Stuart G. Finder and Mark J. Bliton, "Fortitude and Community: Response to Yee and Ford," *The Journal of Clinical Ethics* 23, no. 3 (Fall 2012): 221-3.

# Fortitude and Community: Response to Yee and Ford

*Stuart G. Finder and Mark J. Bliton*

**ABSTRACT**

We revisit questions about the scientific status of the pilot Phase I study of deep brain stimulation (DBS) in early stage Parkinson's disease (PD), as well as questions about enrolling and retaining subjects. In doing so, we highlight a compelling ethical dimension reported to us by patients thinking about becoming research subjects in that study.

In their commentary,[1] Yee and Ford are troubled by what they contend is the uncritical application of pharmaceutical-study frameworks to the conceptual design and description of surgical trials in general and the study of DBS in Early Stage PD in particular. In light of what we learned from responses we received via the ethics questionnaires completed by 22 patients suffering from PD, as reported in this issue of *JCE,*[2] we share their general concern. Likewise, we think researchers, as well as bureaucracies that provide research oversight, should pay more careful attention to patients' understandings and attitudes when planning, organizing, developing, and implementing clinical research.

Indeed, any uncritical application of research frameworks that neglects this necessary attention, and thus fails to be responsive to how patients make a meaningful decision to become a research subject, similarly fails to fulfill the obligations at the root of the informed consent process (in research *or* clinical contexts): to not take advantage of those who are vulnerable.

Nonetheless, Yee and Ford suggest that our work fell into the trap of such a "regulatory misconception" due to our continuing to use the language of "pilot Phase I study," and by our explicit anticipation of the possibility that potential subjects might be vulnerable to issues associated with therapeutic misconception. Focusing on the safety of the DBS device, Yee and Ford contend the patients completing the ethics questionnaires likely understood the questions differently from what we thought we were asking because the safety and tolerability of the device were well established "for several indications, including essential tremor, dystonia, and later stage PD." Then, while confusing "early onset PD" with early stage PD, Yee and Ford go on to say, "the trial for DBS in early onset PD uses the most common, well-studied brain site for treating PD symptoms." Apparently based on the presumption that the stages of PD have a well-understood progression and expression of symptoms, a presumption that runs counter to both patient experience and the medical literature, they state, "the only difference in the Early Stage PD trial is that an intervention is being used earlier in the stage of the disease." On that basis, they conclude, "reasonable patients can already request DBS for early stage PD from their surgeon as an off-label use. . . . It is reasonable that research subjects would participate in a DBS Early Stage PD trial to gain access to the therapy, despite not knowing the

**Stuart G. Finder, PhD**, is Director of the Center for Healthcare Ethics and Associate Professor of Surgery and Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California, *stuart.finder@cshs.org.*

**Mark J. Bliton, PhD,** is Director of Medical Bioethics at Kaiser Permanente Los Angeles Medical Center.

longer term effects, because the procedure is most likely not covered by insurance."

In short, the "regulatory misconception" trap is that "subjects/patients may reasonably want access to the immediate therapeutic benefit of symptom relief," and likewise may not "be interested in long-term disease modification and side-effects." Finally, then, because such aims are "not a goal to which the Phase I label applies," Yee and Ford go on to surmise that the responses of potential subjects (regarding their understanding of the DBS in Early Stage PD study) are likely to be misinterpreted.

Yee and Ford's focus on device safety raises considerations pertinent to surgical clinical trials in general, that much is clear. While that focus continues to be an important area of discussion, we think their commentary misses several crucial points relevant to the ethical dimensions of the DBS in Early Stage PD study in particular. A little more background about the DBS study, and our involvement in it, can thus help to clarify several issues specific to this research.

Three particular points merit mention. First is the scientific status of the DBS study and associated issues of uncertainty. The second concerns two secondary aims of the DBS study: enrolling enough participants and retaining them. Finally, there is the issue of how prospective participants think about and enact their commitment to research in order to help others.

In late 1999 our colleague David Charles, MD, invited us to join his research team; they were finalizing plans for a proposed multicenter randomized controlled trial (RCT) of bilateral DBS of the subthalamic nuclei (STN) in 200 patients with early stage PD. The primary aim of that proposed study was to determine if such DBS would be neuroprotective, that is, would delay the development or slow the progression of Parkinsonian motor symptoms. The motivation for Charles's invitation was his appreciation that potential subjects completing an informed consent document does not necessarily correspond with an understanding of the substantive concerns motivating the need for such forms in the first place. He thus asked us to develop an explicit ethics consultation component within the informed consent process that could better ensure that potential subjects were not only adequately informed, but also would have the necessary understanding of both the research and their participation in it.

Reviews by panels from both the National Institutes of Health and the Food and Drug Administration (FDA), over the course of three years, resulted in the study becoming recast as a pilot Phase I study. Part of the concern was scientific in nature. The FDA was still at the beginning of the process for approving DBS as an intervention for management of refractory PD. In addition, although there was some evidence suggesting DBS of the STN might have neuroprotective results for refractory PD patients,[3] the mechanisms associated with loss of the dopaminergic neurons believed to be the cause of progression of PD were not well understood[4]—and *still are not* well understood.[5] Moreover, because early stage PD brains present a different physiological and clinical picture than that of late stage PD, the potential benefits of neuroprotection by using DBS in early stage PD could only be said to be theoretical. Finally, there was as yet no well-established length of time for the medication wash-out necessary to achieve valid evaluation of symptoms, and the validity of the wash-out needed to be established to generate accurate data for comparisons between the two arms of any future RCT.

Yee and Ford may not have appreciated concerns about safety and tolerability created by the wash-out of medications *for both study arms.* Whether subjects were randomized to receive DBS plus optimal medical therapy or to receive optimal medical therapy alone, every six months for two years (five times total) subjects would return to the research site for an eight-day inpatient evaluation. At that time, DBS and PD medications would be withheld from subjects in the first (surgical) arm, and all PD medications would be withheld from subjects in the second (medical therapy) arm. The needed commitment of subjects should not be missed; yet with their critique of the dominance of pharmaceutical-study frameworks, Yee and Ford maintain a kind of privileging for *safety* as the most significant aim of Phase I trials. As a result, concerns about *tolerance,* in the sense of subjects' ability to tolerate, for example, the rigors of research, seem to be "second fiddle."

Two practical considerations are therefore raised by both randomization and the 40 days (and 40 nights) of follow-up evaluation. First, given the combination of scientific uncertainty and that patients qualifying for a study of DBS in early PD would likely have years of expected adequate response to standard drug therapy, a choice to participate entails taking a set of significant surgical risks. There was thus a reasonable question whether there would be enough interest among potential subjects.

Second, there was considerable discussion about whether, once recruited and enrolled, subjects could be retained due to the study design. Why? In short, if potential subjects felt participation would provide the potential to achieve a therapeutic advantage through early DBS, what would be their response if they were randomized to optimal medical therapy? In other words, if their participation was motivated by a desire to be randomized to the DBS arm, but they were randomized to the control arm of optimal medical treatment, they would confront a simple-to-state, but morally challenging question: "Why should I stay in the study?"

As typically articulated, the reason to remain in a study, even if randomized to a control arm, is that subjects *understand and accept* the idea that participation is for the sake of research, and not primarily for their own physical health. In the context of this study, that sort of understanding and acceptance, even commitment, would be needed for participants to stay enrolled and not drop out during the eight-day-long follow-up stays that include wash-out of all medications. In full recognition that participation in clinical research is voluntary and subjects are free to withdraw at any time, our work was thus designed, in part, to learn what potential subjects were *actually considering* when facing the prospect of such a commitment.

It is that kind of commitment—in the face of vulnerabilities associated with having a progressive and likely terminal disease that may rest on a kind of moral courage—that needs to be understood by future participants and researchers. As Hans Jonas recognized 30-plus years ago, subjects who make a gift of themselves in submitting their bodies to the rigors of scientific and clinical examination, move beyond a mundane sense of obligation to a "larger sphere of moral value."[6] Similar to what Jonas noted when he said the ethical dimension of that sphere "reaches into the sublime solitude of dedication and ultimate commitment,"[7] what potential subjects conveyed was a fortitude forged in dedication and ultimate commitment to others who may have PD in the future.

We found that patients facing the prospect of becoming subjects in a surgical trial such as the DBS in Early PD study do not do so naïvely, nor do they do so without any number of concerns about responsibility. Indeed, their sense of making a commitment within a "larger sphere of moral value" appears to be crucial for making sense, not merely of coming to accept whatever may befall them due to randomization, but also of having PD, and as such, belonging to a community of others who are similarly afflicted.

**NOTES**

1. K. Yee and P.J. Ford, "Regulatory Misconceptions Muddies the Ethical Waters: Challenges to a Qualitative Study," in this issue of *JCE.*

2. S.G. Finder et al., "Potential Subjects' Responses to an Ethics Questionnaire in a Phase 1 Study of Deep-Brain Stimulation in Early Parkinson's Disease," in this issue of *JCE.*

3. P. Limousin et al., "Electrical Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease," *New England Journal of Medicine* 339, no. 16 (1998): 1105-11; F.J. Vingerhoets et al., "Subthalamic DBS Replaces Levodopa in Parkinson's Disease: Two-year Follow-up," *Neurology* 58, no. 3 (2002): 396-401.

4. E. Bezard et al., "Relationship between the Appearance of Symptoms and the Level of Nigrostriatal Degeneration in a Progressive 1-Methyl-4 Phenyl- 1,2,3,6-Tetrahydropyridine-Lesioned Macaque Model of Parkinson's Disease," *Journal of Neuroscience* 21, no. 17 (2001): 6853-61.

5. R. Gordon et al., "Proteolytic activation of proapoptotic kinase protein kinase Cδ by tumor necrosis factor α death receptor signaling in dopaminergic neurons during neuroinflammation," *Journal of Neuroinflammation* 9, no. 82 (2012): 82.

6. H. Jonas, "Philosophical Reflections on Experimenting with Human Subjects" in *Philosophical Essays: From Ancient Creed to Technological Man* (Chicago: University of Chicago Press, 1974), 105-31.

7. Ibid., 119.