Research Article

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Regenerative Medicine

Studying the lay of the land: views and experiences of professionals in the translational pluripotent stem cell field

Aim: The inherent uncertainty of first-in-human trials, combined with the technical complexity of pluripotent stem cells (PSCs), makes early phase PSC studies ethically challenging. Conducting parallel bioethics research based on experiences and views of professionals in the stem cell field is therefore important. **Materials & methods**: We conducted semistructured interviews with various stakeholders to get a lay of the land of ethical issues professionals find relevant to the translation of PSCs. **Results**: We identified four themes in the interviews: the uniqueness of PSCs, the suitability of the current research paradigm, the justification for early phase PSC studies and the involvement of patients and research participants. **Conclusion**: We conclude that a debate should take place discussing the suitability of the current research paradigm for translational PSC studies.

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The discovery of human embryonic stem cells (hESC) in 1998 has led to great expectations of the ability of hESCs to cure many, until now incurable diseases, due to their ability to differentiate into all the different body tissues [1]. This gives them potential to regenerate diseased or damaged tissue. The main point of contention to the use of these cells was the destruction of embryos, which was circumvented in 2007 by the discovery of a second human pluripotent stem cell (PSC), the induced PSC (iPSC), which was generated by reprogramming human adult fibroblasts [2]. However, numerous concerns about the safety of transplanting these two kinds of PSCs into the human body have been raised, such as tumor formation ability and unknown risks due to a lack of precedent trials [3–8].

Geron initiated the world's first first-in-human (FIH) PSC trial in 2010 for patients with spinal cord injury. hESC-derived oligodendrocyte progenitor cells were injected into the site of the injury, with the idea that the cells could remyelinate axons shortly after acute injury. Concerns were raised about the selected participants, the timing of the informed consent procedure [9] and the absence of replication of preclinical evidence in independent laboratories and in larger animals [10]. The trial was halted after a year due to economic–strategic reasons, although in 2013 Asterias acquisitioned the stem cell assets from Geron. Currently, one patient with complete spinal cord injury has enrolled in a Phase I/IIa dose-escalation study [11]. Other trials that have been set up with hES cells, as well as with iPS cells, are aimed at treating, for example, several forms of blindness, and diabetes [12]. Recently, promising data were presented of the safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium in patients with age-related macular degeneration and patients with Stargardt's macular

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dystrophy [13]. In addition, patients and doctors are awaiting the safety data of the first iPSC trial on macular degeneration, which was initiated in 2013, and where recently the transplantation of iPSC-derived tissue of the second patient could not be performed due to genetic mutations in the cells [14].

The high hopes that accompany these trials, in combination with possibly serious risks and the potential vulnerability of research participants, make translating PSCs to the clinic ethically challenging [8]. Moreover, as research participants are not expected to gain any direct benefit in early phase trials, justifying these so-called complex translational trials (i.e., first-in-human trials involving several invasive interventional and study procedures [15]) is more complicated. Many questions arise as how to proceed with PSC studies in a manner that balances a cautious approach with responsible innovation. It is therefore important that ethics research is conducted in parallel with clinical trials. As professionals are confronted daily with the practical, ethical and policy issues in their field, their experience, views and attitudes are highly relevant [16]. Therefore, we conducted semistructured interviews with various stakeholders (Table 1) in the stem cell field to obtain a lay of the land of the ethical issues that arise in the translation of PSCs according to these professionals [17].

Table 1. Background of interviewed stakeholders.

Characteristics	n (n = 23)
Sex:	
– Female	7
– Male	16
Nationality:	
– Dutch	8
– British	4
– American	3
– Canadian	5
– Australian	1
– Japanese	1
– Singaporean	1
Profession:	
– Basic scientist	10
– Clinician	6
– ELSI community	7
Career stage:	
– Junior professionals	4
– Senior professionals	19

ELSI: Ethical, legal and social issues.

In this paper, we reflect on issues that respondents believed to be important for the translational PSC field, and should be a focus of future policy debates.

Materials & methods

Design

We start from the premise that including moral experience stemming from practice can broaden and enrich the ethical analysis of topics of concern in bioethics. We use the concept moral experience to refer to the experiences professionals have with moral- and value-laden issues they have encountered in practice. We have explored the moral experience of professionals in the stem cell field through qualitative research [17]. We conducted semistructured interviews with basic scientists, clinicians and academics as well as others working on the various ethical, legal and social issues (ELSI) from several countries. This method allowed us to obtain a wide range of experiences from different cultural and professional backgrounds as well as different viewpoints (contrast maximization); however, the method is not aimed at generalization.

Respondents

Respondents were selected by purposefully sampling from a list of stem cell researchers in The Netherlands [18], and recruiting members of the International Stem Cell Forum. In total, 35 participants were invited; of these, 23 interviews were conducted. One did not respond and 11 individuals rejected the invitation because they either stopped working in the stem cell field, or could not spare the time. Recruitment was discontinued when saturation was reached and thus no new ethical thematic content was found in the insights and experiences of the interviewees [19].

Data collection

M Habets and A Bredenoord conducted interviews between September 2013 and September 2014. The one-to-one interviews lasted between 60 and 90 min and were initially guided by a topic list based on the existing literature; however, topics evolved following information obtained from completed interviews. As PSCs are currently mostly used in preclinical studies, we asked respondents about their experience with translational ethical challenges in general or with adult stem cells in particular. We also asked their views on (and if possible, their experience with) current and future ethical issues in the field of PSC translational research.

Data analysis

With consent, the interviews were audiotaped and transcribed verbatim. We analyzed the data thematically. Briefly, data from subsequent interviews

were constantly compared with data from preceding interviews. Codes, concepts and themes were formed in the process of analyzing the data. Using NVivo 8 software [20], M Habets independently coded the full transcripts. A Bredenoord read the full transcripts and verified the codes. Quotes of the interviewees drawn on below are representative of the themes we have identified.

Results

We identified the following four themes in the interviews, the uniqueness of PSCs, the suitability of the current research paradigm, the justification for early phase PSC studies and the involvement of patients and research participants.

Theme 1: the uniqueness of PSCs

A first theme that we identified in the interviews concerned the uniqueness of PSC interventions among cell interventions (not to be confused with the moral status of the hESC). Respondents diverged in their views whether PSC interventions are just another (stem) cell intervention, or whether they should be considered an exceptional category of cell intervention.

Some respondents commented that PSC interventions are potentially more risky than other (stem) cell interventions due to both their biological nature, and the required manipulation of the cells before transplantation. Moreover, unlike mesenchymal stem cells (MSC) and bone marrow stem cells (BMSC), no precedent is available for PSCs in clinical research. MSCs and BMSCs have been used extensively in clinical trials, and clinical practice, and have a good safety record.

Especially iPSC-derived interventions are thought to be more risky, as the method of reprogramming introduces genetic mutations, and the epigenetic memory of the cell may influence its differentiation. hESCs are thought to be more stable; moreover, some cell lines have been examined extensively for safety, and are thought to be ready to be introduced in clinical research. "So there's a progression of something which, by and large is safe, and saves lives, to something which is largely unknown in hESCs, but looks like it could be stable, and then you've got iPSCs where we are not quite sure about the stability yet" (Basic scientist, 12).

In contrast, others argue that because it is not the PSCs themselves that are injected into patients, but instead, PSC-derived tissue it is just like any other kind of cell intervention. According to them, it is the end product that is important: PSCs interventions are therefore no different from other stem cell interventions.

In contrast to divisive opinions on the uniqueness of PSCs, most respondents did emphasize a difference in research fields between PSCs, and BMSCs/MSCs. The MSC field is seen as a field where clinicians are willing to take (more) risks by injecting cells, even in the absence of robust scientific rationale. "…there is a tendency to use adult stem cells for all kinds of diseases, whether appropriate or not … and it becomes a fishing expedition…" (Clinician 2).

The PSC field, in contrast, is perceived as a field where basic scientists extensively study the mechanisms, the particulars of the cells and their safety profile before initiating a trial. Some interviewees believe basic scientists to be overcautious. "A scientific debate exists … and on the one hand, the basic scientists say: 'you have to understand the mechanism before you move on' and I would like to say: 'if you do not know whether the drug is efficacious, then why would you want to know the safety?' … We only need to know whether something is safe when we know it works" (Clinician 19).

Theme 2: the suitability of the current research paradigm

The last citation of the previous theme leads us to another remerging theme in the interviews: the suitability of using the current research paradigm (i.e., the structuring of translational research into Phases I, II and III) for translational PSC trials. On this issue too, divisiveness existed, especially regarding FIH studies, which are designed to examine only the safety of a stem cell (-derived) intervention, not its efficacy. First, some clinicians argue that if, in a FIH study, safety is observed but in subsequent studies the product turns out to be inefficacious, the safety studies have been futile and consequently, the exposure of research participants to risks as well. Second, by examining safety first, we may be discarding promising therapies because they do not pass the safety test, whereas it may be possible to increase the safety profile of an intervention, as has been the case with allogeneic hematopoietic stem cell transplantation. "So the regulations want you to do a safety testing so you understand the spectrum of the problems you're going to face. That doesn't mean the drug has to go away. It's the commercial pressure that makes the drug go away. Because what kind of company is going to continue developing a drug that they may face potential litigation against" (Clinician 18).

Third, some respondents worried about the consequences of the strong initial focus on safety on translational efforts of scientists and companies. According to them the enormous emphasis on safety as a first hurdle, blinds some researchers to the need for designing a translational plan, and not merely a plan for Phase I. As a consequence, early phase trial proposals sometimes lack a design for the next stages of research.

Some interviewees suggest this is intensified by the financial markets that react strongly both to successful Phase I studies, but also to the US FDA approval of Phase I studies – leading to the narrow aim of obtaining approval for Phase I studies. In addition, once an intervention is viewed as safe, many subsequent Phase I or II trials may follow, even in the absence of a scientific rationale, as has been the case according to various respondents with MSC interventions. The emphasis on safety has made it difficult for Research Ethics Committees (RECs) to reject proposals for Phase I studies because the intervention has been shown to be safe already. "The risks are minimal. That's the whole point … it's a safety and feasibility trial. So, what's the feasibility? Can you collect bone marrow and derive MSC's? Always feasible. Shown a thousand times. Is it safe? Yes, there's a mass of data showing that it's perfectly safe. So, there's no reason for any regulative authority to say, 'No, you can't do Phase I' [On] what grounds?" (Basic scientist 22).

Fourth, some interviewees question whether research participants should be exposed to risks when the objective of the trial is finding these risks, especially when no direct benefit is expected from the study intervention. Although this is a reason respondents critique the focus on safety in FIH studies, we will report on it in the next theme, because of its importance in the justification of early phase PSC studies.

Theme 3: the justification of early phase PSC studies

A third theme we identified in the interviews concerns the justification of early phase PSC studies. Respondents that were of the opinion that a lack of possible direct benefit for the research participant is unethical, consider the presence of the possibility to benefit a prerequisite for enrolling human subjects: "When it comes to the Geron trial [it is] so expensive and you're recruiting patients, and so in a way, while those patients should absolutely understand that it's a safety trial and they shouldn't have any expectations of success and it's generalizable information versus personal support, I still … think you should have chosen a window where you believe there's an outcome. A possibility of success" (member of ELSI community 21).

To others, the possibility of a benefit, no matter how small, would increase the likelihood of the therapeutic misconception: the misconception of participants that decisions are made solely with their personal care in mind instead of scientific aims [21]. In order to prevent this therapeutic misconception, interviewees emphasize the need for robust informed consent; and not merely robust written consent, but robust consent 'on the ground'; paying attention to all the social signs that pass between participants, researchers, clinicians and research nurses.

In contrast to the divergence in views of the first two themes identified in the interviews, there is consensus on the view that in risky, innovative early phase studies, terminally ill patients should be enrolled. The fact that these patients 'have not much to lose' provides the justification for exposing them to possible risks. Moreover, these patients may wish to participate in generating knowledge, for example for the benefit of relatives, when it concerns a hereditary disease, or for the benefit of other patients.

Some professionals emphasize the need for transparent public reporting of clinical trials as a requirement for justifying the participation of humans in research. If the results are withheld from the public domain, the contribution of participants has been meaningless. "…there is kind of a social contract too that has to be fulfilled … So if this information is going to be buried, then I would say it's absolutely reprehensible that the moral contract has been broken with this particular patient" (Member of ELSI community, 14).

Theme 4: the involvement of patients & participants

A fourth theme regards the involvement of patients and participants in FIH research (design). Many respondents mention the problem of balancing the autonomy of patients and the responsibility of researchers and RECs. Researchers have an obligation to only offer research when it is reasonable to offer, which is complicated in first-in-human research because of the many uncertainties. On the other hand, patients should be able to make their informed autonomous decision; some interviewees believe participants should have more voice in governing high-risk FIH research using innovative interventions, as is illustrated by the following citation: "it should be the case that it is the patient that is involved in making the decision, not institutions in Brussels, the US or The Hague" (Basic scientist 20).

Others, however, are more reluctant because of the hype and high hopes around stem cells. According to them, the public (including doctors) is not well informed when it concerns PSCs. Inaccurate information, in addition to, what some interviewees called, bias of severely ill patients, would prevent patients to make an informed decision. Other professionals reported that therapeutic misconception is no reason to put off enrollment. They argue that we allow patients to make all kinds of decisions on life or death (e.g., do not resuscitate); moreover, we often have misconceptions about risk which we do not find problematic (e.g., we do not prevent people from driving a car because they misconceive the risks of driving versus the risk of flying).

Some interviewees mention that it is important to know when to ask patients to enrol, which should not be in acute settings nor directly after having been diagnosed with a disease, as was done in the Geron trial. For this reason, it was argued, patients with chronic conditions, not acute conditions, should be enrolled in FIH risky studies. Some respondents suggested we could learn when to ask from the process of genetic counseling. In addition, we also need to do 'research on the research' by interviewing research participants, before, during and after a trial. Only through this kind of qualitative research researchers could collect essential data on what it is like to take part in a clinical trial. We need to develop, as one interviewee called it, 'an evidence-based protection'. "Because if we say we are engaged in human research protection, then who's the authority on that? It's the human subject. And so, why don't we talk to human subjects. So we have research ethics boards and what do they do? … They engage in protective imagination. So I protectively imagine what it would be like to be your age, say undergoing some study … but I never asked you about it" (Member of ELSI community 14).

In addition to learning when to ask, some professionals express the view that we should learn who to ask. Doctors should screen patients in a similar manner as individuals are screened for example jury duty. For this too, we would need to know more about research participants. Doctors should learn about the expectations of patients and the reasons for enrolling. What are their wishes, their hopes and their complaints? Moreover, to truly obtain informed consent, researchers or doctors need to have a good conversation with their patients, maybe even an ongoing informed consent process during the trial. "One of my mentors taught me that there are patients who are risk adverse and there are patients who are risk takers. You have to understand your patients before you can understand what treatment you can put them on … you have to spend a lot of time with that first part [of the trial] in a way that our current systems don't recognize all the time. [It has] become a very bureaucratic exercise rather than a real something useful for the patient and for the investigator" (Clinician 18).

Discussion

Our results show that part of the professional community see PSCs as uniquely novel. These professionals feel that in PSC studies the inherent ethical challenges of Phase I trials are intensified due to characteristics of PSCs (theme 1). However, divisiveness on this topic exists, which is not unexpected; it reflects a common pattern detected in argumentations on emerging technologies [22]. First, the innovative character of a new technology is promoted as a revolution. However, because opponents use the innovative character to caution against the many uncertainties of the technology, the innovative character is later downplayed [22]. It is possible that the reason for some stakeholders to view PSCs as 'just' another cell intervention, is to moderate the potential risks. This illustrates the cultural influences on assessments of risks; indeed, risk-assessment is not merely influenced by the state of scientific research [23]; nor is the status of PSCs a mere scientific result. To justify the use of PSCs, scientists may shift the boundary of the status of PSCs.

Although our interest was mainly in the PSC field, both clinicians and basic scientists demarcate this field from the MSC field. They emphasize the differences in fields (theme 1) including research method and professionals. In the PSC field, scientists focus on the basic mechanism and the safety of stem cells. We view this as what has been called 'ethical boundary work' [24]; a boundary is drawn between what is ethically preferred science and which is not [25].

Professionals in the PSC field view their cautious and careful approach with their focus on scientific rationale as morally favored over the more-established MSC-field, because they believe their approach is more 'scientific' [26]. Likewise, some professionals in the MSC-field, believe their translational method is morally preferred because it may lead to a faster drug development and thus to an earlier cure. However, a comment is in order: the concept of MSC has been imprecisely used since the 1990s [27], making it more difficult to exactly discern about which clinical trials interviewees are referring to when talking about the MSC field. Respondents seem to be mostly referring to the many autologous bone marrow stem cell trials in patients with heart disease [28] when they are talking about MSC trials. In general, we observed that many different stem cell concepts are used inconsistently between respondents, which may be reflected in this paper. This is not surprising; distinctions between differentiated, multipotent and pluripotent cell types are becoming more fluid, caused by advancements in the research field [29].

Our results demonstrate that most issues that were raised by professionals in the stem cell field, are not exclusive to their field, but are important in translational science in general. The second theme demonstrates that some professionals have reservations about the suitability of the current research paradigm, that is, the structuring of translational research into the three phases, for PSC translation (theme 2). Especially the focus on safety only in FIH studies has been criticized, because of an absence of possible benefit for research participants and because of a lack of obtaining proof for the mechanisms of efficacy. Although this is prob-

lematic for the translation of medical interventions in general, it is a more urgent and challenging problem for FIH PSC studies (as well as other complex translational trials) because of the higher risks, the irreversibility of the intervention and the fact that there is no precedent for these interventions. Not surprisingly therefore, FIH PSC-derived studies have enrolled patients for whom no treatment is available (anymore), and often have secondary, surrogate endpoints to test for efficacy. However, due to the enrollment of these refractory patients, the use of nontherapeutic dosages and the chosen surrogate endpoints, establishing efficacy is seldom likely. Changing the trial design could increase the chance of finding efficacy, however, this would come at a cost. For example, the use of stable patients would allow for better efficacy testing; however, consequences of unanticipated adverse events are thought to come at a greater cost to these patients. Similarly, to assess efficacy in Phase I trials, researchers could use presumed therapeutic dosages. However, higher dosages are thought to lead to an increased risk of harm. Last, surrogate endpoints need to be carefully chosen, as any additional procedure in a Phase I study will increase the risks involved. A careful balance thus needs to be found between minimizing risks to research participants and assessing efficacy in Phase I PSC trials.

As has been proposed for the development of cancer vaccines, possibly a better FIH study design would be a focus on safety, determination of dose and schedule and a proof-of-principle of biologic activity demonstrated by carefully planned endpoints [30]. This latter focus on biological activity of the mechanism would be beneficial for both the MSC and the PSC field. For the former it may prevent extended controversies on therapeutic effects; for the latter, it may prevent terminating the development of possibly effective interventions with identified side effects.

Surprisingly, the new regulatory framework in Japan favors the 'old' paradigm of identifying safety first, and thus contrasts with the view we identified in the interviews. The new law in Japan can give conditional, time-limited market approval for regenerative medicine products, when the safety of the product is confirmed and an exploratory study has predicted likely efficacy [31]. The intention may be similar: fast tracking the drug approval process for regenerative medicine products. However, in Japan, the emphasis is still on safety; efficacy will be proven once it has limited market-approval, and thus Phase II and III are omitted in this regulatory framework. In our study, respondents suggest testing safety and efficacy in first-in-human studies; not omitting efficacy trials, but advance it to the first phase.

Furthermore, theme 3 demonstrates another reason for examining efficacy in first-in-human studies, namely. creating a possibility for research participants to gain a benefit.

The results show that some professionals feel that participants should have at the very least a possibility to benefit when enrolling in FIH studies. This again reaffirms a longstanding debate in the research ethics literature on the justification of early phase studies [32–34]. On the one hand, it is viewed as unethical to expose research participants to risks without any potential to benefit; on the other hand, due to the current focus on safety only in early human trials, we may be discarding promising interventions. Moreover, the emphasis on safety should not hinder safeguarding the scientific rationale of a study. Just as allowing such direct benefits in early phase trials would be a strategy to justify FIH research, other respondents view an increased involvement of both patients and participants as necessary to justify PSC studies (theme 4). The need for patient involvement in the set up and design of clinical trials has long been recognized [35] and their involvement has been growing [36]. In contrast to the voice of patients, or patient representatives, less emphasis has been placed on the voice of the research participant. This is surprising, as only research participants can determine whether enrolling in a study has benefited them. And this is important, because the anticipated benefits must be proportional to the potential harm in clinical research according to international documents on ethical conduct. These benefits consist of direct benefits due to the intervention; collateral benefits, which are benefits due to enrolling in the trial; and aspirational benefits, or social value. Collateral benefits, such as rewards for participation or altruistic motivations, are not seen as legitimate justifications for enrolling participants in research. However, recent literature has shown that some participants view helping others, besides personal benefit, as the main reason to partake in clinical research [37,38]. Solidarity would be a strong basis for robust informed consent; possibly, this view on the problematic nature of collateral benefits, needs renewed discussion.

Qualitative research is necessary to learn about the reasons participants enroll, their expectations, needs, hopes and their experience as a participant [39]. Studies on the experiences of research participants have mainly been carried out to improve recruitment and retention of participants [40], However, we need to learn from participants to achieve evidence-based participant protection [41]. The perspectives of research participants are important to researchers and RECs, and may also enable future participants to make better-informed decisions [39]. In addition, it could facilitate bridging the gap between bioethical ideals and clinical reality [42]. Indeed, some respondents implicitly discussed

this gap by drawing attention to the bioethical ideal of respecting patient autonomy by the informed consent process, and the reality of the current formalized (empty) informed consent process [42].

Conclusion

We conclude that a debate should be held on the appropriateness of the current research paradigm for PSC interventions. The emphasis on safety in the current paradigm of phasing research ensures on the one hand a steering away of interventions that have side effects, but may be efficacious, and, on the other hand ensures continuous early phase research in safe, but possibly nonefficacious interventions. In addition, the discussion on the possibility of participants to directly benefit in first in human research may need to be reopened.

Future perspective

With the intensification of clinical trials in regenerative medicine, such as PSCs, tissue engineering and biomaterials, we believe it is necessary for interdisciplinary working groups to rediscuss the appropriateness of the current research paradigm, as was done for cancer vaccines [30]. The risks of these early phase complex translational trials may be considered too high to not allow participants to gain any direct benefit. Furthermore, although safety should be the primary considerations, we may sometimes be obliged to simultaneously test for efficacy, provided this will not compromise safety. It is

Executive summary

Introduction

- Early phase pluripotent stem cell (PSC) trials are ethically challenging. Here, we reflect on issues that respondents believed to be important for the translational PSC field, and should be a focus of future policy debates.

Methods

- We conducted semistructured interviews with various professionals in the stem cell field to get a lay of the land of ethical issues relevant to the translation of PSCs.

Results & discussion

- The uniqueness of PSCs:
  - Some professionals in the stem cell field view PSCs as an exceptional category of cell interventions with enhanced risks to research participants;
  - Others view PSC interventions as no different from other stem cell interventions as it is the end product, and thus the derived tissue that is transplanted;
  - This movable boundary of the (unique) status of PSC is partly influenced by the public's view of risks on the intervention.
- The suitability of the current research paradigm:
  - Some clinicians argue that if safety is observed but the end product is not efficacious, the safety trials have been pointless;
  - Others point out that by examining safety first, we may be discarding promising therapies because they do not pass the safety test;
  - Some interviewees question whether research participants should be exposed to risks, when there is no chance of them benefiting from the intervention tested;
  - We believe it is important that interdisciplinary working groups discuss the suitability of the research paradigm for PSC.
- The justification of early phase PSC studies:
  - For some respondents, the possibility of a benefit is a prerequisite for enrolling human subjects, even though this would increase the likelihood of the therapeutic misconception;
  - Consensus exists among interviewees that in risky, innovative trials, terminally ill patients should be enrolled. However, in actual fact, the first-in-human PSC studies are using treatment refractory, but not end-of-life patients.
- The involvement of patients & research participants:
  - Some interviewees mention that it is important to know when to ask patients to enrol; others emphasize it is important to know who to ask;
  - We need to learn about the views and attitudes of research participants through qualitative research with research participants, in order to improve research protection.

Conclusion

- Our main findings are that a debate should be held on the appropriateness of the current research paradigm for PSC interventions. The emphasis on safety in the current paradigm of phasing research may not be applicable to high risk, innovative and invasive human research.

important that we learn more about the experiences of participants. With the first results of PSC Phase I studies coming out, it is time we initiate these discussions.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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