Kimberly M. Yee and Paul J. Ford, "Regulatory Misconception Muddies the Ethical Waters: Challenges to a Qualitiative Study," *The Journal of Clinical Ethics* 23, no. 3 (Fall 2012): 217-20.

# Regulatory Misconception Muddies the Ethical Waters: Challenges to a Qualitative Study

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**ABSTRACT**

In "Potential Subjects' Responses to an Ethics Questionnaire in a Phase I Study of Deep-Brain Stimulation in Early Parkinson's Disease,"[1] Finder, Bliton, Gill, Davis, Konrad, and Charles undertake informed consent research on what they describe as a Phase I trial of deep brain stimulation (DBS) for Parkinson's disease. We argue that the authors should have more carefully characterized the nature of the DBS study at the start of their clinical study.

The application of pharmaceutical frameworks for conceptualizing and describing surgical research trials continues to muddy the ethical waters when it comes to informed consent. In this issue of *The Journal of Clinical Ethics,* Finder and colleagues fall prey to a type of "regulatory misconception" among those who design, review, and regulate surgical research trials that is of particular ethical importance.[2] These authors express a concern that potential research subjects might mistakenly understand the use of deep brain stimulation (DBS) at the early stage of Parkinson disease (PD) "as a kind of step forward, of getting treatment earlier, and hence as a way of gaining therapeutic advantage." The authors imply that since the study is conceptualized as a Phase I trial ( a trial conducted to establish safety and tolerability only) in an early disease population, that potential subjects could suffer under a therapeutic misconception (TM) due to vulnerability. In pursuing an understanding of subjects' attitudes, the authors provide important narrative data on which to reflect about informed consent in complicated surgical device research. However, TM cannot be properly demonstrated in the analysis of their ethics endeavor due to a regulatory misconception used by the scientific investigators to frame their clinical study.

It appears that the research participants answered a different set of questions than the ethics researchers thought they were asking. This study serves as an example of problems in the current designing and framing of complicated surgical trials in which both research and therapeutic components exist. The report by Finder and colleagues provides an opportunity for further discussions on these broad challenges. Using a "Phase I" label for the DBS for Early

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Stage PD[3] trial is accurate only in the framework of disease modification as a goal, and not regarding whether the subjects could reasonably expect improvement in their current symptoms. To describe the study in this manner leads researchers and subjects away from a more robust understanding of the relationships between the intervention (DBS) and the research endeavor. The National Institutes of Health states that Phase I clinical trials are done to test a new biomedical or behavioral intervention in a small group of people (for example, 20 to 80 subjects) for the first time to evaluate safety.[4] The governmental web repository *clinicaltrials.org* defines Phase I trials as "initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients."[5] The DBS for Early Stage PD study does not clearly fit either of these definitions and is not truly a Phase I trial with respect to testing the safety of placing a DBS lead in the subthalamic nucleus (STN) to control PD-related symptoms.

The safety and tolerability of the DBS device is well established in humans for several indications, including essential tremor, dystonia, and later stage PD.[6] Unlike the controversy regarding the humanitarian device exemption[7] granted for the use of DBS for obsessive compulsive disorder, in which Fins and colleagues argued that a new brain site constituted a different set of potential risks,[8] the trial for DBS in early onset PD uses the most common, well-studied brain site for treating PD symptoms, that is, the STN. The only difference in the Early Stage PD trial is that an intervention is being used earlier in the stage of disease. Further, trials of complex brain devices often have a very small *n*, even for more pivotal trials, so the number of subjects is not the controlling factor for the label of Phase I for this trial. Finally, the study is a randomized control trial with blinded reviewers, which does not normally occur in a safety and tolerability study. In shoehorning the study into a Phase I description, the nature of the weight of prior evidence about the safety and efficacy of the devices is forgotten.

The researchers conducting the underlying DBS Early Stage PD trial should be lauded for trying to break the standard surgical research mold in undertaking a pilot study prior to a wide scale adoption of "hundreds of thousands" of patients in the early stages of PD. The development of research in trials for substantially similar surgical approaches often takes place only after a procedure has been adopted as a preferred care path. Ashton and colleagues make this point nicely: "When randomized trials of an invasive procedure are conducted, it is often after the procedure has been widely used in some cases in hundreds of thousands of patients and doubts have emerged about its utility."[9]

Although the researchers in this DBS Early Stage PD study have avoided this error of only doing a study after wide scale adoption, they have made a different type of error in characterizing their pilot study as a Phase I study. Reasonable patients can already request DBS for early stage PD from their surgeon as an off-label use—but with little chance of reimbursement from insurance. Under the guidelines of the Centers for Medicare & Medicaid Services (CMS), STN DBS for PD is reimbursable for advanced idiopathic PD and persistent disabling PD symptoms or drug side-effects.[10] 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 longer term effects, because the procedure is most likely not covered by insurance. The research subjects would be under no misconception about the reasonable expectation that DBS would help to control PD symptoms, such as tremor, in the near term. Finder and colleagues concede this when they write, "if individuals thought they were likely to take the risks of surgery eventually . . . they might have elected to take these risks now when healthier. Taken together, their decision to enroll could be understood as proactive (as opposed to being based on misunderstanding)."[11] The research subjects/patients may reasonably want access to the immediate therapeutic benefit of symptom relief (not a goal to which the Phase I label applies) and not be interested in long-term disease modification and side-effects.

This type of regulatory misconception, wrongly labeling a study, can lead to weak ethical analogies between similarly labeled trials. Whether this is utilized as casuistry or some less formal way of thinking, it poses a challenge to ethical reasoning. Finder and colleagues make this slip when they cite the similarity of their findings to another informed consent review for a Phase I PD trial. The comparator is a gene transfer trial for an intervention that has no proven indication for PD, or any other disease.[12] The cited study is an early stage safety and tolerability trial looking at the outcomes of when the insertion of an adenovirus with a gene transfer payload was placed into the STN. The surgical research trial that Kim and colleagues cite in this article is truly a Phase I trial. The stage of development and knowledge of STN DBS is far more advanced than for gene transfer technology, which makes a substantial moral difference in the potential applicability of the comparison. Consistency of conceptualization and labeling of trials provides an opportunity to properly compare the foundational elements of study for an ethical analysis.

The study underlying the article by Finder and colleagues may have been more properly compared to the Phase III study entitled Early Randomized Surgical Epilepsy Trial (ERSET). ERSET was designed as a prospective study evaluating the efficacy of standard surgical treatment for patients with earlier stage refractory epilepsy than what is usually indicated. The subjects were randomized to receive either continued medical therapy alone or resective surgery.[13] This is an appropriate comparison because resective brain surgery for later stage epilepsy has been proven to be just as effective as DBS for later stage PD. Characterizing the early DBS trial as a Phase II or III trial, as with ERSET, would have provided a better ethical analogy and a much stronger argument.

There may be hesitancy to expand the enrollment numbers needed for a Phase II trial in a population earlier in their disease course because of a perception that these are a particularly vulnerable population. However, the cohort of patients with early onset PD is less vulnerable in several ways than the late stage PD patients who have participated in research in past trials. The early stage cohort has not yet exhausted oral medications and has not suffered the debilitating symptoms of PD for years. Hence, they should be considered less medically or situationally vulnerable than those who have been already enrolled for DBS studies for late stage disease. In this way, vulnerability should be less of a concern for consent of these individuals and should not make researchers hesitant in designing larger scale trials.

This brings us to the ethics questionnaire composed of 13 open-ended questions used to gage participants' understanding for safety and tolerability of neurostimuation in early stage PD found in the article by Finder and colleagues. For the investigators, the questionnaire is framed perfectly as focusing only on the Phase I portion of the DBS project, that is, to find dosage and tolerability of devices that may later lead to a longitudinal study of whether a device is disease modifying by being neuroprotective. However, reasonable research subjects are going to provide answers to the questionnaire framed in terms of the whole process of receiving DBS that has been proven to ameliorate (even if it is for a shorter time) standard PD symptoms such as tremor. This becomes clear in the ways in which these individuals answered the questions as reported by Finder and colleagues. The respondents understood that getting DBS will likely help their symptoms such as tremor. Unfortunately, because this was a survey rather than an in-person interview, the investigators were not in a position to probe further for an understanding of the perceived mismatch or interpretation. In the end, the ethics investigators tried to ask questions only about the research study portion that was characterized as safety and tolerability. Generally, the research subjects seem to answer in a more holistic fashion about symptom improvement and early access to therapy. The authors' data and our reflections call attention to the need to reconfigure frameworks and labeling for surgical device trials. The new paradigm of consent of focusing on the "meaning" of the voluntary research participation that Finder and colleagues believe is needed must start with a bet-

ter characterization of the whole endeavor to which research participants are agreeing.

**NOTES**

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

2. This is a version of the larger problem of collapsing categories or over inclusion of kinds within a category in such a way as to undermine the meanings or create stereotypes that do not properly apply to an entire class of objects or ideas.

3. P.D. Charles et al., "Deep brain stimulation in early Parkinson's disease: Enrollment experience from a pilot trial," *Parkinsonism & Related Disorders* 18, no. 3 (2012): 268-73; "Deep brain stimulation (DBS) for early stage parkinson's disease (PD)," 2012, *http://clinicaltrials.gov/ct2/show/NCT00282152?term=b-stn+dbs+early+stage+PD&rank=1,* accessed 30 August 2012.

4. "Glossary of Terms for Human Subjects Protection and Inclusion Issues," 2001, *http://grants.nih.gov/grants/peer/tree_glossary.pdf,* accessed 30 August 2012.

5. "Glossary of clinical trials terms," 2008, *http://clinicaltrials.gov/ct2/info/glossary# phasel,* accessed 30 August 2012.

6. G. Deuschl et al., "A randomized trial of deep-brain stimulation for parkinson's disease," *New England Journal of Medicine* 355, no. 9 (31 August 2006): 896-908; P. Krack et al., "Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced parkinson's disease," *New England Journal of Medicine* 349, no. 20 (13 November 2003): 1925-34; K. Ostergaard and N. Aa Sunde, "Evolution of parkinson's disease during 4 years of bilateral deep brain stimulation of the subthalamic nucleus," *Movement Disorders: Official Journal of the Movement Disorder Society* 21, no. 5 (May 2006): 624-31.

7. "Humanitarian Device Exemption," 2010, *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm,* accessed 30 August 2012. A humanitarian use device (HUD) is a device intended treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the U.S. per year. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions that affect small patient populations. The HUD provision of the U.S. Food and Drug Administration (FDA) regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases that affect small populations. To obtain an HUD approval, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that a device is effective for its intended purpose. The application, however, must contain sufficient information for the FDA to determine that a device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment

8. J.J. Fins et al., "Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder," *Health Affairs* 30, no. 2) (February 2011): 302-11. A device manufacturer must demonstrate that no comparable devices are available to treat or diagnose the disease or condition and that they could not otherwise bring the device to market. An approved HDE authorizes marketing of an HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated.

9. C.M. Ashton et al., "Ethics and methods in surgical trials," *Journal of Medical Ethics* 35, no. 9 (1 September 2009): 579-83.

10. Decision memo for deep brain stimulation for parkinson's disease (CAG-00124N), *http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx@@@NCAId$$$21***NcaName$$,* accessed 30 August 2012.

11. See note 1 above.

12. S.Y. Kim et al., "An approach to evaluating the therapeutic misconception," *IRB* 31, no. 5 (September-October 2009): 7-14.

13. J. Engel et al., "Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy: A Randomized Trial" *Journal of the American Medical Association* 307, no. 9 (9 March 2012): 922-30.