings to research procedures.” (Lidz et al. 2003)

Some define it more broadly: Includes other types of beliefs/statements.

- Any of the following seen as contributing to TM (Henderson et al., SSM, 2005):
 - are motivated by personal benefit, or
 - hope or expect benefit, or
 - fail to appreciate scientific purpose as main purpose.

“[T]here is not yet a consensus about how to operationalize TM...” (Appelbaum et al 2004)

Brief Description of Interview Study

- Aim: To understand how PD patients make their decisions to participate in RCT that has sham control arm.
- Subjects from two PD RCTs with sham arm
 - Spheramine Phase IIb (Titan Pharmaceuticals)
 - 71 subjects in RCT across 10 sites → interviewed 31 /56 subjects from 5 sites
 - Also interviewed 7 decliners
 - CERE-120 Phase II (Ceregene)
 - 58 subjects in RCT across 9 sites → interviewed 30/43 subjects from 7 sites
 - Also interviewed 3 decliners
- N=71 in interview study (61 enrollees; 10 decliners)

Brief Description of Study, cont'd

- Retrospective interviews*
 - Spheramine study—after blind broken (years after surgery)
 - CERE 120 study—after surgery (months after surgery)
- Semi-structured interview
 - Open-ended questions with multiple probe questions as needed; sequenced for naturalistic conversation
 - Qualitatively analyzed

*NB: Part of an ongoing study that includes prospective interviews.

Demographics and baseline clinical data

	Enrollees N=61	Decliners N=10
Age (years) (mean/SD)	59.2 (7.2)	61.7 (5.5)
Female, n(%)	21 (34.4)	2 (20.0)
Married, n(%)	44 (72.1)	8 (80.0)
Ethnicity n(%)		
White	59 (96.7)	9 (90.0)
Black	1 (1.6)	1 (10.0)
Asian	1 (1.6)	0
Education (N/%)		
High school or less	16 (26.2)	2 (20.0)
Some college	10 (16.4)	1 (10.0)
College degree	25 (41.0)	2 (20.0)
Post college	9 (14.8)	5 (50.0)
Duration of PD (years) (mean/SD)	12.1 (4.3)	15.2 (4.7)
Schwab & England score (mean/SD) (CERE-120 subjects only)	80.5 (9.2)	83.3 (7.6)

Motivation for participation

“What is your main reason(s) for participating in the [study name]?”

	Enrollees N=61
Desire for own PD to improve	37 (57.8)
Altruistic motivation	7 (10.9)
Dual motivation	16 (25.0)
No cost	2 (3.1)
Other	2 (3.1)

Responses can exceed 61 because some subjects made additional comments.

- Over 80% had direct personal benefit as a reason.
- Altruism as a reason in 36% (sole reason in only 11%)

“Would you participate if there was no chance of any direct personal benefit?”

Responses	Enrollees N=61
Yes- helping others/future patients is important to subject	20 (31.7)
No- there would have to be some chance of direct personal benefit in order to participate	25 (39.7)
Maybe, but would be less likely	7 (11.1)
Not at the stage of disease where subject is now; maybe if subject’s PD was more advanced would consider this	5 (7.9)
Question doesn’t make sense/why would researchers design a study where subjects wouldn’t have a chance for benefit	3 (4.8)
Not sure	2 (3.2)

Hopes and expectations of benefit

“Realistically, what do you think the chances are of your PD improving (or slowing down)?”*

Responses	Enrollees N=61
No chance at all	-
Very low chance	2 (3.3)
Modest chance	14 (23.0)
Good chance	18 (29.5)
Very good chance	20 (32.8)
Gives quantitative answer greater than 50%	4 (6.6)
Tried not to think about it	2 (3.3)
Other	1 (1.6)

*The first 5 response options were provided to the subjects, therefore not open ended.

“Would you say that you are ‘hoping for’ benefit or ‘expecting’ benefit?”

Responses	Enrollees N=61
Hoping	41 (67.2)
Expecting	15 (24.6)
Both	4 (6.6)
Other	1 (1.6)

What is the basis for their hope or expectation of benefit?

“Do you recall what the researchers told you/what the IC stated, in regards to your chance for benefit?”

Responses	Enrollees N=61
Were positive about likelihood of direct personal benefit	8 (13.2)
Were negative about likelihood of direct personal benefit (or downplayed likelihood of benefit)	5 (8.2)
Didn't give any specific or general indication of probability of direct personal benefit	31 (50.8)
Subject states his/her beliefs re likelihood of benefit not based on what researchers stated	11 (18.0)
Can't recall	5 (8.2)
Missing	1 (1.6)

Understanding the nature of the RCT

“What are the main goals or intentions of the study?”

Responses	Enrollees N=61
To see if [experimental rx] works (no mention of safety testing)	47 (73.4)
To test efficacy and safety of [experimental rx]	11 (17.2)
To see if [experimental rx] should be offered to general PD population	4 (6.3)
Other	1 (1.6)

Responses do not add up to 61 because subjects may have made more than one comment that was coded.

“Is the primary goal to benefit the subjects participating in the study, or future PD patients?”

Responses	Enrollees N=61
1. Primarily intended to help those participating in study	5 (7.5)*
2. Primarily intended to help future PD patients	30 (44.8)
3. Primarily intended to advance science/gain knowledge	8 (11.9)
Both 1 and 2	13 (19.4)
Both 2 and 3	4 (6.0)
Sponsor’s interest	4 (6.0)
To help other diseases, not just PD	1 (1.5)
Other	1 (1.5)
Missing	1 (1.5)

*All 5 indicated that the goal of the study was to test the safety and efficacy of the experimental treatment (see previous slide).

Do the 15 subjects who said they “expect benefit” misunderstand the purpose of the RCT?

Responses	“Expect” to benefit N=15
1. Primarily intended to help those participating in study	1
2. Primarily intended to help future PD patients	9
3. Primarily intended to advance science/gain knowledge	2
Both 1 and 2	2
Both 2 and 3	1

It appears that “expecting” benefit does not imply misunderstanding the purpose of the RCT.

How does subject reconcile the tension between goals of study and desire for direct personal benefit?

Responses (N/%)	Enrollees N=61
Understands main goal is to advance science/help future PD patients but subject's main motivation is to receive benefit	26 (41.9)
Disagrees there is tension/feels the two are compatible	8 (12.9)
Understands subjects may benefit, but subject's main motivation is to help advance science/treatment of PD	6 (9.7)
Out of subject's control/tries to just remain positive	3 (4.8)
Might help subject down the road in the future	1 (1.6)
Not applicable (i.e., subjects not mainly motivated by direct personal benefit)	4 (6.5)
Other responses	3 (4.8)
Missing	10 (16.4)

Understanding of/attitude toward sham surgery condition

“What was your initial reaction to finding out there would be a sham surgery group?”

Responses	Enrollees N=61	Decliners N= 10
Negative reaction (disappointed, concerned, surprised, etc.)	24 (39.3)	8 (80.0)
Neutral reaction (not surprised or concerned, etc.)	32 (52.2)	2 (20.0)
Positive reaction (strengthens study, makes study more rigorous, etc.)	4 (6.6)	-
Missing	1 (1.6)	-

“What is the purpose of having a sham surgery group? Why do researchers need to have a sham condition?”

Responses	Enrollees N=61
Need to control for placebo effect	36 (54.5)
To make study legitimate/rigorous (no specific mention of placebo effect)	21 (31.8)
FDA requires it	5 (7.6)
Can't determine if subject understands purpose of sham surgery	2 (3.0)
Other	1 (1.5)
Missing	1 (1.5)

Responses do not add up to 61 because subjects may have made more than one comment.

“Usually placebos are risk-free (like taking a sugar pill), but sham surgery placebos involve a neurosurgical procedure. **What do you think about the fact that sham surgery involves an invasive procedure?**”

Responses	Enrollees N=61
Understood need for control group, so accepted this	33 (45.8)
Risks of sham surgery seemed acceptable	15 (20.8)
Trusted researchers and so accepted this/deferred to researchers	7 (9.7)
Accepted this/understood need for this, but still has some negative feelings concerning invasiveness	4 (5.6)
Understood need for control group, but disagreed with inclusion of sham surgery	3 (4.2)
Felt this was acceptable in light of later offer of gene transfer/implants	2 (2.8)
Other	6 (8.3)
Missing	2 (2.8)

Responses do not add up to 61 because subjects may have more than one comment.

“Researchers told subjects that if they ended up being assigned to the sham surgery group, they might still have the chance to receive the [experimental treatment] as part of another study after this study is over. **How are researchers going to decide if the [experimental rx] will be offered later?”**

Responses	Enrollees N=61
Understands conditions under which it would be offered	43 (70.5)
Would automatically be offered/ no preconditions	8 (13.1)
Not sure what conditions must exist	5 (8.2)
Can't determine if subject understands conditions for later offer of gene transfer	4 (6.6)
Other	1 (1.6)
Missing	1 (1.6)

“Please explain what influence [the later conditional offer of experimental intervention] had on your decision to participate, if any.”

Responses	Enrollees N=61
Necessary condition/strong reason for participating	21 (34.4)
Some influence	26 (42.6)
Didn't influence decision	3 (4.9)
Missing	11 (18.0)

Worrisome vs. Ideal?

SUBJECT A

It didn't take long for me to decide that it was really the best thing for me. . . There aren't too many other things I can try out there, you know, and I need to try something.

SUBJECT B

...I feel an obligation to the Parkinson's community that I need to do what I can do to improve the lot of the people. You know, I'm not a Washington person. I'm not a lobbyist. I can't do those things, but I can do studies.

In fact, Subject A and Subject B are the same
person

Upon further probing and questioning over the course
of the interview, this subject said:

“The reason I want to do it though is because as nice
as it would be to have a positive effect on me, it’s
better yet that future people have the benefit of my
experience having done it. So they don’t have to
repeat history.”

Main Summary Points

- Most volunteer hoping it will help their PD, with great deal of optimism/expectation about potential for benefit.
- The optimism/beliefs about benefit appears not to be based on explicit statements from researcher/ICF; rather, we suspect two main reasons:
 - It is difficult to be motivated by desire for benefit and at the same time state that such benefit is unlikely.
 - Most ICFs are necessarily uncertain about potential benefit—cannot say there is no chance, yet no ‘accurate’ positive estimate possible.
- For most, this motivation/optimism appears compatible with intact understanding of purpose of research and need for sham condition.
- Small minority of subjects may require additional attention to optimize informed participation.

Implications?

- Relationship between motivation and understanding is more complex than it seems → Need to avoid simplistic interpretation of subject statements.
- Suggestions for informed consent conversation:
 - Don't treat IC as only a matter of information transfer.
 - Treat it as an opportunity to help people make good decisions → specifically: Incorporate discussion of subject motivation and expectation into the IC discussion.