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“I Want to Do It, But I Want to Make Sure That I Do It Right.” Views of Patients with Parkinson’s Disease Regarding Early Stem Cell Clinical Trial Participation

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ABSTRACT

Background: First-in-human clinical trials with stem cells for Parkinson’s disease (PD) are on the horizon. Their epistemic success depends on ensuring the participation of a sufficient number and appropriately diverse group of patients with PD. Their ethical soundness requires that the research community ensures that subjects’ decisions about whether to participate or not are consistent with participants’ values, motivations, and goals. We sought to identify PD patients’ knowledge, concerns, and expectations regarding early-phase stem cell research in PD. **Methods:** We conducted five semi-structured focus groups with patients with PD. Group discussions were recorded, transcribed, and coded to identify participants’ knowledge, concerns, and expectations regarding participation in early stem cell clinical research in PD. **Results:** Four themes were generated from our data analysis: (1) participants’ skepticism about the potential benefits of these trials; (2) their desire to obtain information about various aspects related to this research; (3) a recognition that accessing available knowledge was often difficult; and (4) the relevance of trusting relationships with various stakeholders. **Conclusions:** Participants expressed skepticism about the immediate impact of stem cell research. Nonetheless, such skepticism often reflected an appropriate consideration of the risks and potential benefits of participating in high-risk clinical trials. Despite their skepticism, participants were eager to learn more about stem cell research and clinical trials processes. They identified consistently trusted avenues of knowledge on these topics, but they often found it difficult to access relevant information or to determine its value.

KEYWORDS

Stem cell clinical trials; Parkinson’s disease; focus groups; recruitment of subjects; autonomy; trust

Introduction

Parkinson’s disease (PD) is a common and disabling neurodegenerative disorder, affecting more than 2% of the population older than sixty-five years old (Cuenca et al. 2019). Unfortunately, current medical interventions have critical limitations and no cure exists for the disease. Recent advances in stem cell and gene transfer research offer potential curative strategies (Raza, Anjum, and Shakeel 2019). Several groups of investigators are advancing knowledge of stem cell technology and it seems likely that the next few years will see first-in-human clinical trials with stem cells for patients with PD (Parmar, Torper, and Drouin-Ouellet 2019; Barker et al. 2017; Yasuhara et al. 2017). These trials involve the transplantation of dopaminergic cells derived from stem cells in order to replace dopaminergic neurons in the midbrain (Parmar, Torper, and Drouin-Ouellet 2019; Barker et al. 2017; Yasuhara et al. 2017).

These early trials raise a variety of well-known ethical concerns. Research with embryonic stem cells brings up questions regarding the moral status of embryos (Krimsky 2015). Stem cell research in general—whatever the source—also raises fears about hype and abuse (Knoepfler and Turner 2018), concerns about the existence of adequate preclinical safety and efficacy testing (Barker et al. 2018; Kimmelman et al. 2009; Fung and Kerridge 2013), and worries about appropriate informed consent (Lo and Parham 2009; de Melo-Martín, Hellmers, and Henchcliffe 2015). Nonetheless, early phase clinical trials are necessary to determine the safety and efficacy of new interventions in human beings and to advance knowledge.

Importantly, the epistemic and ethical success of stem cell clinical trials for PD critically depends on ensuring the participation of an adequately informed and appropriately diverse group of patients with PD.

While recruitment difficulties plague clinical trials in general (Rodriguez and Harrington 2019; Treweek et al. 2018; Jones and Cipriani 2019), early-phase stem cell clinical trials face a higher level of potential misconceptions that can negatively affect study participation (Caulfield et al. 2016). Because of the heterogeneity of PD and the fact that patients with PD are often elderly, disabled, and can have cognitive impairments, concerns about recruitment are particularly salient in the context of these trials (Mathur et al. 2015; Picillo et al. 2015; Reijula et al. 2017).

Recruitment problems can lead to premature terminations or to extensions of clinical trials and thus to the waste of scarce human and economic resources (Baldi et al. 2017; Kitterman et al. 2011). Poor recruitment may also reduce the statistical power of trials and affect internal and external validity, leading to inconclusive or non-generalizable results (Carlisle et al. 2015). Insofar as the research produced under these conditions can fail to be socially valuable or scientifically valid, it would also be unethical as it will expose subjects to risks without compensating benefits (Emanuel, Wendler, and Grady 2000).

At the same time, evidence indicates that subjects who do participate in early phase clinical trials have unrealistic expectations about possible benefits of participation, with most of them misestimating their personal potential for benefit (Pentz et al. 2012; Jansen et al. 2011; Halpern, Paolo, and Huang 2019). Studies also show that clinical trial participants are often inadequately informed about various aspects of their involvement (Henderson 2015; Eisenhauer et al. 2019; Malik and Cooper 2018; Godskesen et al. 2013; Koyfman et al. 2016). A significant amount of evidence likewise indicates that they harbor serious misunderstandings about research, often failing to comprehend the different goals of medicine and research and the significance of research methodologies such as randomization and the use of placebo (Mandava et al. 2012; Lidz et al. 2015; Nguyen Thanh et al. 2015; Reijula et al. 2018). All of these problems undermine people's ability to provide an autonomous authorization (Halpern, Paolo, and Huang 2019; Jansen et al. 2016). They can also erode warranted trust in the research enterprise (de Melo-Martin and Ho 2008).

Safeguarding the epistemic and ethical soundness of early phase stem cell trials for PD thus requires not only that researchers ensure the social and scientific validity of these trials but also that they foster subjects' autonomy. That is, the research community needs to ensure that subjects' decisions about whether

to participate or not are consistent with participants' values, motivations, and goals. To determine how best to do so, we sought to identify patients' knowledge, concerns, and expectations regarding early-phase stem cell research in PD. It seems clear that recruitment strategies uninformed by potential participants' views are unlikely to further subjects' autonomy. On the other hand, examining potential participants' concerns, knowledge, and preferences about stem cell trial participation can help us devise strategies that promote their autonomy not only by limiting obstacles to obtaining a valid informed consent, but by ensuring that participating or failing to do so is consistent with the considered values and judgments of patients with PD.

Methods

Focus groups were selected for this research because they allow for the expression of a range of perspectives from many people on a given subject (Krueger and Casey 2009). This matched the study's intended purpose of learning about patients' knowledge, concerns, and expectations with respect to research participation in early phase stem cell clinical trials. Participant recruitment occurred in two waves, as we used the principle of theoretical saturation to determine when to cease data collection (Krueger and Casey 2009; Morgan, Krueger, and King 1998). The study was approved by the IRB at Weill Cornell Medical College.

Recruitment flyers were posted in neurology clinics at our university and distributed at PD patient support groups. Interested patients were asked to call and invited to attend one of the scheduled focus groups. Participants had a diagnosis of PD, ability to give informed consent, and were able to speak and understand English.

Focus groups were conducted over the course of four months and were facilitated by at least two of the authors. Before each group began, we obtained informed consent from participants and each participant completed a paper demographics form, which included questions about whether they had previously participated in a research study and the approximate date of their PD diagnosis.

For all groups, the facilitators used the same open-ended, semi structured interview guide, which was organized around two domains: (1) personal experiences with PD and biomedical research, and (2) recommendations for the running and structuring of clinical trials (Table 1). Participants were first asked to share

Table 1. Interview guide.**Phase I: Personal Knowledge and Experience**

- What do you know about clinical trials broadly, and stem cells more specifically?
- How and where did you acquire this information?
- Have you ever participated in a clinical trial?
- How do you assess potential risks and benefits of research and treatment?
- What are these risks and benefits?
- What are your expectations for the outcome of stem cell trials?

Phase II: Clinical Trial Specifics

- How should recruitment for clinical trials be conducted?
- Who do you think would be the ideal candidate for an early phase trial?
- What kinds of information should these people have before making a decision?
- Are there any common misconceptions you think should be specifically addressed?
- How would you know that you were making an informed decision to participate?

Phase III: Wrap Up and Clarification of Stem Cell Knowledge

- *Opportunity for facilitators to provide accurate information about stem cell trials*
- What would make you more likely to participate in a stem cell trial?
- What would make you less likely to participate in a stem cell trial?
- Is there anything we did not ask you about that you think is important to share?

and discuss their understanding of both clinical research in general, as well as stem cell research specifically. Following an initial conversation, the lead researchers provided accurate information on the aims of early-phase clinical trials, as well as the current status of stem cell research in PD. This structure was developed to gain access to patients' understanding of the material both prior to and after being informed of these subjects.

Interview guides were developed by the authors, in consultation with a neurologist and clinical psychologist, through an iterative process of discussion, revision, and reorganization. Guided by the principle of theoretical saturation, the point at which "no new or relevant data seem to emerge regarding a category" (Strauss and Corbin 1990, 188), the authors engaged in ongoing reflection and discussion about the progression of the groups. All groups were conducted in English and lasted approximately one hour and a half. Participants received no financial compensation.

Data analysis

Focus groups were audio-recorded on two digital tape recorders and transcribed verbatim by one of the authors or a graduate research assistant. All data were stored on a secure server and only accessible to study team members. Analysis was conducted using an inductive form of thematic analysis (Braun and Clarke 2013). Initially, all members of the research team independently line-by-line coded the transcripts of two focus groups. The team met to extract these open codes and organized them into a thematic codebook. Using the codebook, focus group transcripts were reviewed and re-coded in a "round robin" style, with two members of the research team coding independently, ensuring a different pairing of authors for each

transcript. Discrepancies in coding were addressed through group discussion, following which the data was entered into Dedoose (version 8.0.35), a qualitative data web application that allows researchers to identify varying code utilization, as well as frequency of codes used in tandem with each other. This information guided group discussion around the development of themes.

Results

We conducted five focus groups with a total twenty participants. Between five and eight people were invited for each group, and final attendance ranged from three to six participants. Discussions lasted about ninety minutes. Eleven participants (55%) identified as female and nine (45%) identified as male. The overwhelming majority of participants identified their race as Caucasian (85%), with the remaining participants identifying as Asian (10%) or not selecting a race (5%) (Table 2).

Analysis of the data generated four themes relevant to patients' desire and ability to participate in early clinical trials with stem cells in ways that are consistent with their values. They included (1) participants skepticism about the potential benefits of these trials; (2) their clear desire to obtain information about a variety of aspects related to this research; (3) a recognition that accessing available knowledge about stem cell trials was often difficult; and (4) the relevance of trusting relationships with various stakeholders. Below we describe these themes in detail.

Skepticism about potential benefits

When prompted to discuss the consequences of participating in early clinical trials for PD involving stem cells, our participants considered whether the decision

Table 2. Participant demographics.

Demographic variables	<i>n</i> (%)	Mean (SD)
Sex		
Male	9 (45%)	
Female	11 (55%)	
Age		72.7 (7.75)
Years Since Diagnosis		6.80 (4.67)
Ethnicity		
Asian	2 (10%)	
White	17 (85%)	
Not reported	1 (5%)	
Hispanic or Latino	17 (85%)	
No	3 (15%)	
Not reported	3 (15%)	
Highest Level of Education	9 (45%)	
Some college, no degree	3 (15%)	
Bachelor's degree	6 (30%)	
Master's degree	4 (20%)	
Professional school degree/PhD	14 (70%)	
Employment status	6 (30%)	
Employed	4 (20%)	
Unemployed	2 (10%)	
Not reported	3 (15%)	
Household Income	2 (10%)	
\$20,000-\$50,000	5 (25%)	
\$50,000-\$100,000	4 (20%)	
\$100,000-\$150,000	4 (20%)	
\$150,000-\$200,000	2 (10%)	
>\$200,000	11 (55%)	
Not reported	3 (15%)	
Relationship Status		
Single	11 (55%)	
In a relationship	8 (40%)	
Married	1 (5%)	
Widowed		
Previous Research Participation		
Yes		
No		
Not reported		

to enroll would be worthwhile, expressing a degree of skepticism about the benefits of participation. One major highlight of this phenomenon was participants' ability to weigh the risks and potential benefits of joining a trial. Some of the risks participants discussed included physical dangers related to invasive surgeries, a worsening of the disease, and death. Participants also entertained more subtle risks, such as concerns about the burdens placed on loved ones in the case of an unsuccessful trial, or worries that participating in an early phase trial might prevent them from joining later—perhaps more promising—ones. Similarly, some of the potential benefits participants considered were relatively concrete, including disease cure, reduction of PD symptoms, and halting the progress of the disease. However, participants also discussed less direct possible benefits, such as those that could result from reducing the medications needed to manage the disease:

Group 2 Participant 3 (G2P3): And the more medication you take, the more side effects you also have. And the benefit of stem cell surgery, if it's successful to even a certain percentage, you reduce your medication and have less side effects.

They also considered possible psychological benefits, such as the ability to help others:

G2P2: You have to appeal to something that's very subjective. A person's own feeling of idealism and willingness to participate in such a risky thing. The only mode to really convey, "I hope it helps me, but I'm doing it for others."

Importantly, participants not only described some risks and potential benefits, but also made judgments about balancing these risks and benefits in the context of their own personal values:

G3P1: Yeah, I think that it's worse - than dying - is, is coming out of it, out of the treatment worse off. And you become a burden on other people. This is something that um - burdening someone, somebody else is not the same for each of us. But if it's important to you, that burden is something that I think is worse than expiring.

Other participants made such evaluations recognizing the uncertainties and wondering whether they could manage them:

G2P3: My question is, so, if I participate in trial one, if I'm not going to benefit, should I do it or not? Should I wait for trial two, or three? So I need to know what stage I am, what I fit into, which category I fit into. [...]. If, next thing is, if I qualify for trial one, and not for trial two, I'll still do it because if it benefits someone else I'm for it 100% actually. And I'm a very strong believer in stem cells actually. So, I want to do it, but I want to make sure that I do it right. Right place at the right time.

Participants showed the ability to think appropriately about risks, potential benefits, and uncertainties involved in participating in an early-phase clinical trial. Nonetheless, they also expressed significant skepticism about the scientific community's present level of knowledge and were concerned about whether researchers know enough to embark on these types of trials:

G5P5: ... I'm curious to know how they can be cultivated, why they think they can train them, because stem cells are stem cells and everybody knows that stem cells are kind of cool, but they can't seem to, kind of, bark up the right tree. So I'm curious to know how they're going to go about that and why they have a reason to believe that it actually works or whether they've got so far in this to believe this is something worthwhile doing.

Indeed some of our participants expressed frustration at what they perceived as insufficient progress in the field:

G4P2: I find it appalling that we're sitting and discussing this fifty years since they've come out with dopamine. Fifty years and they've come out with nothing else to help us, fifty years. They should all be lined up against the wall.

Some participants also expressed skepticism about biomedicine's priorities. In the case of the above participant, the concern was related to whether researchers were working on the right problem. This individual continued to discuss the lack of progress on some potential medicines to help manage PD symptoms:

G4P2: So in the meantime, we do nothing. So if we're sitting here for an hour discussing stem cell, which is extremely valuable, I mean it sincerely, and they can't even get out a nose spray to help us.

At times concerns about biomedicine's priorities focused on the fact that other conditions were receiving more attention from researchers and regulators. For example, after expressing frustration for the slow progress in the treatment of PD, the same participant commented on the availability of other medications:

G4P2: It's a disgrace, but, but, but Viagra. We have 50 kinds of Viagra. Now what I suggest they do is give a Parkinson's patient Viagra and see them, I mean, what, carry on with Viagra. How many forms of Viagra do you need? I mean, really.

For other participants the skepticism was a natural result of many years spent observing various proposed cures and treatments ultimately fail to deliver on their promise:

G5P6: I wonder if maybe my concern is that ... I have the longest diagnosis, it sounds like, and I've been through so many hopes and collapses.

Desire to know

Despite their skepticism regarding the impact of stem cell research and regardless of their views about a possible involvement in early phase clinical trials, participants throughout the focus groups regularly demonstrated a desire to know more about a variety of topics. They were interested in learning more about stem cells:

G1P1: [...] I saw a stem cell and I wanted to hear the conversation on it. And that's what I'm interested in. I want to know more about stem cells and what's the progress being made.

They also wanted more information about clinical trial processes:

G3P3: And I just wanted to know ... so I'm not quite clear about the different clinical progressions, clinical trial one, two, three. How long do you have to wait after clinical one is done before you decide to go forward? Um, and then I know there are questions about have they been done in primates before you do the human trials, um, and what type of stem cells are these, are they from your own body or from another source? Um and those are some of the basic questions.

And they sought general information about PD:

G1P1: [I am participating here because I want] information. Again I like to be involved in the whole Parkinson process, in whatever way I can.

One interesting component of participants' desire to know was the varying depths of knowledge that individuals felt they needed in order to make an informed decision. Some wanted significant amounts of information:

G3P3: ... I would just want to be completely flooded with as much information as the doctors had and the researchers had. What were previous trials, when were they done, what were the results [...] just a body of knowledge from different people because everybody has a different take on stem cell research but I think information is power, so the more information the better - of risks and, just, information.

While others seemed more concerned with how the information related to their needs:

G3P4: The thing to do is distinguish between useful and not useful information. The analogy I think is that let's say you know how to drive a car, but you don't need to know how the engine works.

Regardless of the depth of desired knowledge, participants' expressions of interest in knowing was particularly striking to team members both for its consistency throughout all focus groups, and the degree to which the desire to know could overtake the direction of the group conversation. This pattern occurred in a variety of ways. For instance, a line of inquiry would often shift to swapping information on various PD treatments and interventions:

G5P2: I'm going to add something: hydration.

G5P4: What?

G5P2: Hydration is very, very, very important. And there's been studies on, on cadavers and people with dementia and they all have dehydrated brains, and you know the brain is 30% water, and I find that that

makes a huge difference [...] The other thing, physical therapy and speech therapy are two things that I find very, very helpful - those three things.

G5P6: Speech therapy has been very good for me. Yes, totally changed my life.

G5P2: And physical therapy, too, physical therapy is-

G5P1: Physical therapy is good.

At other times, participants were hoping to gain a deeper understanding of some particular issue and asked the team their questions directly:

G2P2: My question to you is, what are your criteria for picking somebody or not choosing somebody? [...] Are you considering psychological, a person's psychological state?

At the end of the focus groups, many individuals noted their gratitude to be able to leave the space with significantly more knowledge than they had before:

G2P4: What was helpful to me is getting all this information. Dr. [NAME] said I probably wouldn't be a candidate [in an early stem cell clinical trial]. But that was not enough for me to hear. Hearing today what you said educated me and I can make my own decisions.

While participants expressed a desire to acquire more information, they also displayed insight into the fact that not all of their questions could be answered due to the scientific community's limited understanding of certain phenomena.

G1P2: What I think that I would want [regarding information] is unavailable because it hasn't been done yet. So, um, that's an issue.

Insight into the current limitations of scientific understanding is an important lens for individuals who are trying to obtain information while considering participation in an early phase clinical trial. Nonetheless, prospective participants with this insight may be prone to confuse questions that the research community has not yet been able to answer with information that is currently available, but relatively complex. Indeed, barriers to accessing and comprehending information was another prominent theme in the focus group discussions.

Difficulty accessing available knowledge

Although participants regularly displayed a desire to increase their knowledge on a range of subjects, some also contended that they have difficulty accessing

available knowledge. This difficulty was partly experienced because of the resources needed in order to gain and comprehend existing information. Time was one such significant resource:

G3P2: And going to the conferences can be good but you...you often times have five speakers that you want to listen to and you have to choose one. So, um, so it's really hard if you don't know ahead of time who...you know, who's what and what they're going to talk about.

Participants also discussed the struggle to sort through and prioritize their attention due to the breadth of data that is available:

G5P5: But um, there's a lot of information out there...probably 1% of it's probably valuable, and unfortunately as a community we don't seem to know enough yet to make an informed decision when you're talking with your internalist, neurosurgeon, or neurologist....

Money was another resource highlighted as a barrier to people's ability to access information:

G3P4: So the other thing is that journals and periodicals are very expensive. [University] have an excellent library, but understandably they don't let journals out to the general public. So you have to be a student or researchers there to read the real scientific news. So I don't know what the solution is other than if some someone rich would say, "Ok, I can build a library for you and then supply all the journals that you'll ever need without you paying anything."

Participants also observed that addressing barriers related to time and money would still be insufficient, as a certain level of expertise is often needed to make sense of desired information:

G2P3: The problem with medical journals is that you read an article and they don't simplify it. They write it in medical terms which is not always understandable for patients actually.

Individual participants gave various responses to this concern. Some of them sought out experts for their opinions: "I ask Dr. [NAME] a lot of questions, every time I come, I come with a list of questions," (G2P4). Some participants spoke to how they used their own expertise to help make sense of the information they accessed, "I have a PhD in economics [...] so it's statistics that helps me there," (G5P6). Still others worked to become expert themselves:

G2P2: I get most of my information from the internet as well. And the publications of the Parkinson's Foundation and the, uh, Michael J. Fox Foundation. Um, and then that guides me to something else. I look at something and then it'll say something about

the disease, I'll click on that and then I'll go further and further.

While individuals may attempt many of these strategies, it should also be noted that some people, for various reasons, choose to disengage entirely from medical information:

G4P1: And I, just as an aside, I read very much less than most people about my Parkinson's. It just upsets me, and whatever's going to happen is going to happen.

Trusting relationships

Because patients often face barriers when accessing information about stem cells research and clinical trials processes, they are dependent on clinicians, researchers, and community groups to acquire information about these topics. Trusting relationships are thus essential for patients with PD to be able to obtain relevant information. As one of our participants put it:

G5P5: So treat me like a kindergarten school, just take a big red crayon and write yes or no, because ultimately I don't have the 30 years' experience you have, I don't have this information and there are not that many people who I could go to with that, so somewhere I'm going to trust [team member's name] eyes, your eyes, you know I'll talk to [G5P4 name], I'll talk to [G5P6 name] about all the stats, I was paying attention, which is all really fascinating for me and somewhere in there I'll make a gut check and that'll be it for me.

Participants expressed appropriate trust in their clinicians, often a source of pertinent information on issues related to PD, and in researchers as a source of data on new advancements in the field. For instance, participants commented on contacting researchers to talk to them about stem cells and other innovations:

G3P3: [...] I went to the World Parkinson's conference in Oregon, and I always go up afterwards and ask the lecturers about their topic, and there were some stem cell people at the World Parkinson's Conference about three years ago, and then we are very lucky to be in [...] because they have so many wonderful, you know, world leading, um, researchers and so whenever there's a conference, I attend, and again I'm very, very good about buttonhole-ing people and finding out more about the research.

Our participants also relied on foundations and community groups to access information. Foundations, such as the Michael J. Fox Foundation or the Parkinson's Foundation were a primary source of reliable information for most of our participants.

Most of them use the internet to access information disseminated by these organizations:

G2P3: I go to different websites. Michael J. Fox Foundation, Parkinson's Association, all these. I read articles, brain magazines every month [...], so I get a lot of information from that.

However, participants were also clear that they acquire a significant amount of the information about PD, research on stem cells, and new investigations from various community groups:

G3P2: And we all, if we find something interesting, will send that information in to one of our groups... one of our, [Coordinator Name], and he takes it and distributes it to everyone who is in the city Parkinson's group, or the Dance for PD group, so it, um, every day I get two or three things that say something about Parkinson's that... yeah, and you contributed some... some things in there and you get it from patients.

Significantly, lack of trust in clinicians or researchers undermines people's ability to benefit from existing information. When participants expressed mistrust of the research community, for instance, they also called attention to concerns about the reliability of scientific and medical information. In the words of one of our participants:

G3P2: Um, and it does seem that it (information about stem cell research) is sort of cloaked in mystery, that the actual, you know, that they're keeping it a secret so that they can hold it for themselves as a way to fix things and that it won't get out and someone else will take it, but meantime we don't have access to the actual facts.

In the same vein, participants called attention to certain motivations from researchers that raise suspicion:

G1P1: [...] Right, right there. They (researchers) want to be the ones to come out with it so they make money on it. I think that medicine should be... especially something for a very serious illness. To the common good should be considered more than the individual who is going to come out with the cure.

Of course, trust in various stakeholders and attention to their motivations was relevant not only regarding the credibility of information but also concerning whether people would consider enrolling in clinical trials. As one participant indicated when discussing possible reasons to participate in stem cell trials:

G2P2: I think that ultimate, first of all I think those of us with long relationships with the doctors would be a very important factor. I mean [Dr.'s Name], I've

been with her since the beginning, I would trust her. That's number one.

Similarly, trust affected people's willingness to rely on research funded by various sources. Hence, the fact that a trusted stakeholder was the founder made the researcher itself more reliable. As one participant stated:

G4P1: In that case, the fact that it's being funneled through the Michael J. Fox would be more than enough for me.

Similarly, stakeholder's motivations were also considered when questioning the scarcity of research funding for stem cell research.

G2P1: The problem is we're expecting pharmaceutical companies to fund that drug is that it's not a drug. It's not something they're going to sell and profit from. If the stem cell insertion works, it's going to be done surgically. You're not going to be buying a medicine or a pill. If anything you're going to be buying less *levodopa* or no *levodopa*. [...] So they're sort of putting themselves out of business.

Discussion

Recent advances in stem cell research suggest that first-in-human stem cell trials for PD are likely imminent (Parmar, Torper, and Drouin-Ouellet 2019; Barker et al. 2017; Yasuhara et al. 2017). Questions about appropriate recruitment for high-risk clinical trials are thus particularly salient. The epistemic soundness of these trials requires an appropriate number of potential participants willing to join (Carlisle et al. 2015). At the same time, it is vital that individuals interested in participating arrive at that decision with an adequate understanding of both the research aims and what can reasonably be expected from these early trials. Ensuring the ethical appropriateness of these trials also requires that prospective participants have sufficient information to be able to weigh the risks and potential benefits in light of their personal values.

We sought to identify the knowledge, concerns, and expectations of patients with PD regarding early phase stem cell research in PD. Our data provides insight into important issues relevant to the epistemic and ethical success of early-phase stem cell clinical trials for PD. First, although participants expressed a general skepticism about the immediate impact of stem cell research, such skepticism often reflected an appropriate consideration of the risks and potential benefits of participating in a high-risk clinical trial. Participants' considerations revolved both around how

participation could affect their own health as well as how trials results could influence global treatment of the disease. This result is consistent with other evidence that suggests that considerations about benefits to themselves and others are primary motivations of patients with PD to participate in clinical trials, and that the decision of many who chose to engage in "stem-cell tourism" was best understood as the result of hope for "small, yet significant improvements" in day to day life (Valadas et al. 2011; Petersen, Seear, and Munsie 2013). Participants also recognized that their own personality traits, including how risk-averse they may be, could affect their desire to take part in an early-phase clinical trial. Likewise, they were attentive to various factors—such as information from animal experiments, more knowledge about efficacy, and less uncertainty about results—that they thought would need to be in place before they would consider participating in such trials. Attention to all of these considerations during decision-making aligns with the goal of recruiting a pool of prospective participants who are able to make autonomous decisions based on their values and interest.

Second, though prospective participants can attend to relevant factors when thinking about participating in high-risk clinical trials, they also expressed frustration regarding the priorities of the research community. This finding is particularly important, as evidence suggests that people's trust in the research enterprise is related to their perceptions about the benefits that science can bring to society. For instance, polled European and US patients expressed distrust when research failed to contribute to the common good, such as the development of drugs with only short-term health benefits, or when the needs of neglected patient groups are ignored (Kessel 2014). A significant amount of studies, many of them involving populations that are underrepresented in clinical trials, have shown that trust (or lack thereof) in the scientific community affects people's willingness to participate in research (Scharff et al. 2010; Onyeneho et al. 2019; Hildebrand et al. 2018; Agoritsas, Deom, and Perneger 2011). The scientific community thus needs to be attentive to the fact that frustration regarding research priorities can negatively affect prospective participants' trust and, with it, their willingness to participate in research in which they might otherwise be interested.

Third, despite their skepticism, participants' desire to know more about stem cell research and the process of clinical investigations signals that they might still be open to considering participation in an early-

phase clinical trial. This is consistent with evidence from other studies that show that patients with PD would like to learn more about participating in clinical trials (Heusinkveld et al. 2017). In fact, the often-voracious curiosity that individuals had toward any research on PD in general, and stem cell research in particular, suggests that some prospective subjects who choose to opt out may not be making this choice due to a lack of interest or an experience of ambivalence toward the research itself. In this light, the difficulty that participants experienced in accessing and understanding available knowledge is particularly troubling for several reasons. First, insofar as some prospective participants for early-phase stem cell clinical trials might wish a high level of information, difficulty in acquiring it may be an obstacle to their potential participation. Indeed, studies have shown that lack of information regarding research opportunities presents a barrier to clinical trial recruitment (Clark et al. 2019; Mathur et al. 2015). Thus, potential participants who would require a certain depth of knowledge to opt-in may screen themselves out of participation. Risk-takers, who might be less concerned with a lack of information, could then become the primary research participants in these early trials. Although risk-taking attitudes might be an important aspect of clinical trial participation, it seems clear that the clinical and research community should be more concerned with ensuring that a broader pool of potential participants is available. Second, those individuals who do end up participating might be less informed than they could otherwise be. Again, this is also consistent with the numerous studies that show that many research participants have an inadequate understanding of the research process (Mandava et al. 2012, Lidz et al. 2015, Nguyen Thanh et al. 2015, Reijula et al. 2018). Given that lack of understanding about research processes can contribute to the therapeutic misconnection (Mandava et al. 2012, Lidz et al. 2015, Nguyen Thanh et al. 2015, Reijula et al. 2018), and thus to participants' ability to provide autonomous decisions, attention to this concern is particularly relevant. Third, clinicians, who are trusted sources of information, seem to be failing to disseminate relevant information to potential participants (Mathur et al. 2015). This is a loss because they are particularly well placed to provide information that is relevant to their patients' needs and values.

The relationships between access to information and trust in the sources of such information is also an important finding of our study. When participants

spoke about the sources of information, they highlighted the PD community, clinicians, and major foundations as trusted sources. Scientific knowledge is increasingly complex, abstract, and reliant on intricate technological devices. As our participants indicated, making sense of scientific phenomena requires a significant amount of expertise at a level that most prospective participants in early-phase stem cell clinical trials are likely to lack. Thus, to understand particular scientific phenomena, prospective subjects must first trust experts in order to rely on the information they provide (Scheman 2001). Insofar as trusted sources such as clinicians are not disseminating relevant information in ways that are understandable and easily accessible to those who need it, the research community is failing in its duty to make knowledge available to the public. Moreover, it is also squandering the opportunity to reach prospective participants who might require more information in order to feel comfortable joining a clinical trial. The field of PD research is actually well suited to disseminate information that patients find reliable, due to the rich and actively engaged PD community. To the extent that researchers are hoping to improve recruitment practices, calling upon these resources to provide more information about both stem cell research as well as clinical trials processes would be one particularly powerful avenue to pursue. Similarly, given that clinicians are one of the most trusted sources of information, they should be more attentive to the informational needs of their patients. Of course, concerns about appropriate information are also important not only for trial recruitment purposes but also in the context of clinical care. Some possible strategies identified in the literature that could help with dissemination of information and recruitment involve attention to infrastructure of the research program, the experience of the study team, the use of internet-based approaches, and the burdensomeness of participation (Hall, Moore, and Comella 2018; Picillo et al. 2015).

Our study sheds some light on the knowledge, concerns, and expectations of patients with PD regarding participation in early-phase stem cell clinical trials, but it has a number of limitations. Due to the small, nonrandom sample of participants, findings are not generalizable to the PD patient community. Although we made efforts to recruit a diverse range of participants for the focus groups, the sample was relatively homogenous in regards to race and ethnicity, with participants primarily identifying as white. Recruitment occurred within a major urban setting in

the United States, which could contribute to a limited range of participants' sociopolitical perspectives. As a study that aimed at exploring prospective participants' attitudes regarding participation in clinical trials, we are particularly aware of the fact that the missing voices of individuals who decline to participate in any research, even a low-risk focus group study, are very important. Nonetheless, our participants had different experiences, educational levels, experience with research participation, and familiarity with the topics of discussion, which was relevant to the study aims and resulted in a rich discussion. Although the semi-structured nature of the focus groups enabled us to guide participants toward relevant topics of conversation important to the research questions, it might have also directed participants to place greater or less saliency on certain subjects than they might have otherwise. However, we took care in structuring and running each focus group to foster and encourage conversation between participants with minimal interruption, in the hopes of mitigating this risk.

Participants in our study expressed difficulty accessing comprehensible information on current stem cell knowledge, clinical trials processes, and opportunities for research participation. This was a source of frustration. They also expressed some skepticism regarding the promises of stem cell research as a cure for PD, a skepticism that was intensified by concerns about research priorities for PD. Importantly, this skepticism did not lessen their interest in acquiring relevant information. They also identified consistently trusted sources of information, which gives the research community important avenues to ensure that prospective participants have access to the information they need in order to consider joining early-phase stem cell clinical trials and that can allow them to give meaning to such information in light of their values and interests.

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Author contributions

IdMM conceived of the study with the collaboration of MH and KH. All three authors contributed to design, data collection, and data analysis. IdMM and MH drafted the manuscript, all three authors contributed critical review and approved the final version of the manuscript.

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Conflicts of interest

No potential conflict of interest was reported by the author(s).

Ethical approval

This study was approved by the institutional review board at Weill Cornell Medical College.

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