Published in final edited form as:
IRB. 2009 ; 31(5): 7–14.

An Approach to Evaluating Therapeutic Misconception

Scott Y. H. Kim, MD, PhD,
Associate Professor in the Department of Psychiatry, the Bioethics Program, and the Center for Behavioral and Decision Sciences in Medicine, University of Michigan, Ann Arbor, MI

Lauren Schrock, MD,
Clinical Fellow in the Department of Neurology, University of California, San Francisco

Renee M. Wilson, MA,
Associate Project Manager in the Department of Neurology, University of Rochester, Rochester, NY

Samuel A. Frank, MD,
Assistant Professor in the Department of Neurology, Boston University School of Medicine

Robert G. Holloway, MD, MPH,
Professors in the Departments of Neurology and Community & Preventative Medicine, University of Rochester

Karl Kieburtz, MD, MPH, and
Professors in the Departments of Neurology and Community & Preventative Medicine, University of Rochester

Raymond G. De Vries, PhD
Professor in the Departments of Medical Education, Obstetrics & Gynecology, Sociology and the Bioethics Program, University of Michigan

Abstract

Subjects enrolled in studies testing high risk interventions for incurable or progressive brain diseases may be vulnerable to deficiencies in informed consent, such as the therapeutic misconception (TM). However, there is a continuing debate about the definition and measurement of TM, making assessments of TM controversial. In this qualitative pilot study of persons enrolled in a phase I test of gene transfer for Parkinson's disease, we developed and tested an interview guide focusing on how the subjects made their decision to participate, with an emphasis on understanding the *subject* as the unit of interest, rather than focusing only on isolated statements. The results indicate that a subject's understanding of the purpose of research is best explored in juxtaposition to the subject's motivation for participation. Doing so reveals potential avenues for measuring and preventing TM.

Keywords

informed consent; gene transfer; Parkinson's disease; therapeutic misconception; qualitative research

Corresponding author: Scott Y. H. Kim, MD, PhD, Bioethics Program, 300 North Ingalls Street, 7C27, Ann Arbor, MI 48109, USA, 734-936-5222, fax 734-936-8944, scottkim@med.umich.edu.

This study was reviewed and deemed exempt by the Institutional Review Boards at the University of Rochester and the University of Michigan.

Parkinson's disease is a progressive, incurable neurodegenerative disorder. Because medications become less effective and more burdensome as the disease progresses, there is an increasing focus on novel interventions to treat PD, including deep brain stimulation, gene transfer, and cell transplants.[1] In addition to Parkinson's disease, scientists are using invasive methods to target other nervous system conditions such as tetraplegia,[2] dementia,[3] disorders of consciousness,[4] refractory mood and anxiety disorders,[5] Huntington's disease,[6] and other conditions.[7]

A natural worry is that persons with severe neurological or psychiatric disorders may be so desperate for a cure that they are particularly vulnerable to exploitation in such high risk research studies. Given the widespread concerns about the therapeutic misconception (TM) in research, it is natural to ask how vulnerable such persons are to TM. It is becoming increasingly apparent that this is not a straightforward question. Although TM was first described over twenty-five years ago by Appelbaum et al.,[8] the concept remains unsettled. Some authors have questioned the ubiquity and ethical importance of TM,[9] others have suggested a classification of TM related phenomena,[10] while still others have expanded the categories of ethical concern.[11] Two research teams have recently reported a high prevalence of TM,[12] but these teams acknowledge that there is a "lack of agreement in the conceptual literature, [researchers] have not defined or measured [TM] in the same way"[13] and that TM has been "used by various authors to denote a number of related, but not always identical, concepts" and "…there is not yet a consensus about how to operationalize TM."[14]

A recent workshop report on the "draft dimensions" of TM demonstrates the continuing evolution of the topic.[15] The report notes the disagreements among the authors and proposes the following definition: TM occurs when individuals fail to understand that the "defining purpose of clinical research is to create generalizable knowledge." The definition explicitly excludes (because of a lack of consensus) any statement regarding whether therapeutic benefit from a trial can be "counted as a study purpose," and whether overestimation of benefits is part of TM. In this context of considerable disagreement among bioethicists, there is also a recognition that research subjects often make statements that are apparently inconsistent[16] or statements that are in some degree of tension. In particular, a significant proportion of persons who are motivated by, and perhaps expect, therapeutic benefit from early phase gene transfer trials apparently do so despite showing understanding of the scientific purpose of the research.[17]

Given this wide range of ideas about, and definitions of, TM, we began a research program that steps back from the traditional approach that defines TM a priori and then examines isolated statements of research subjects to see if they indicate TM. Instead, our approach examines the key domains discussed in the TM literature—domains such as motivation for participation, understanding of science, perception of and attitude toward benefits and risks, etc.—in the context of the overall decision-making process of the subjects. This approach emphasizes the *research subject* as the unit of interest, *in addition to* focusing on the isolated statements made by the subject. We report here on a pilot interview study of subjects enrolled in a highly invasive, early phase, first in human gene transfer experiment for Parkinson's disease. Our goal was to test an interview guide designed to elicit a narrative of how subjects decide to participate in high risk research studies and to analyze their responses by focusing not only on their specific statements in isolation but also to contextualize them within each subject as the unit of interest.

METHODS

Participants

The subjects were individuals who had participated in a phase I gene transfer trial. They had undergone a neurosurgical procedure that inserted an adeno-associated virus (AAV) borne glutamic acid decarboxylase (GAD) gene into the subthalamic nucleus.[18] Subjects had advanced PD; their main alternatives for treatment were deep brain stimulation or other surgical intervention. Exclusion criteria for the gene-transfer study included substantial cognitive dysfunction on neuropsychological testing, medical contraindication to surgery, secondary or atypical parkinsonism, and substantial psychiatric illness. More details of the subject's characteristics and of the phase I gene transfer study can be found elsewhere.[18]

Eight of the twelve subjects enrolled in the trial participated in our interview study. Three subjects did not wish to be contacted; one subject declined after initially agreeing. The average age of interview participants was 60.5 years (SD 6.4) and 7 of 8 subjects were male. (Below, we refer to all subjects in the masculine to avoid identifying the female subject. Also, subject numbers used below do not correspond to order of entry into the phase I study.) The average number of years since diagnosis of our interviewed subjects was 10.6 years (SD 3.4) (range 7–15 years). The subjects were interviewed on average 21 months after the gene transfer surgery (range 14 to 29 months).

Procedure

Telephone interviews were conducted by RW. Detailed notes were taken during all interviews. Six of the eight interviews were also audio-taped (technical problems occurred during the interviews with S6 and S8) and transcribed.

Measures

Conditional Probe Interview (CPI)—The CPI is a semi-structured interview guide. It elicits a chronological narrative of how the subject came to make the decision to participate while exploring the subject's motivations (including perception of direct benefit, and any rationales underlying them), understanding of the purpose and design of the research (including their subjective reactions to them), and perception and attitudes toward risk and potential societal benefits (including probes for any active altruistic motivations). Each section begins with open- ended stem questions. The interviewer encourages as much spontaneous response to these stem questions as possible. Based on previous studies and existing literature, the CPI contains well-developed probes and clarifying questions that anticipate the need to follow up in order to clarify meanings of general statements that research participants make. The interview takes about 45–60 minutes. The CPI is available from the corresponding author.

Analysis

The transcripts (or, in 2 cases, detailed notes) were read by two of the authors, in order to develop a preliminary coding scheme. Then, for the purposes of this report, four of the authors read the transcripts and notes, guided by two goals. First, the transcripts were specifically coded for the domains listed in the Table, focusing on the subjects' motivation for participation, understanding of the purpose of the research, other influences on decision-making, and—of particular importance to contextualizing the subject's various statements in juxtaposition to each other—how they related their understanding of the purpose with their motivation for participation. Second, novel or recurring themes contributing to the decision-making were noted. Coding was finalized during a conference of four coders. During the conference, each transcript was reviewed in detail: codes were compared and a consensus

achieved through discussion. Throughout the analysis, the statements of an individual subjects were not just coded individually but also were examined together for that subject, as seen in the Table, in order to provide a understanding of each subject as a unit of interest.

Human Subjects

This interview study was deemed exempt by the Institutional Review Boards at the University of Rochester and the University of Michigan.

RESULTS

The results of the analysis are summarized in the Table.

Motivation for Participation

Despite the fact that the GAD gene transfer study was a phase I study, the prospect of potential therapeutic benefit was a prominent theme for all but one subject. Five subjects clearly stated that their primary motivation for participating in this phase I study was a desire for therapeutic benefit. For example, S2 stated that "it was more of a selfish thing" and that his "biggest motivator was that outside long shot chance that this thing would work." Some of these five subjects did mention a motivation to help others but overall that motivation appeared to play an uncertain role. S4: "My main goal, the bottom line, was to get better. The second goal was to help other people… I: So your first goal was to get better yourself? S: Yeah, get better. Absolutely." Or as another subject put it, "Really, I must say I wasn't altruistic. I wasn't. To be perfectly honest, I didn't think in those terms about doing it for the science and the world, although later on I said, 'well, if I could help somebody else, if this helps somebody else, it would be fine.'"(S7) Another subject (S3), when asked whether he would have considered participating if he knew ahead of time that he would not benefit and that the only benefits would be scientific and societal, replied, "On a scale of 1 to 5, it probably would have been a 3."

There were two subjects (S1 and S8) who expressed therapeutic benefit as at least one of their motivations but who did appear to have another active motivation. As one subject (S1) put it, "My feeling was that I wanted to be involved in something that if I didn't get help, maybe my contribution would help other people;" he went on to say the two motivations "were a tie." What distinguished these two subjects was that when asked whether they would have participated even if they had known that there was no chance of personal benefit, they stated they would have. S8 gave an affirmative answer even though he said his *primary* motivation was a benefit to himself. But he made it clear that self-benefit was not his only motivation, at one point noting that his primary care doctor had tried to dissuade him from enrolling in the gene transfer study, asking "why not let someone else try it?" S8 explained that if no one volunteers, then we'd have no progress in advancing research, and that someone has to "step up to the plate." Thus, these two subjects were qualitatively different from those who mentioned helping others as a reason but for whom altruism as an independent motivating role was less certain.

We categorized one person (S6) as an altruist because his primary motivation was the desire to help future patients with PD by volunteering for the study. Although he stated that hope for personal benefit was a motivator, he added it "would be ridiculous" to expect benefit. He talked about how scientific advance is incremental, about how he wanted to "give back," and spoke extensively about how he could not imagine being selfish and how he wanted to help advance research and science of PD. Indeed, he felt that he was a good candidate for the study because he had no family to worry about.

Understanding of Purpose of Study

Thus, at least one element that often raises concerns about TM—subjects' focus on therapeutic benefit in a phase I study—was present among these subjects. How did this focus on personal therapeutic benefit affect the subjects' understanding of the purpose of the research?

We found one subject (S7) in whom the desire for therapeutic benefit affected his understanding of the purpose of the research. His lack of understanding seems to have resulted from a lack of caring about the purpose of the study because he was so focused on what might happen to him: "I: What did you think was the main purpose? S7: Umm. You know the truth is I don't know. I don't know what I thought…I really don't remember thinking about what they were trying to accomplish as much as how it was going to affect me"; and, "I wasn't sure at the beginning, to tell you the truth, even though I went through the study. Then I realized that what they were trying to do was to see if there was any harm done. That was really the basis of the study."

The remainder of the subjects, despite some variations, understood that the primary purpose was scientific or for the benefit of future PD patients. Three subjects unambiguously identified the primary purpose of the study as safety testing (S1, S2, S6): "…they wanted pretty much to prove, in my mind anyway, that it was a safe procedure."(S2) Three others (S3, S4, S8) identified safety testing as a purpose but also mentioned assessing "efficacy." One subject (S5) mentioned only the test of efficacy as the purpose. Of those four who mentioned efficacy as a purpose, further probing revealed that they all understood that the primary purpose was to help future patients with PD rather than to help the participants of the phase I study. It appeared that some subjects mentioned testing efficacy as a purpose because they were also including the overall process of developing GAD gene transfer as a therapy for PD beyond the more limited scope of the phase I study (despite the fact that the informed consent document clearly distinguished between the two). As S4 stated, "Well, generally in the long run, it was to help Parkinson's. In the short run, it might help me, but mainly they were emphasizing this is a new procedure and they didn't know what was really going to happen, so let's see." Likewise S5 identified the purpose as "To see… what effect the gene therapy had on the progress of Parkinson's" and when asked specifically whether it was to help him or to increase knowledge to help other Parkinson's patients, he said, "To help others." Finally, one subject (S3) mentioned "efficacy" in a way that raised the question of how he understood the meaning of "efficacy" as he seemed to use "safety and efficacy" as a shorthand for "scientific purpose": "They were trying to see if a Parkinson's patient would actually get any benefits from the gene therapy and then, more importantly than that was the safety and efficacy of the actual procedure."

Perception of Potential Benefit and Other Influences on Decision to Participate

Because therapeutic desire was such a common motivation, we examined the subjects' perception of potential therapeutic benefit and the bases for that perception. We asked each subject: "Realistically, what did you think your chances were of your PD improving as a result of participating?" with five response options, and the responses were distributed as follows: No chance (no subject), very low chance (S6), modest chance (S2, S3, S4), good chance (S1, S5, S7, S8), and very good chance (no subject). We asked the respondents to commit to one of the five response choices but an examination of the subjects' full responses surrounding their answer contained considerable nuances that would have been missed had we recorded their answers simply as a multiple choice question. S1's response choice was, "I would say I went into it thinking there was a good chance…"(S1) But what S1 says before and after expressing that choice is quite telling: "I went into it with a positive mind. I would say I went into it thinking there was a good chance, but that was a guess, gut feeling.

I went into it with great confidence. I went in and I was very calm and very hopeful." In other words, the true meaning of this subject's answer (even to a direct multiple choice question) is not captured well by simply looking at the response option he chose. This tendency to express the likelihood of benefit as part of one's need for optimism can confound our understanding of subjects' perception of benefit, and requires an analysis of the subject's statements in the context of his overall approach to the research study, rather than judging those statements in isolation. As S8 noted, "Optimism, positive thinking is something you have to have." Otherwise one has to accept the disease and its progression, and "[he, S8] didn't want to." This need to understand the context (and perhaps the purpose) of a subject's statements regarding likely therapeutic benefit was echoed in S2 who stated that he felt there was a "modest chance" of direct benefit when asked directly with the above question but later talked about it as an "outside long shot chance" in the context of how his motives fit in with the overall scientific purpose of the study.

We also examined whether the subjects' perception of potential benefit was based on what they read in the informed consent form or what they were told by the researchers. For most subjects, they made a point of saying that they were *not* promised or told to expect therapeutic benefits. During a discussion of what information from the researchers mattered to him most, one subject (S2) talked about what he wanted to hear:

> "S2: Well, what I wanted was that after I was all healed [from the surgery], that I'd have significant improvement or just some improvement. Either one of the two I'd take.
>
> I: Okay. Do you remember what they did tell you, you know, about your chances for…
>
> S2: Well, the chances were that I wasn't going to improve."

Others expressed the uncertainty and lack of information regarding benefits, (S3) "They told me that, you know, they didn't have a whole lot of information on it, first of all. They had only done one patient at that point, and they gave me the information as to how he had felt before and after he had had the procedure done, and it was very, very new." S4 pointed out that the neurosurgeon told him "the first time he saw me he'd rather I do the deep brain stimulus than the other one [i.e., gene transfer] … He just felt that I'd have more guaranteed results."

One common theme was a sense of confidence that the subjects developed toward the surgeon (or the study team in general). "His personality—I had great confidence in him… his thoroughness, his patience, his time with us…" (S1) Another subject had "blind faith" in the surgeon (S8) while another subject felt he was someone "that they can do what they say they'll do."(S6) Thus, we found that a trusting relationship was important to most of our subjects.

Although one subject (S6) specifically did not want to know what was happening with other subjects in the study, for most others, knowing that persons who had gone before them in the study were "doing OK" was a very important factor. Knowing that there were "no negative happenings" (S2) was something that greatly interested the subjects, and played an important part in their 'chance worth taking' reasoning (see below). "… I felt pretty comfortable with it, you know, the fact that I was the [n^{th}] one and nothing had happened to the other [i.e., others who went before]." The information about other subjects came from sources outside the study as well because this was a high profile gene transfer study with prominent media reports. The first subject's identity became known and was featured in the news. Some subjects mentioned this: S3 said, "And the information I had gotten also from, you know, the news article they had with him on CNN, and I felt pretty good about that…"

Relationship Between Motivation and Understanding of Purpose

One of our subjects (S7), at least at the time of enrolling in the study, appeared to be under a misconception that was driven by his desire for therapeutic benefit. This subject was so focused on "how it was going to affect me" that he disregarded the scientific purpose of the study. In fact, he felt that "they [researchers] were going to be my doctor, but that wasn't the case. The case was that [his own doctor] was still my doctor… I was very confused about where [his own neurologist] fit in and where the other doctors fit in at [the research hospital]." Thus, at least in this one case, the subject resolved the tension between his motivation (for benefit) and the study's purpose by focusing on the desire for therapeutic benefit, to the point of ignoring and therefore misunderstanding the stated purpose of the study.

For S6 who primarily had an altruistic motive, there was a natural congruence between his motivation and his understanding of the purpose of the study. In fact, as we saw above, he tended to talk about his motivation specifically in relation to his statements about the scientific purpose of the study. For S6, his purpose in participating was the study's purpose; there was no tension.

For the two subjects who were motivated by both benefits to self and societal/scientific benefit, the reconciliation of the understanding of the purpose and their motives was not that difficult. As Subject 8 put it, although he stated that the desire for personal benefit was a stronger motivation than the desire to help others, the latter is a firm conviction as well, as when he said, "I want to stop this [PD]" and "I'm just a piece of the puzzle… If it helps me, it's a bonus."

What about the four remaining subjects (S2-S5)? Their primary reason for participation was the desire for therapeutic benefit and yet all of them evidenced an understanding that the purpose of the study was scientific rather than therapeutic (despite ambiguities regarding whether "efficacy testing" was a goal). These subjects tended to frame their decision as a *chance worth taking*, a kind of a gamble, which acknowledged the long odds (congruent with their understanding of the study's purpose as not to benefit them directly). Indeed, one subject (S2) stated: "I always go with the voice that is going to benefit me maybe, but the chances are pretty slim. It's like throwing the Hail Mary pass. You know it's probably going to be missed by the guy in the backfield. He's not going to make the catch, but he's there anyway. Give it a shot." Objectively he understood that the purpose of the study is scientific; subjectively, he saw participation in it as a personal gamble worth taking. He went on: "Not that they ever gave an indication that it was going to cure me. As a matter of fact, they did just the opposite, but I always had that little bit of hope that, you know, that maybe something would happen." Another subject (S4) recognized that his decision was based on his subjective reasons: "I: What would you say overall, what motivated you the most as far as your decision to participate? S4: Uh, just an intuitive feeling that it would work. 80% of the time, my intuition is very strong. This time I was wrong…." and "[i]ntuition and some inner belief. Some spiritual sense. I don't know. I don't know what really determines."

Other Notable Themes: Action Orientation, Decision-Making Approach, and Risk Tolerance

Our primary goal in our research program is to understand how a subject may or may fall into a misconception about the study, in the context of his or her overall decision-making process about research participation. In this regard, one of the most notable themes was the "action orientation" of these participants, something that has been noted in the literature.[19] Seven of 8 persons reported that even at the very earliest stages of decision making, they were already inclined to participate: "As soon as I read it in the paper, I was interested"(S4) and "As soon as I read the ad. I thought it had my name on it."(S5)

Most of our subjects started from a position of strongly wanting to participate, and filtered and weighed information they encountered in relation to that initial inclination: "I: Do you remember, did this initial inclination ever change along the way? In other words, were you ever leaning away from participating at any point? S3: No, I did not. I was pretty much the whole time just more and more excited."(S3) They filtered information through a premise they already held: "There wasn't enough information to tell me to don't do it."(S2) Thus, our subjects did not begin their contact with the researchers as *tabula rasa*; rather, they were 'motivated' listeners.

In fact, although the perception of and tolerance for risks is an obviously important theme, what was notable in our interviews was that risk was *not* a strong influence on their decision-making. Partly this was the result of our design: we interviewed only enrollees who had already made a decision to tolerate the risks. But the subjects' attitudes toward risk and potential adverse events are best understood in this action-orientation framework: for them, risks were important only in so far as whether they were sufficient to defeat their initial inclination. For example, S4 stated that "I was pretty confident. There wasn't much they could say to disincline me [to participate]." S4 said in response to a question about his views about the risks: "There was a 1% chance you'd get a stroke, 1% chance you'd get a heart attack, 1% chance you'd get bleeding in the brain? These were tiny percentiles. They were not going to happen. I wasn't really concerned about that." Or S1: "I: Were there risks? S1: Sure. I didn't worry about them, but yes. I mean, they were going into my brain…" In this regard, as noted above, the fact that other participants had gone before them without major adverse events was often sufficient to answer the question of whether the risks were too high.

DISCUSSION

It is increasingly clear that the evaluation of TM is a complicated task, fueling disagreement about its definition and hence about the best way to measure it. Our approach in this pilot study was to examine the various statements made by a subject that have potential implications for TM in the context of the subject's overall narrative of learning about and deciding to participate in the research study.

Our study revealed patterns of decision-making by subjects in a highly invasive phase 1 trial. We observed that PD patients who volunteer for an early phase intervention study are significantly motivated by a desire for therapeutic benefit. This desire leads the subjects to seek out more information but it also serves as a kind of filter or subjective organizing principle for how they process the large amounts of information they receive from the research team and outside sources. Subjects process information using the following types of questions: Is there some chance that I *could* benefit from participating? Are there any significant red flags, i.e., are there compelling reasons *against* participation? Do the people and the institutions involved seem trustworthy?

However, while most subjects process study information in terms of their desire for therapeutic benefit, this does not mean that they do not understand the scientific purpose of the study.[20] Indeed, most subjects with this therapeutic desire understand the scientific purpose of the research and also recognize the tension between their desire and the purpose of the study. They reconcile their motivation and their understanding by describing their choice as a kind of calculated gamble (some finite chance of benefit + risks that seem tolerable + researchers who seem trustworthy + personal intuitions = chance worth taking). Was their perception of potential therapeutic benefit inordinate, based on misinformation, or both? We did not see evidence for this. There are variations of course. In one case, the desire

for therapeutic benefit was so absorbing that it prevented the subject from understanding, or even caring about, the purpose of the study. Another subject was truly an altruist.

What are the implications of our findings? First, our work opens up new ways to study TM and related phenomena in research subjects. We did not start with an a priori conception of TM and then examine the subjects' statements that may show evidence of TM. Instead, we attempted to understand the potentially worrisome statements that research subjects sometimes make, and tried to place them in context of the overall decision-making process employed by research subjects. This "within subject analysis" approach allowed us to understand how a research subject might be motivated by more than one reason, whether subjects' perceptions of potential benefit are expressions of hope or expressions of probabilities (and whether they are based on misinformation), and how they reconcile any tensions between their motivations for participation and their understanding of the purpose of the research.

Others have pointed out the pitfalls of treating informed consent merely as an information imparting process, rather than as a more human process involving a variety of psychological [21] and communicative [22] expectations. If we conceptualize informed consent as merely a matter of information transfer, then the focus will be on improving the information content; thus, it is not surprising that most of the focus of IRB oversight of informed consent is on the content of the informed consent form. The results of our pilot study gives some clues to how we might move beyond this information transfer model to enhance informed consent.

Specifically, research subjects should be seen as *motivated* information seekers. Most patient-subjects, even in a phase I study, will approach the research looking for potential therapeutic benefit. This therapeutic orientation is indeed a potential threat to adequate understanding for some (e.g., S7). But our results show that it need not be. People seem to have quite understandable "styles" of reconciling their motivations with their understanding that do not compromise understanding. Thus, perhaps the informed consent conversation should include the following: "Mr. Jones, now that we've had a chance to review the study in detail, it would be helpful for me to know what you are hoping for by participating in this study. Can you tell me in your own words why you would like to participate?" Most likely, the subject will express a hope or desire for personal benefit. The researcher can then clarify that that is not the same as the scientific purpose of the study. By *explicitly* juxtaposing the subject's motivation with the scientific aims of the study, the subject is challenged to reconcile his or her therapeutic motivation with a study's purpose that is not primarily to benefit him or her. In the course of the conversation, the researcher would then gain a sense of whether the subject is prone to disregarding crucial information because of a blinding focus on therapeutic potential, or whether the subject clearly understands the purpose and nature of the study but is an optimistic gambler (whose statements about expectations of benefit are not misconceptions but perhaps more a reflection of a need to maintain a hopeful outlook in his gamble), or whether the subject is truly an altruist.

Our study has significant limitations. First, this was a retrospective study, relying on the recollection of our subjects on average 21 months after the gene transfer surgery. Interviewing the subjects prospectively or much closer to the time of enrollment could have given different results. For example, the subjects' understanding may be good due to the fact of having experienced a study, or their answers may be more altruistic in retrospect (although most of our subjects were not shy about stating self-interested motive.) Second, it is a small study and the results are obviously preliminary. Third, despite our method of relying on four independent coders and a consensus conference, there may be room for different interpretations. Finally, research subjects with different illnesses facing different

types of research projects may exhibit a different response. For instance, all of our subjects seem to have undergone repeated and thorough informed consent discussions with their research teams—something that will surely vary from study to study.

Despite these limitations, our pilot study provides initial evidence to support a novel approach to studying TM and related phenomena. Specifically, the study shows that research subjects' potentially worrisome statements must be interpreted in a much more contextual manner—as elements of the overall decision-making process of each individual subject—rather than judged as isolated statements. Doing so may lead to a better understanding of the various style or approaches that subjects take in deciding to participate in research, which in turn may suggest ways to improve the informed consent process.

Acknowledgments

We thank Andrew Feigin, MD for assistance in coordination with Neurologix, Inc.

References

1. Lozano AM, Dostrovsky J, Chen R, et al. Deep brain stimulation for Parkinson's disease: Disrupting the disruption. The Lancet Neurology. 2002; 1(4):225–231.Kaplitt MG, Feigin A, Chengke T, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. The Lancet. 2007; 369(9579):2097–2105.Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. NEJM. 2001; 344:710–719. [PubMed: 11236774]
2. Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006; 442(7099):164–171. [PubMed: 16838014]
3. Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. Neurology. 2003; 61(1):46–54. [PubMed: 12847155] Tuszynski MH, Thal L, Pay M, et al. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nature Medicine. 2005; 11:551–555.
4. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007; 448(7153):600–603. [PubMed: 17671503]
5. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005; 45(5):651–660. [PubMed: 15748841] Greenberg BD, Malone DA, Friehs GM, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology. 2006; 31(11):2384–2393. [PubMed: 16855529]
6. Dunnett SB, Rosser EA. Cell therapy in Huntington's disease. NeuroRx. 2004; 1:394–405. [PubMed: 15717043]
7. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. Journal of Neurosurgery. 2007; 107:1004–1014. [PubMed: 17977274] Damier P, Thobois S, Witjas T, et al. Bilateral deep brain stimulation of the globus pallidus to treat Tardive Dyskinesia. Archives of General Psychiatry. 2007; 64(2):170–176. [PubMed: 17283284]
8. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: Informed consent in psychiatric research. International Journal of Law & Psychiatry. 1982; 5(3–4):319–329. [PubMed: 6135666]
9. Agrawal M, Emanuel EJ. Ethics of phase 1 oncology studies: Reexamining the arguments and data. JAMA. 2003; 290(8):1075–1082. [PubMed: 12941681] Sreenivasan G. Does informed consent to research require comprehension? Lancet. 2003; 362:2016–2018. [PubMed: 14683665] Miller FG. Ethical significance of ethics-related empirical research. JNCI Cancer Spectrum. 2002; 94(24): 1821–1822.Kimmelman J. The therapeutic misconception at 25: Treatment, research, and confusion. Hastings Center Report. 2007; 37(6):36–42. [PubMed: 18179103]
10. Horng S, Grady C. Misunderstanding in clinical research. IRB: Ethics & Human Research. 2003; 25(1):11–16. [PubMed: 12833900]

11. Jansen LA. The problem with optimism in clinical trials. IRB: Ethics & Human Research. 2006; 28(4):13–19. [PubMed: 17036434]
12. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: Frequency and risk factors. IRB: Ethics & Human Research. 2004; 26(2):1–8. [PubMed: 15069970] Henderson GE, Easter MM, Zimmer C, et al. Therapeutic misconception in early phase gene transfer trials. Social Science & Medicine. 2006; 62(1):239–253. [PubMed: 16000230] Lidz CW, Appelbaum PS, Grisso T, et al. Therapeutic misconception and the appreciation of risks in clinical trials. Social Science & Medicine. 2004; 58(9):1689–1697. [PubMed: 14990370]
13. See ref. 12, Henderson et al., 2006.
14. See ref. 12, Appelbaum et al., 2004.
15. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: Defining the therapeutic misconception. PLoS Medicine. 2007; 4(11):e324. [PubMed: 18044980]
16. See ref. 12, Appelbaum et al., 2004.
17. See ref. 12, Henderson et al., 2006.
18. See ref. 1, Kaplitt et al., 2007.
19. Kim SYH, Holloway RG, Frank S, et al. Volunteering for early phase gene transfer research in Parkinson disease. Neurology. 2006; 66:1010–1015. [PubMed: 16540601]
20. See ref. 9, Agarwal et al., 2003.
21. Weinfurt KP. Discursive versus information-processing perspective on a bioethical problem: the case of 'unrealistic' patient expectations. Theory and Psychology. 2004; 14(2):191–203.
22. Manson, N.; O'Neill, O. Rethinking Informed Consent in Bioethics. New York: Cambridge University Press; 2007.

Table

How the subjects in a phase I gene transfer study for Parkinson's disease talk about their motivations, understanding, and other influences on their decision to participate.

Subject	Motivation for Participation	Understanding of Purpose of Study	Perception of Benefit and Other Influences on Decision to Participate	Relationship Between Motivation and Understanding of Purpose
1	Dual motivation	To test safety	- Trust in neurosurgeon - Denies researchers made specific statements indicating participants would benefit - Intuitive feeling - Hope and optimism	Dual motivation allows reconciliation: Understood purpose (safety) but still *hoped* for benefit.
2	Benefit to self	To test safety	- Previous subjects doing OK - Hope and optimism - Denies researchers made specific statements indicating participants would benefit	Chance worth taking: "It's like throwing the Hail Mary pass…"
3	Benefit to self	To test safety To test efficacy (For future PD patients)	- Previous subjects doing OK - Positive media portrayal - Hope and optimism	Chance worth taking: "I mean I was willing, you know, to try it anyway."
4	Benefit to self	To test safety To test efficacy (For future PD patients)	- Denies researchers made specific statements indicating participants would benefit - Allure of gene transfer technology - Intuitive feeling - Hope and optimism - Trust in research team	Chance worth taking: "There wasn't much to lose."
5	Benefit to self	To test efficacy (For future PD patients).	- Previous subjects doing OK - Positive tone of informed consent discussion - Denies researchers made specific statements indicating participants would benefit - Science behind the trial: "the results in the lab with monkeys"; "the preparation that they had gone through"	Chance worth taking.
6	Altruism	To test safety	- Science behind the trial: "the theory behind the procedure." - Denies researchers made specific statements indicating participants would benefit - Trust in neurosurgeon - Hope and optimism	Motivation is congruent with the objective purpose of the study.
7	Benefit to self	Failed to appreciate the purpose.	- Influence of previously enrolled subject in GAD study - Trust in neurosurgeon - Positive tone of informed consent discussion - Denies researchers made specific statements indicating participants would benefit - Previous subjects doing OK - Hope and optimism - Positive media portrayal of gene therapy	Did not care to understand the purpose at the beginning: "…I really don't remember thinking about what they were trying to accomplish as much as how it was going to affect me."
8	Dual motivation	To test safety To test efficacy (For future PD patients.)	- Trust in neurosurgeon - Denies researchers made specific statements indicating participants would benefit - Scientific reasons: S8 was later in the study so got "more of the gene" - Hope and optimism - Previous subjects doing OK	Dual motivation allows reconciliation between motivation and understanding of purpose: "If it benefits me, that's a bonus."