RESEARCH ARTICLE

Comparison of Enrollees and Decliners of Parkinson Disease Sham Surgery Trials

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ABSTRACT: Concerns have been raised that persons with serious illnesses participating in high-risk research, such as PD patients in sham surgery trials, have unrealistic expectations and are vulnerable to exploitation. A comparison of enrollees and decliners of such research may provide insights about the adequacy of decision making by potential subjects. We compared 61 enrollees and 10 decliners of two phase II neurosurgical intervention (i.e., cellular and gene transfer) trials for PD regarding their demographic and clinical status, perceptions and attitudes regarding research risks, potential direct benefit, and societal benefit, and perspectives on the various potential reasons for and against participation. In addition to bivariate analyses, a logistic regression model examined variables regarding risks and benefits as predictors of participation status. Enrollees perceived lower risk of harm while tolerating higher risk of harm and were more action oriented, but did not have more advanced disease. Both groups rated hope for benefit as a strong reason to participate, whereas the fact that the study's purpose was not solely to benefit them was rated as "not a reason" against participation. Hope for benefit and altruism were rated higher than expectation of benefit as reasons in favor of participation for both groups. Enrollees and decliners are different in their views and attitudes toward risk. Although both are attracted to research because of hopes of personal benefit, this hope is clearly distinguishable from an expectation of benefit and does not imply a failure to understand the main purpose of research. ©2012 *Movement* Disorder Society

Key Words: Parkinson's disease; sham surgery; therapeutic misconception; decision making; gene transfer

The participation of patients with serious medical conditions in research studies with significant risks remains controversial. Concerns continue to be raised that those who enroll in such research are "unrealistic" in their expectations.[1] In PD research, studies involving sham surgery controls have been particularly controversial, with concerns that these older patients with serious illnesses are being exploited.[2] The concern is that patients with serious illnesses are so desperate that they may be making less than optimal decisions when they participate. Such concerns involve claims about how patients make decisions regarding research participation. Thus, understanding how patients with PD, in fact, make decisions to participate

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Funding agencies: This publication was made possible, in part, by the Michael J. Fox Foundation for Parkinson's Research (Rapid Response Innovation Award), the National Institute for Neurological Disorders and Stroke (R01-NS062770), and the National Center for Research Resources (UL1 RR024160), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research.
Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 1 September 2011; **Revised:** 30 November 2011; **Accepted:** 9 January 2012
Published online 7 February 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.24940

in highly invasive studies provides important insights into how informed consent for such studies can be optimized.[3] In this regard, a comparison of those who agree to participate with those who decline to do so may provide unique insights. For example, do those who enroll in research have more advanced disease or have more symptoms (perhaps making them more "desperate") than those who decline? Do enrollees have a higher expectation of benefit or lower expectation of risks than decliners? Or is it that the decliners and enrollees have different values or attitudes toward risks and potential benefits?

In this study, we interviewed actual participants and decliners of two industry-sponsored PD randomized, clinical trials involving a sham surgery control and compared them in the following ways. Are the groups different in their demographic or clinical characteristics? Do they view reasons for and against participation differently? Do they have different perceptions and attitudes regarding risks and benefits of participation?

Patients and Methods

Participants

Participants were enrollees and decliners of two early-phase intervention trials for PD. Enrollees were persons who had enrolled and undergone the primary study intervention. Decliners were individuals who discussed the trial with a member of the research team, but who ultimately declined participation in the trial. The STEPS trial was a multicenter phase II efficacy trial of an intervention utilizing human retinal pigment epithelial cells that secrete levodopa (L-dopa).[4] Subjects were randomized to receive experimental injections bilaterally or a sham surgical procedure involving bilateral incisions and full-thickness burr holes. The trial enrolled 71 subjects across 10 sites; five of those sites agreed to ask their enrollees and decliners whether we could contact them about participating in our interview study. We interviewed 31 of 56 (55%) enrollees at those sites and also 7 of 16 decliners (44%). The second study, the CERE-120 trial, was a randomized, clinical trial of a modified adeno-associated virus vector with a gene for neurturin.[5] The sham surgery involved bilateral partial-thickness burr holes. This study involved nine sites across the United States; seven of nine sites agreed to ask their enrollees and decliners whether we could contact them, and we interviewed 30 of 43 enrollees (70%) and also 3 of 9 decliners (33%).

As a result of sponsor requests, the time frame from when enrollee subjects had their surgery to when their interview was conducted differed across the two trials. CERE-120 enrollees were approached for interviews approximately 1 month after they had undergone surgery. Twenty-six (86.7%) of the enrollee interviews took place between 1 and 9 months after their surgery; four interviews took place more than 9 months after their surgery. Of the 3 decliners interviewed from the CERE-120 study, 2 decliners were interviewed less than 9 months after discussing the CERE-120 study with the research team. At the request of the sponsor, 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 2 years postsurgery, 10 (32.3%) interviews between 2 and 4 years after surgery, and 14 (45.2%) occurred greater than 4 years postsurgery. The decliners were approached any time after they officially declined participation. Four decliners were interviewed between 2 and 4 years after discussing the STEPS study with researchers, whereas 3 were interviewed less than 2 years after recruitment discussions.

The interviews were conducted by telephone and were recorded and transcribed, except for one interview for which interviewer notes were used because of technical difficulties.

The institutional review boards of the University of Rochester and the University of Michigan deemed the study exempt from federal regulations.

Measures

This was part of a larger overall study that involved both qualitative and quantitative measures. The results of the qualitative analysis will be presented elsewhere.

Attitudes Toward and Perception of Risk and Benefits

We obtained a risk tolerance score by asking the subjects how much risk, defined as the likelihood of one or more serious adverse events occurring to them, that they would tolerate and still participate in their respective clinical trial. Subjects were reminded of the risks as follows: "The possible risks and discomforts of participating in the [clinical trial] were described to you by the research team conducting the trial and in the informed consent you signed. Some of the risks that were mentioned include: depression, hallucinations or delusions, bleeding or blood clot in the brain, seizures, dyskinesias, worsening of neurologic condition, infection, or heart attack."

The response was elicited using a "ping-pong" method.[6] In this procedure, the interviewer elicits willingness to participate at 0% risk, then goes to 100% risk, then bounces back and forth in 10% increments until the willingness to participate reverses; then, finer increments are used to arrive at the highest likelihood of risk that they would tolerate. Persons not willing to participate even at 0% risk were assigned a score of −1 to allow for nonparametric analyses.

A personal benefit requirement score was elicited using the same technique. Subjects were asked how

much personal benefit (defined as the likelihood of improving to the point where they could with medications "function almost normally with few side effects") they would require for them to participate in their respective trial. Persons not willing to participate, even at 100% likelihood of benefit, were assigned a score of 101.

A societal benefit requirement score was obtained by asking the subjects how much societal benefit, defined as researchers finding "a cure for PD within 10 years as a result of the study," they would require to participate, *even if they knew they themselves would not benefit by participating*. Persons not willing to participate, even at 100% likelihood of societal benefit, were assigned a score of 101.

Finally, subjects were asked for their perception of likelihood of risk involved ("what percent chance of risk to yourself were you expecting?") and their perceptions concerning the likelihood of benefit to themselves and to society ("what percent chance of benefit to yourself [or society] were you expecting?"). These scores are the subject's risk perception score, personal benefit perception score, and societal benefit perception score, each with a possible range of 0 to 100.

Ratings of Reasons For and Against Participation

This measure assesses a series of reasons related to participation in a clinical trial—six reasons in favor of participation and eight against participation—and reflects how strong a factor each reason was in the decision whether to participate in the respective clinical trial.[6] The response categories were "not a reason," "minor reason," "moderate reason," and "strong reason." These were given numeric scores of 1 through 4 for analysis.

Demographic and Clinical Background Information

Basic demographic information (e.g., age, gender, education, race and ethnicity, marital status, and employment status) was collected. Background information on the subject's PD status was also collected (i.e., number of years since diagnosis, ability to perform certain activities of daily living, and past research participation).

Analysis

Descriptive data (i.e., means, medians, frequencies, and percentages) were calculated. For demographic variables, a two-group t test was used when testing means and Fisher's exact test was used to compare frequency data. When comparing ordinal responses (i.e., reasons for and against participation) or probability estimates between the enrollee and decliner groups (i.e., the risk and benefit preference and perceptions scores), nonparametric (i.e., Mann-Whitney's) tests were used.

We also conducted an exploratory logistic regression analysis to assess the predictors of enrollment to the trial among the various risk and benefit requirement and perception scores, which were adjusted for demographic and clinical variables that were different between the two groups in bivariate analysis (namely, education and number of years with PD).

TABLE 1. Comparison of Demographic and Clinical Characteristics Between Enrollees and Decliners

Characteristics	Enrollees (N = 61)	Decliners (N = 10)	P Value*
Age (years; mean/SD)	59.2 (7.2)	61.7 (5.5)	0.24
Male (no./%)	40 (65.6)	8 (80.0)	0.48
Race (no./%)			
White	59 (96.7)	9 (90.0)	0.37
Black	1 (1.6)	1 (10.0)	
Asian	1 (1.6)	0	
Years of education (no./%)			
<High school	1 (1.7)	1 (10.0)	0.05
High school	15 (25.0)	1 (10.0)	
Some college	10 (16.7)	1 (10.0)	
College degree	25 (41.7)	2 (20.0)	
Postcollege	9 (15.0)	5 (50.0)	
Married (no./%)	44 (72.1)	8 (80.0)	0.72
Years since PD diagnosis (mean/SD)	12.1 (4.3)	15.2 (4.7)	0.08

*Two-group t test for continuous variables and Fisher's exact test for categorical variables.
Abbreviation: SD, standard deviation.

Results

Seventy-one subjects participated in our study: 61 enrollees and 10 decliners (Table 1). Enrollees and decliners were similar in most respects, except that the decliners had a higher level of education ($P = 0.05$) and had a trend toward longer period since diagnosis ($P = 0.08$).

Perception of and Attitude Toward Risks and Benefits

Enrollees and decliners differed in their perceptions of, and tolerance for, risks (Table 2). Decliners perceived the trials as carrying greater chance of harm than did enrollees (15% versus 4% chance; $P = 0.003$). Decliners were willing to tolerate up to 11% chance of a serious adverse event, whereas enrollees were willing to tolerate up to 19% chance of such an event ($P = 0.04$).

In terms of perception of, and requirement for, potential benefits from the study intervention, enrollees were willing to participate at a lower likelihood of benefit to self, as compared with decliners (21% versus 45%; $P = 0.01$). However, enrollees and decliners

TABLE 2. Comparison of Enrollee and Decliner Risk Preference/Benefit Requirement Scores and Risk/Benefit Perception Scores*

Variables	Enrollees (N = 61)	Decliners (N = 10)	*P* Value**
Risk tolerance	19 (10–30)	11 (3–20)	0.040
Risk perception	4 (3–10)	15 (5–40)	0.003
Personal benefit requirement	21 (20–30)	45 (20–93.5)	0.010
Personal benefit perception	70 (50–75)	60 (50–70)	0.150
Societal benefit requirement	90 (70–101)	101 (75–101)	0.240
Societal benefit perception	87.5 (80–90)	80 (75–80)	0.010

*Scores are presented as median score (interquartile range).
**Mann-Whitney's test.

did not differ in terms of their perceptions of likelihood of direct personal benefit, with both groups giving fairly high median estimates of benefit at 70% for enrollees and 60% for decliners ($P = 0.15$).

Both groups saw potential societal benefit as quite likely, but with enrollees perceiving a greater chance of benefit to society than decliners (88% versus 80%, respectively; $P = 0.01$). When asked about the minimum likelihood of societal benefit required for their participation assuming they themselves would not benefit, there was no significant difference between the two groups. Enrollees would participate only if there were a 90% chance or more of societal benefit. The decliners' median score was 101 because the majority said they would not participate when there was no chance of direct personal benefit, even if there were a 100% chance that researchers would make major advancements in the treatment of PD as a result of the trial.

In the logistic regression model that included all six scores (correlations among which were modest, ranging from −0.38 to 0.37, suggesting no collinearity across predictors), which was adjusted for education and years living with PD, only risk tolerance (odds ratio [OR] = 1.36; 95% confidence interval [CI]: 1.05–1.75) and perception (OR = 0.77; 95% CI: 0.60–0.99) scores significantly predicted participation status. The two variables from bivariate analysis—personal benefit requirement and societal benefit perception scores—that were significantly different between enrollees and decliners were not significant in the multivariate model.

Ratings of Reasons For and Against Participation

In their ratings of reasons against participation, enrollees and decliners showed clear differences (Table 3). For decliners, "It seems too dangerous" was a "strong reason" not to participate, whereas for enrollees, it was a "minor reason" (3.7 versus 2.0; $P < 0.001$). A similarly significant difference was evident for the reason "I don't like the idea of brain surgery." Although being a "guinea pig" and the burden of participating in research were also rated higher as reasons against participation by decliners than enrollees, both groups tended to see these as minor reasons.

It is notable that the reason against participation that was rated the lowest by both groups (in fact, rated as "not a reason," on average, by both groups) was the fact that the purpose of the study was not solely to benefit the subjects directly.

In terms of reasons in favor of participation, enrollees endorsed the reason "It's better to do something rather than just waiting for my PD to get worse" as a "strong reason" in favor of participation (mean score, 3.9), whereas decliners saw it as a "moderate reason" (mean, 3.0; $P < 0.001$). This was the top-rated reason for participating for enrollees. Both enrollees and decliners rated "I hope that it will help my PD" as a strong reason in favor of participating, and there was no significant difference in the rating between the groups. Altruistic reasons (e.g., "helping other patients with PD" and "contribute to science") did not distinguish between the two groups, because both groups rated these as"moderate" reasons in favor of participation. Enrollees more strongly endorsed the reasons "I expect it will help my PD" and "I need to try this for the sake of my loved ones," compared to decliners ($P = 0.04$ and 0.05, respectively), although these

TABLE 3. Comparison of Ratings of Reasons Against and Reasons for Participation Between Enrollees and Decliners*

Reasons	Enrollees (N = 61)	Decliners (N = 1 0)	*P* Value**
Reasons against participation			
It seems too dangerous.	2.0 (0.8)	3.7 (0.6)	<0.001
I don't like the idea of brain surgery.	2.5 (0.7)	3.4 (1.0)	0.003
I don't want to be a guinea pig.	1.6 (0.7)	2.5 (1.1)	0.020
The purpose of the study was not solely to benefit me directly.	1.1 (0.3)	1.2 (0.4)	0.460
It seems like a lot of work for me to be involved in this kind of study.	1.3 (0.5)	1.9 (0.9)	0.020
Reasons in favor of participation			
I hope it will help my PD.	3.8 (0.4)	3.9 (0.3)	0.660
I would be helping other patients with PD.	3.1 (0.8)	3.2 (0.9)	0.860
It's better to do something rather than just waiting for my PD to get worse.	3.9 (0.3)	3.0 (0.9)	<0.001
Maybe it might help me in the long run, if the research succeeds.	3.0 (0.8)	2.4 (1.0)	0.080
I want to contribute to science.	2.9 (0.9)	2.7 (0.9)	0.470
I expect it will help my PD.	2.5 (1.1)	1.8 (0.9)	0.040
I need to try this for the sake of my loved ones.	2.8 (1.0)	2.1 (1.1)	0.050

*Values are expressed as mean (standard deviation); range of scores: 1 = not a reason; 2 = minor reason; 3 = moderate reason; 4 = strong reason.
**Mann-Whitney's test.

reasons were at the bottom of the list for both groups in terms of importance.

Discussion

There continues to be a concern that research subjects enter even risky studies out of unrealistic desires for therapeutic benefit and that this clouds their understanding of research design.[1,7] We attempted to address this concern by asking what distinguishes those who enroll versus those who decline to participate in a sham surgery-controlled, randomized, trial for PD.

Enrollees did not have more advanced disease; indeed, there was a trend toward decliners having had PD longer. This is consistent with our previous finding using a hypothetical scenario, in which those willing to participate in a phase I gene-transfer study of PD had slightly milder disease.[6] The decliners in our study were more educated than the enrollees, although this was because of half of the decliners having postcollege education, rather than the enrollees being poorly educated; in fact, 57% of the enrollees had college education or higher.

The risk/benefit perception and requirement scores and the ratings of reasons for and against participation provided a coherent picture of why some volunteer for sham surgery research while others do not. Although unadjusted analysis showed that risk perception and risk tolerance, as well as attitudes toward personal benefit and perceptions of societal benefit, were different between the two groups; the adjusted model showed that only risk tolerance and risk perception scores were predictive. This is consistent with the ratings of reasons for and against participation, where the most robust differences between the two groups had to do with perception of danger and wariness toward brain surgery. Further, the relatively high scores for perception of potential personal benefit (60%–70% chance) and societal benefit (80%–88% chance) are congruent with ratings of ''hope of benefit'' and altruism being as moderate to strong reasons, but they did not distinguish between the groups. Although expectation of benefit was a stronger motivation for the enrollees, it was not a strong reason overall.

Consistent with our previous study using a hypothetical scenario, we found a significantly greater action orientation (e.g., ''It's better to do something rather than just waiting for my PD to get worse'') among the enrollees than decliners.[6]

Another important finding is the juxtaposition of two items: Though both groups gave the lowest rating (as a reason against participation) to ''The purpose of the study was not solely to benefit me directly,'' they gave their highest rating to ''I hope it will help my PD'' as a reason in favor of participation. This provides evidence that, consistent with other studies,[3,8,9] research participants can *understand* that research is not solely to benefit them even though they may be *motivated* by hopes of benefit. As others have noted, it is important not to assume that being motivated by a desire for benefit implies a faulty understanding of research[9,10]—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. Supporting this interpretation is the fact that the respondents clearly distinguished between hope and expectation of benefit and gave higher ratings to altruistic and proscience reasons than to ''expect to benefit'' as a reason for participation.

This study had limitations. First, because we interviewed actual enrollees and decliners, the numbers were quite small. This was especially true for the decliner group—which consisted of only 10 subjects—because it is relatively uncommon for persons who seek out and have discussions about a research study to decline. On the other hand, it may be that the differences between enrollees and decliners we found were conservative estimates, given that decliners who are still willing to be interviewed may be more proresearch. Second, the interviews were retrospective and may have been colored by the actual decisions made as well as the passage of time. However, the results of this study are quite similar to our prospective (but hypothetical scenario-based) study comparing those who were willing and unwilling to participate in a neurosurgical gene-transfer study for PD.[6] Both studies, for example, found that the most potent predictors of participation were risk perception and risk tolerance, along with an action orientation. Third, any study eliciting layperson estimates of probabilities must acknowledge the well-known limitations of such exercises,[11] such as the lay public's tendency to use probability statements for nonmathematical purposes.[12] Thus, we emphasize not the absolute numbers, but rather the relative comparison between the two groups. For example, the relatively high estimates of potential personal benefit given by both groups must be interpreted in light of the fact that both groups clearly endorsed ''hope'' for benefit as a stronger reason for participation than ''expectation'' of benefit.

Although both risk and benefit information are important, they are important in different ways. When discussing risks, researchers should be aware that such information may indeed be the pivotal factor in a patient's decision to participate. This creates a heightened responsibility to ensure that risk information is both user-friendly and accurate and not simply a catalog of items to fulfill regulatory requirements. In regard to benefit information, researchers should assume that most potential subjects (whether they end up enrolling or not) will be motivated by hope for benefit. The focus should be not on eradicating this

orientation, but on ensuring that it does not lead to a misunderstanding; this can be accomplished by acknowledging the subjects' therapeutic motivation while contrasting it with the scientific purpose of the study's aims and design.[3] Optimal informed consent for therapeutic intervention trials, especially when disease-altering treatments do not exist, will require working *with* the therapeutic orientation of subjects rather than ignoring or working against it.

Acknowledgments: The authors thank Ceregene, Inc. and Raymond T. Bartus, Ph.D., Executive Vice President and Chief Scientific Officer, for thoughtful comments on the study and access to the patients who were involved in their CERE-120 phase II clinical study. The authors also thank William J. Marks, Jr., M.D., for his assistance in recruitment and planning, Titan Pharmaceuticals, Inc., for their cooperation, and the subjects who so generously gave their time and shared their experiences with us.

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