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Research Report

Recruitment and Retention in Clinical Trials of Deep Brain Stimulation in Early-Stage Parkinson's Disease: Past Experiences and Future Considerations

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Abstract.
Background: Clinical trials are often hindered by inadequate patient recruitment. Overly optimistic investigator predictions of participation can lead to unmet recruitment goals and costly trial extensions. A patient-focused approach estimating recruitment in clinical trials may provide higher accuracy.
Objective: To predict the feasibility of recruitment in a future deep brain stimulation (DBS) in early-stage Parkinson's disease (PD) multicenter trial by understanding motivations and concerns to participation of past and potential future DBS in early-stage PD clinical trial subjects.
Methods: To identify motivating factors and barriers influencing trial participation, an end-of-trial survey was administered to subjects enrolled in a DBS in early-stage PD pilot trial with subjects randomized to receive DBS plus optimal drug therapy (DBS+ODT) or ODT alone (NCT#00282152, IDE#G050016). Pilot trial survey results were analyzed in conjunction with results of a previously-reported survey querying patients with early-stage PD about potential participation in a trial for DBS in early-stage PD with similar inclusion/exclusion criteria.
Results: Pilot trial subjects reported high levels of satisfaction with their participation in the trial. Similar motivations and barriers to participation were expressed in comparable proportions by subjects who successfully completed the pilot trial and patients with PD considering enrollment in a comparable study.
Conclusions: The FDA has approved a prospective, randomized, double-blind, phase III, multicenter, pivotal clinical trial evaluating DBS in early-stage PD (IDE#G050016). These results suggest that the successful recruitment and retention of early-stage PD subjects, as observed in the pilot trial, is attainable in a future pivotal trial.

Keywords: Parkinson's disease, deep brain stimulation, surveys, questionnaires, clinical trial, patient recruitment, recruitment methods

INTRODUCTION

One of the most common, yet often preventable, causes of failed clinical trials is inadequate recruitment and retention [1]. A recent analysis of National

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Library of Medicine phase 2 and 3 registered clinical trials found that 29% were terminated early or were completed with less than target enrollment [2]. Clinical trials commonly suffer from delayed or inadequate recruitment, which can result in costly extensions of the original timeline [3]. Inaccurate recruitment estimations are often rooted in physician predictions rather than forecasts based on input from past and potential trial participants [3].

Patient recruitment is a frequent barrier in Parkinson's disease (PD) clinical trials [4]. The reasons are not always apparent and may differ across stages of the disease and include availability of relatively good symptomatic treatments for early-stage disease, the extended time frame of trials, and the complicated nature of treatment regimens as well as trial designs [5]. Additionally, treatment-specific considerations such as fear of surgery may also play a significant role [6].

One strategy to address barriers to recruitment and retention is to incorporate lessons learned from patient experiences of completed clinical trials of similar design and disorders. By considering feedback from past study participants, the focus shifts away from the physician and toward the patient, more directly addressing the origins of impediments in recruitment and retention. Patient questionnaires seeking feedback about participation feasibility for future studies also help to understand the interests of potential trial participants [7]. Therefore, a two-pronged patient-focused approach including results from a survey of prospective participants (1), coupled with retrospective responses of past study participants (2), may be more informative. Analyzing responses to questions that explore which trial design elements affect recruitment and retention provides a logical methodology to better predict and enhance recruitment and retention in future clinical trials.

Vanderbilt University completed a prospective, randomized, single-blind clinical trial evaluating the safety and tolerability of subthalamic (STN) deep brain stimulation (DBS) for the treatment of early-stage PD. Based on results from the pilot, the FDA has approved the conduct of a multicenter, double-blind, pivotal trial investigating DBS in 280 people with early-stage PD (IDE#G050016) in which all subjects will be implanted with DBS and then randomized to receive active or inactive DBS. Despite the pilot trial achieving its recruitment goal with exceptional recruitment following initial screening criteria (30/30, 100%) and subsequently maintaining excellent retention (29/30, 93%) rates, the feasibility of scaling up recruitment of subjects nearly ten-fold with early-stage PD for a multicenter surgical trial is unknown [8–10]. Therefore, a patient satisfaction survey (pilot trial survey) was administered after the conclusion of the trial in order to learn from subjects' experiences regarding what factors contributed to the trial's successful recruitment and retention. Here we report results of the patient satisfaction survey from the pilot trial of DBS in early-stage PD.

Previously, an independent survey was conducted in conjunction with other collaborators using The Michael J. Fox Foundation for Parkinson's Research (MJFF) online clinical study platform, Fox Insight [11]. The survey was designed to explore motivational factors and barriers among patients with early-stage PD across the US for potential participation in a DBS clinical trial [11]. In the discussion, we compare these studies which prove complimentary prospective and retrospective patient insights regarding pre-trial and post-trial attitudes. By understanding the motivations and barriers to trial participation of past and potential subjects, we attempt to predict feasibility of recruitment in the future pivotal trial. The fundamental similarities of these two cohorts of patients with early-stage PD suggest that the planned multicenter, pivotal trial will experience similarly successful recruitment and retention as the single-center pilot trial.

MATERIALS AND METHODS

Characteristics of the organization and participants of the survey DBS study

A trial completion study, surveying subjects following their last assessment, was performed in conjunction with the Vanderbilt pilot trial of the safety and tolerability of STN-DBS for the treatment of early-stage PD. In the pilot trial, 30 patients with early-stage PD (Hoehn & Yahr Stage II off medication, age 50-75, medication duration between six months and four years, without dyskinesia or other motor fluctuations) provided written informed consent and were randomized 1:1 to bilateral STN-DBS plus optimal drug therapy (ODT) or ODT alone and followed prospectively for two years (NCT#00282152, IDE#G050016, IRB#040797). Study design, baseline characteristics, enrollment, operative experience, and outcomes are published elsewhere [8, 9, 12–15]. Only one subject failed to complete the study, dropping out early, after the baseline visit (see below). After the pilot trial

Table 1
Respondents' demographics

Characteristic	Pilot trial ($n = 29$)[A,B]	Fox Insight ($n = 158$)[C]
Age		
Mean	61 ± 6.4	61 ± 5.4
Range	51–74	50–70
Gender (%)		
Female	3 (10%)	83 (53%)
Male	26 (90%)	75 (47%)
Race/ethnicity (%)		
Caucasian	100%	94.9%
Hispanic or Latino	0.0%	2.5%
Asian	0.0%	1.3%
African American	0.0%	0.0%
More than one	0.0%	1.3%
Disease duration (years)	2.1 ± 1.8	1.9 ± 1.0
Mean L-dopa equivalents at baseline (mg/day)	453 ± 265	N/A
Employment status (%)		
Employed	62% (18)	43% (68)
Unemployed/retired	38% (11)	57% (90)

[A]Baseline characteristics; adapted from Charles et al., 2012 [9]. [B]Twenty-seven out of 29 subjects with at least one follow-up visit from the pilot trial completed an anonymous patient satisfaction survey at the conclusion of the study. [C]Adapted from Heusinkveld et al., 2016 [11].

concluded, all 29 subjects who completed the study were mailed an internally developed, IRB-approved (Vanderbilt IRB#040797) patient satisfaction survey.

Survey

The anonymous patient satisfaction survey focused on subjects' satisfaction with medical treatment including interpersonal aspects such as clinician encounters and information provided during the trial as well as factors influencing their original decision to participate in the trial. Additionally, treatment-specific questions were asked (DBS+ODT versus ODT) to understand subjects' satisfaction with their treatment group and experience, as well as their future treatment plans.

The general questionnaire for all subjects consisted of 34 questions and the DBS+ODT and ODT treatment specific questionnaires consisted of 17 and 7 questions, respectively. Survey questions were presented in one of four formats: (1) multiple choice-select one answer, (2) multiple choice-select all that apply, (3) free text response, and (4) agree/indifferent/disagree. Free text responses were categorized qualitatively according to theme.

RESULTS

Demographics

After the pilot trial concluded, 27 of 29 subjects (93%) who completed the pilot trial returned the survey. The demographics of the respondents are displayed in Table 1. For convenience, the demographics are displayed alongside those of the prior Fox Insight survey to facilitate a comparison in the subsequent discussion. The pilot trial subjects had a mean age of 61 ± 6.4 (Table 1) and an average disease duration of approximately two years. The pilot trial subjects were 100% Caucasian and 10% female.

Pilot trial enrollment influences

Table 2 reports results of the pilot trial survey. Common themes, including trends in motivations and concerns, are presented.

Motivations, fears, and burdens

Pilot trial survey respondents stated their primary motivations for enrolling in the study were a desire to advance medical research (85%), receive the best medical treatment for PD (70%), learn more about PD (59%), and be considered for DBS (56%). By contrast, the most frequently listed fear impacting participation by pilot trial survey respondents was surgery related concerns (44%), while 11% of respondents indicated they had no fears related to participating. When asked about burdens experienced during the pilot trial, the most common response was that no part of the study was burdensome (37%). Other burdens included the financial commitment (i.e., travel, time off work) (30%),

Table 2
Pilot trial survey results

All Respondents ($n = 27$)	Number	%
Hoped to be randomized to^		
DBS	24	89%
Medication	2	7%
No opinion	1	4%
Motivating factors of participation*		
To advance medical research	23	85%
To get the best medical treatment for PD	19	70%
To learn more about PD	16	59%
To get deep brain stimulation	15	56%
To meet other patients with PD	10	37%
Other	2	7%
Benefits of participation*		
Contributing to PD research	24	89%
Learning more about PD	23	85%
Meeting other people with PD	21	78%
Receiving additional healthcare for PD	11	41%
Other	5	19%
Fears#		
Surgery	12	44%
PD worsening/not improving	5	19%
None	3	11%
Other	4	15%
No response	3	11%
Burdens*		
No part of the study was burdensome	10	37%
Financial commitment	8	30%
Neuropsychological testing	7	26%
Washout periods	7	25%
Time commitment	4	15%
UPDRS testing/daily CRC evaluations	2	7%
Other	2	7%
Reactions to participation^	Initial/24 months	Initial/24 months
Family and friends		
Positive	24/25	89%/93%
Negative	2/0	7%/0%
No opinion/indifferent	1/2	4%/7%
Neurologist		
Positive	23/21	85%/81%
Negative	1/0	4%/0%
No opinion/indifferent	3/5	11%/19%
No response	0/1	0%/4%
Informed consent process•		
Presented sufficient information about study	26/1/0	96%/4%/0%
Presented sufficient information about participation	27/0/0	100%/0%/0%
Provided accurate expectations	27/0/0	100%/0%/0%
Process was helpful	23/4/0	85%/15%/0%
Staff•		
Principle investigator was available to answer all questions	27/0/0	100%/0%/0%
Research team communicated effectively	27/0/0	100%/0%/0%
Healthcare quality^		
Have received better healthcare	12	44%
Have received worse healthcare	0	0%
Healthcare did not change	14	52%
No response	1	4%
Overall experience and recommendations•		
Experience in clinical trial was positive	27/0/0	100%/0%/0%
Would enroll in another clinical trial	22/4/1	81%/15%/4%
Would recommend participating in a clinical trial to a friend/family member	27/0/0	100%/0%/0%

(*Continued*)

Table 2
(*Continued*)

DBS+ODT Group ($n = 13$)		
Relieved to be randomized to DBS^	13	100%
Considered dropping out•	0/0/13	0%/0%/100%
Would recommend DBS to other PD patients•	12/1/0	92%/8%/0%
Fears^		
Surgery-related complications	7	54%
Device-related complications	2	15%
Stimulation-related complications	2	15%
Greatest benefits of DBS#		
Tremor reduction	6	46%
Symptom reduction/slowing of PD	3	23%
Quality of life improvement	2	15%
Other	2	15%
Greatest drawbacks of DBS#		
No drawbacks	6	46%
Surgery-related	3	23%
PD-related	2	15%
Study procedure-related	2	15%
ODT Group ($n = 14$)		
Relieved to be randomized to optimal drug therapy only^	2	14%
Considered dropping out•	2/1/11	14%/7%/79%
Plan on receiving DBS in the future•	3/5/4	21%/36%/29%

^Patients were prompted to select only one response. *Patients were permitted to select as many responses as applicable. #Patients responded via free text and responses were qualitatively categorized. •Patients were permitted to select agree, indifferent, or disagree (agree/indifferent/disagree).

neuropsychological testing (26%), and the week-long therapeutic washout periods (26%).

External support

Nearly all subjects felt strongly supported in their decision to participate in the pilot trial throughout the study. At 24 months, the majority of pilot trial survey respondents indicated that their family and friends (93%) and local neurologist (72%) felt positively about their participation in the clinical trial, and none reported negative reactions towards their participation.

Withdrawal considerations

Although no pilot trial survey respondents randomized to DBS+ODT stated they considered withdrawing from the study, two respondents randomized to ODT reported considering withdrawal. As noted above, one pilot trial subject randomized to ODT withdrew after the baseline visit due to financial/family reasons and did not receive a survey [8].

Pilot trial experience

Pilot trial survey responses targeting respondents' experiences in the study are described:

DBS surgery benefits and drawbacks

Subjects randomized to DBS+ODT were asked in free text response questions about the greatest benefits and drawbacks to receiving DBS. Tremor reduction was the most common, freely cited benefit of DBS (46%), followed by additional clinical improvements (symptom reduction, perceived slowing of PD progression, and improved quality of life) (38%). When asked about drawbacks of DBS, 46% of participants freely stated there were no drawbacks, while time commitment and washout periods were noted by one respondent each (8%).

Future DBS and clinical trial participation recommendations and considerations

The majority (92%) of respondents randomized to DBS+ODT indicated they would recommend DBS to other PD patients. Despite a majority of respondents randomized to ODT hoping to be randomized to DBS (89%), only 21% stated affirmative plans to receive DBS in the future.

When asked whether their experience in the clinical trial was positive, all survey respondents agreed (100%). Additionally, 100% of survey respondents would recommend participation in a clinical trial to a friend or family, however, only 81% would participate in another trial themselves.

Staff interactions and informed consent process

All pilot trial survey respondents agreed that the trial's principle investigator (PI) was available to answer all of their questions (100%). All respondents also agreed that the PI and members of the research team communicated with them effectively.

When subjects were asked whether sufficient information relating to the purposes, aims, and design of the study was presented, almost all agreed they had been (96%) and one (4%) was indifferent. All (100%) subjects agreed the informed consent process provided accurate expectations of the trial and all (100%) agreed they were presented sufficient information concerning their participation in the study. While no subjects stated the informed consent process was unhelpful, 15% felt indifferent towards its helpfulness.

DISCUSSION

The presented survey represents the second phase of an effort to optimize recruitment and retention of subjects for a multicenter trial of DBS in early-stage PD by focusing on patient priorities, concerns, and experiences across the spectrum of involvement. Vanderbilt University successfully recruited 30 subjects for a pilot trial evaluating the safety and tolerability of DBS for the treatment of early-stage PD, thereby meeting the study's recruitment goal. Only one subject subsequently withdrew from the study, and did so very early on, after the patient's initial baseline assessment. Determining what factors contributed to the high enrollment and retention is important if such success is to be replicated in subsequent trials. The primary utility of these investigations is to analyze the feasibility and to provide more accurate estimates of recruitment and retention for a much larger planned multicenter pivotal trial.

In the first phase of this process of examination, Vanderbilt University researchers, in collaboration with MJFF, explored the perspectives of patients who would qualify for the planned trial [11]. In the second phase of investigation presented here, patients who have undergone a single-center pilot trial were surveyed after completion of the trial and their responses are reported here. While the two surveys queried nearly identical populations with regard to both demographics and disease duration (Table 1), the cohorts differed fundamentally in one notable respect. Whereas the Fox Insight survey explored the views of patients with early-stage PD considering hypothetical participation in a future DBS trial, the pilot trial survey retrospectively queried perceptions of subjects who actually completed a DBS clinical trial of a like design.

The surveys, therefore, are most powerful when considered together since they provide insight into the opinions of patients with early-stage PD with complementary experiences, those considering participation in a DBS trial, and those who have just completed a DBS trial. The demographic similarities of the two populations facilitates qualitative comparison between results from the pilot trial survey and the Fox Insight survey (Table 1). The similarities are not accidental, since the Fox Insight survey by design used similar inclusion criteria as the pilot trial for survey selection, which will also be used in the planned pivotal trial.

Beyond the potential for personal benefit, both pilot trial subjects and Fox Insight survey respondents endorse a strong sense of altruism as a primary motivating factor for trial participation: they want to help themselves, but more importantly, they want to help others. The most reported motivation for participating in the pilot trial was to advance medical treatment for PD (85%), demonstrating a collective sense of identity among patients who suffer from PD. The second most common motivating factor was to receive the best medical treatment for PD (70%). The same interaction of macro and micro level motivations was observed through the Fox Insight survey results which indicated the desire to help research and future patients with PD (75% and 81%, respectively) was nearly as important as was the possibility of slowing PD symptoms (92%) or receiving health benefits from DBS (84%) [11].

With regard to potential impediments to participation in a DBS trial, respondents of both studies listed fear of DBS surgery or concern for PD worsening during trial participation as the major barriers to participation. Interestingly, these concerns were much greater for Fox Insight survey respondents who had not participated in a trial (85% and 87%, respectively) than pilot trial survey respondents who had completed the trial (44% and 19%, respectively). Possible reasons for this dichotomy may be due to the fact that once a risk has passed without realization (no major complications were observed in the pilot trial), the recalled pre-trial fear of the possible poor outcome may be altered (i.e., recall bias) [16]. Another possibility is that the pilot trial self-selected a cohort of subjects with less fear of potential risks and thus a greater willingness to participate. The retrospective

design of the pilot survey is a limitation with regard to all responses since the low rate of complications influences the respondents recall bias to all questions regarding pre-trial patient considerations.

Patients also weigh the possible burdens a trial may impose when considering enrollment and continued participation in a trial. While financial commitment, neuropsychological testing, and washout periods were identified as the primary burdens of participation in the pilot trial (Table 2), only two respondents, both randomized to ODT, reported considering withdrawal. Thus the vast majority (93%) of pilot trial survey respondents did not report contemplating withdrawing from the trial, a significantly higher percentage than the 75% of interested Fox Insight respondents who indicated they would be unlikely to withdraw.

More importantly, nearly half (46%) of pilot trial respondents randomized to DBS+ODT reported no drawbacks to trial participation, and 92% would recommend DBS to other patients with PD. These results suggest that subjects with PD enrolled in similarly designed trials may also perceive only modest burdens associated with participation and are unlikely to consider withdrawing.

Subject education on procedural expectations of clinical trials is known to influence overall satisfaction of participation [17]. Pilot trial survey respondents reacted positively to the trial's multistep enhanced informed consent procedure (Table 2). This process aimed to educate potential subjects on their role in the study. The extensive subject education prior to enrollment likely contributed to the extremely low dropout rate in the pilot trial (3%) [8, 9]. The same enhanced informed consent procedure will be implemented in the future pivotal trial. Additionally, pilot trial survey respondents noted very high rates of satisfaction with staff and clinicians, open communication, familial and clinician support, and the thoroughness of information provided about the study and procedures.

The results of the presented pilot survey and the preceding Fox Insight survey are not only congruous with each other, they are also consistent with prior studies. A cross-sectional study of 91 patients with PD enrolled in multiple clinical trials between 2002 and 2007 also found advancing medical research and receiving the best medical treatment as key motivation factors among respondents and the risk of adverse effects as a major concern [4]. In another study examining the reluctance of patients with PD to undergo DBS surgery, fear of side effects was similarly identified as a primary deterrent to pursuing the therapy [6]. The study examined 186 patients with PD who underwent DBS surgery, noting that preoperatively, the patients were nearly equally divided into groups categorized as either reluctant or nonreluctant to DBS. A shift in attitude of those originally reluctant to DBS was then noted and attributed primarily to increased confidence in their clinician's recommendation, encouragement from family, financial assistance for surgery, and learning more about DBS [6]. The findings support the contention that addressing pre-surgery experiences and decision factors can significantly reduce fear of DBS for PD and heighten trial retention.

There are limitations to this analysis. The retrospective pilot trial survey required respondents to remember feelings and events from the early phase of trial involvement, at time many years prior, introducing the possibility of recall bias. Time and subsequent experiences, including personal pilot trial experiences, allow for memory inaccuracies and hindsight bias, which potentially influenced responses [16]. Optional survey participation introduced selection bias, potentially skewing responses. Although optional survey anonymity encouraged honesty, underlying or unrealized motivations, such as the desire to be a good subject, possibly influenced responses [16]. Similar motives could have also influenced Fox Insight respondents. Fox Insight survey respondents indicated high levels of interest; however, their membership and active participation on the MJFF website suggests they represent a very motivated cohort of patients with early-stage PD. Additionally, the pilot trial was an open-label study for subjects in which half were randomized to receive DBS, while the Fox Insight survey asked respondents to consider a double-blind trial in which all subjects would receive a DBS system but be randomized to active versus inactive stimulation during the two-year trial.

Results from a patient satisfaction survey provide information about the expectations and experiences of subjects who completed the DBS in early-stage PD pilot trial. Their experience-based responses parallel the motivational factors and concerns identified by an independent cohort of patients with early-stage PD considering participating in a DBS trial queried through Fox Insight, as well as those of patients with PD who underwent DBS both within and outside the confines of a clinical trial. The FDA has approved the conduct of a prospective, randomized, double-blind, phase III, multicenter, pivotal clinical trial

evaluating DBS in early-stage PD (IDE#G050016). The high level of interest expressed by potential subjects through the Fox Insight survey is encouraging for recruitment and retention in the future trial. Furthermore, similarities in motivations and concerns of both past and potential subjects, in conjunction with a well-constructed study design, suggests the successful recruitment and retention observed in the pilot trial may be replicated in the future multicenter, pivotal trial of DBS in early-stage PD.

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CONFLICT OF INTEREST

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