PERSPECTIVE

# Future needs for informed consent in stem cell clinical trials in neurodegenerative diseases

Translation of recent advances in stem cell research into clinical trials for restorative therapies for human disease is accelerating dramatically, with a strong focus upon neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). It is likely that first-in-human intracerebral transplantation of cells derived from human embryonic stem cells (hESC) and inducible pluripotent cells (iPS) will occur within the next few years (Tabar and Studer, 2014) and intraspinal transplantation of hESC-derived cells has been recently reported in ALS. As clinical trials are planned and implemented, it will be critical to attend to the ethical framework necessary for responsible translation of these scientifically compelling, but risky, interventions in humans. In particular, these clinical trials will present a variety of challenges to the informed consent process (de Melo-Martín et al., 2015). We therefore review barriers to obtaining a truly informed consent in early phase stem cell clinical trials in neurodegenerative conditions, and we describe procedures and interventions that have been investigated to potentially address and overcome these barriers.

**Challenges to obtaining a truly informed consent in stem cell-based trials in neurodegenerative disorders:** A truly free and informed consent occurs when an individual is competent to act, receives a thorough disclosure of the research, understands the information provided, acts voluntarily, and consents to participation. Barriers to disclosure and assessment of capacity are particularly relevant in clinical trials of stem cells for neurodegenerative disorders, as indicated in **Figure 1**. The element of disclosure necessitates that researchers give subjects any information that could affect a prospective participant's decision to enroll in the study, and thus requires conveying highly complex scientific information in ways that can be understood by participants. First-in-human trials involve uncertainty regarding risks and potential benefits. Data from previous transplant trials, from sources other than hESC or iPS cells, have raised awareness of risks. Case reports have included tissue overgrowth and mass lesions after fetal striatal cell transplantation in HD, and one case of fatal cyst formation after fetal mesencephalic tissue transplant in PD. Moreover, possible acute or chronic rejection has been suggested after fetal cell transplantation. Additionally, provision of information on cell provenance will be highly important to some participants, as although hESCs for transplant studies will be grown in the laboratory, they are originally derived from early human embryos and may therefore provoke concerns based upon religious and moral objections.

Competence or capacity judgments distinguish potential participants able to make certain decisions autonomously from those who cannot, and in the latter case a surrogate decision-maker will be needed in order to proceed. However, assessment of capacity is particularly difficult in people who have cognitive impairment, and this is common in neurodegenerative diseases. For example, even mild cognitive impairment (MCI) in PD may compromise people's ability to understand the elements of a study, and to make decisions. However, not all individuals with MCI are thought to lack capacity, highlighting the need for robust instruments for determining capacity. For instance, one study in PD found that for individuals classified with borderline and impaired cognition by standard clinical rating scales, expert judgment determined that over half were competent to consent (Karlawish et al., 2013). Conversely, in those assessed as cognitively normal by standard instruments, 17% were judged to lack capacity to give consent. Therefore, although it would be desirable to lighten the burden of testing on study patients and staff, evaluation by a psychiatrist experienced in assessing capacity is essential. Given the progressive cognitive decline associated with many neurodegenerative diseases, understanding of key research elements may be compromised during long-term follow up in a study. It is likely that at least some participants will lose capacity as time progresses. Therefore, although not recommended as "stand-alone" tests at the time of enrollment, standardized assessments of both cognition and capacity may play a role in monitoring over time.

Multiple studies have examined patients' difficulties in understanding key research components. Such difficulties often result in the therapeutic misconception (TM), a failure, affecting both researchers and participants, to distinguish the aims of research *versus* clinical care. In contrast to clinical care, which aims to provide the best medical care for an individual, research has a primary goal of answering a scientific question. The failure to distinguish research participation, in which a researcher seeks to obtain valid data, from medical treatment, in which a person seeks to maximize clinical health benefits, may undermine the informed consent because it can lead subjects to underestimate the risks and overestimate the potential benefits of research participation (Lidz et al., 2004). TM has been documented in several studies of neurodegenerative disorders. For example, 5 of 8 participants in a phase I study of gene therapy in PD responded that their primary motivation for enrolling was therapeutic benefit (Kim et al., 2009). The phenomenon is apparent across various neurodegenerative diseases. Another study assessing the impact of the expressions used in consent documents to convey potential benefits of participating in a hypothetical phase I trial of stem cell transplantation in ALS found that variations in language regarding benefits had significant effects. Even in those respondents expressing an appropriate understanding of uncertainty surrounding potential benefits, estimates of probable benefit were higher when benefit was "not guaranteed" rather than when there was a "very small" chance of benefit (Kim et al., 2015). This suggests that even when participants readily comprehend the inherent uncertainty in risks and benefits, they may still be influenced by subtleties of language in an informed consent form.

**Potential solutions to improve informed consent:** The examples above demonstrate that even when clinical researchers are well intentioned and take time to explain the study and ascertain understanding, the complexity of a cell

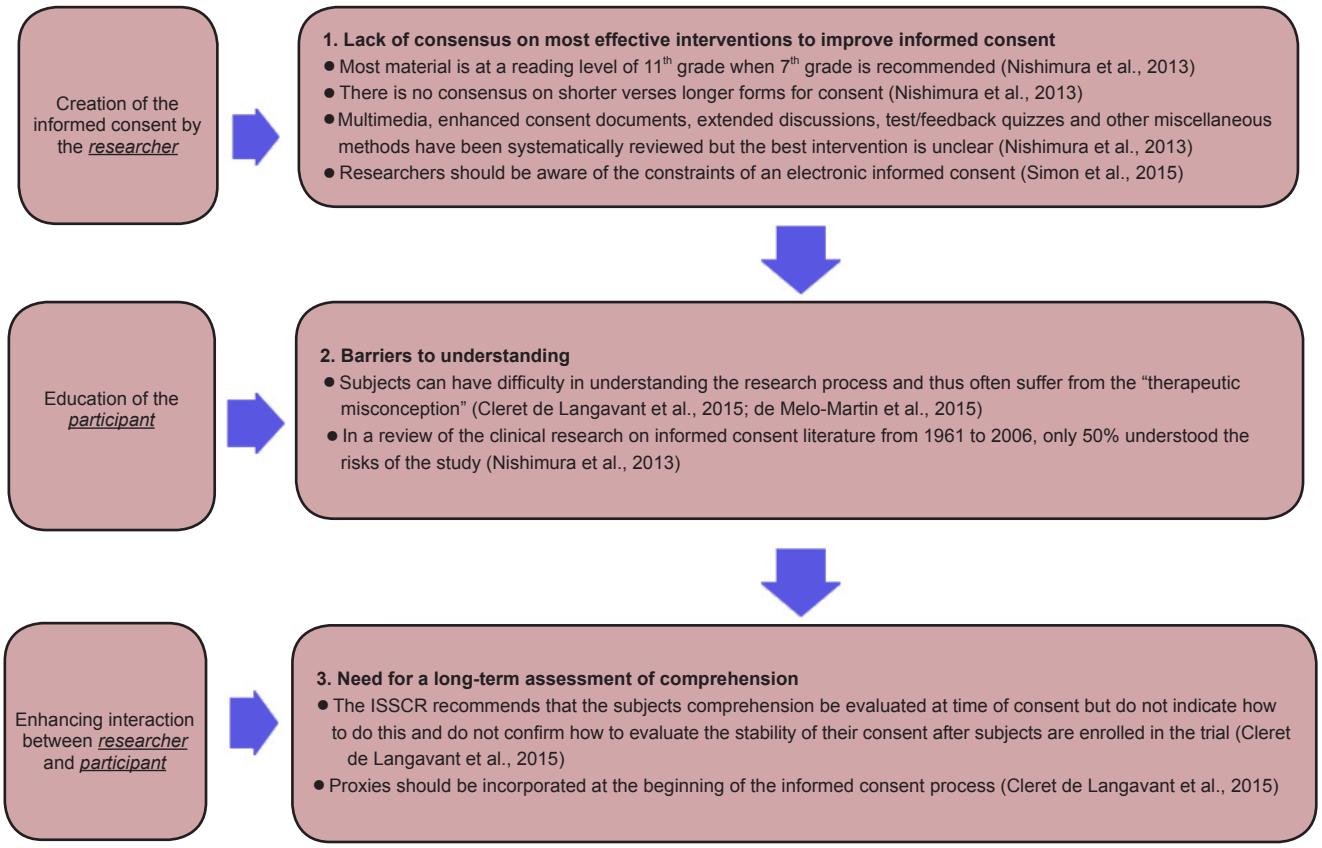


**Figure 1 Key aspects of the informed consent process.**

transplant trial demands a more rounded approach. Existing studies have attempted interventions on three aspects of the informed consent process: the researcher, the participant, and enhancing the interaction between the two (**Figure 1**). Targeted interventions to improve the informed consent process have employed a variety of methods, such as improving readability of consent forms, assessing comprehension either formally with quizzes or informally with feedback conversations, providing study material, modifying the duration of the informed consent process, and expanding the team involved (Nishimura et al., 2013).

A number of interventions have now been evaluated that aim to deliver research information in ways that improve retention and understanding by participants. Although not yet undertaken in cell transplant clinical trials, these studies describe approaches that may be incorporated into these trials in the future. For example, in a study of informed consent in a biobanking initiative, an enhanced informed consent process using multimedia or interactive interventions resulted in superior understanding of the purpose, components, and risks of the biobanking study among participants enrolled via the enhanced process (Simon et al., 2015). In a study of prospective oocyte donors, an hour-long audio-visual group presentation and 30-minute individual counseling with endocrinologists resulted in a statistically significant difference in subjective and objective comprehension scores (Skillern et al., 2014). In a longitudinal study of retention of informed consent information in fetal tissue transplantation trials for HD, a consent questionnaire for assessing comprehension of complex scientific information during the informed consent process had a significant impact on long-term comprehension scores and satisfaction with information provided (Cleret de Langavant et al., 2015). In particular, the addition of tablet- or web-based information might supplement in-person discussion and provision of printed materials. In considering what information to provide, using such technologies will be key to convey complex scientific information that is understandable and complete, yet avoids information overload. Thus incorporating input not only from experienced scientists and clinical researchers, but also patient community representatives will likely be helpful.

The popular media hype about stem cell research can also complicate the researcher's role in the informed consent process, as it contributes to TM. In particular, it may be unclear that administering stem cells for neurodegenerative diseases involves unproven treatments. In addition to potential subjects' interaction with the research team, there are reliable independent sources of information towards which potential study participants can be directed. For example, the International Society for Stem Cell Research (ISSCR) provides a patient handbook including questions that patients may review on a patient education page (http://www.closerlookatstemcells.org).

In clinical trials that involve an experimental stem cell-based intervention, informed consent should not be considered a one-time event but an ongoing process that is operative for long-term follow up. Once participants are consented, they will then need to provide ongoing consent/

assent. It is during this extended follow-up that a proxy is likely to play an increasingly important role. Hence, involving a proxy early in trial participation may be advisable for several reasons. First, early involvement allows the proxy to be familiar from the beginning with study requirements. Second, it allows participants and their proxies to talk and discuss goals so that when the participant loses capacity, the proxy can make decisions that are consistent with the values and desires of the participant. Third, early involvement of proxies also helps establishing a relationship between researcher, participant and proxy (Cleret de Langavant et al., 2015).

**Conclusions and future directions:** A variety of neurodegenerative disorders are thought to be amenable to restorative therapies using stem cell-based interventions. However, many studies raise concerns that "standard" consent processes may be insufficient to ensure that potential study participants' decisions to enroll in such trials are indeed autonomous. Although some of these concerns are common to all trials, the significant uncertainty regarding the risks and potential benefits of stem cell trials in neurodegeneration makes the need for development of guidelines for researchers imperative. The critical need for a truly informed consent, with independent regulatory review and oversight to maximize respect for patient autonomy and minimize potential impacts of conflicts of interest for researchers, is highlighted by the ISSCR "Guidelines for the Clinical Translation of Stem Cells" (2008, accessed at http://www.isscr.org/docs/default-source/clin-trans-guidelines/isscrglclinicaltrans.pdf). We further suggest that conveying complex and nuanced scientific information and reducing the effects of the therapeutic misconception could be addressed by extended consent procedures that might take place over time, and that might incorporate tablet-based or web-based materials. Researchers will need support in the use of expanded consent processes that may involve multimedia. Attention needs to be paid to increased time burden, avoiding the potential for information overload, and to ensuring that the use of multimedia is not used as a substitute of discussion and conversation (Nishimura et al., 2013; Simon et al., 2015). The recognized need for long term follow up also necessitates changes in how capacity is assessed over time, and how to address a situation in which a subject loses capacity, for example due to progressive cognitive decline associated with some neurodegenerative disorders. Indeed, if this condition is not met it may compromise the long-term success of the program. As the field as a whole works towards consensus, we recommend close collaborations, not only between preclinical and clinical research teams, but also with bioethicists and individuals (usually psychiatrists) skilled in assessing capacity, and local Institutional Review Boards (IRBs) familiar with issues particular to a given geographic region or culture.

***Funding:*** *Claire Henchcliffe receives grant support from: NYSTEM, NIH/NINDS. Inmaculada de Melo-Martín receives grant support from: NYSTEM. This work was also supported by the Solomon Family Foundation and CV Starr Foundation.*

***Presentation at meetings:*** *Part of this work has been presented at: NYSTEM 7th Annual Meeting, May 14-15 2015, New York, NY, USA; 19th International Congress of Parkinson's Disease and Movement Disorders, June 14-18, San Diego, CA, USA; ISSCR 2015 Annual Meeting, June 24-27 2015, Stockholm, Sweden.*

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***doi:** 10.4103/1673-5374.169632* ***http**://www.nrronline.org/*
***How to cite this article:** Hellmers N, Obeng-Aduasare Y, de Melo-Martín I, Henchcliffe C (2016) Future needs for informed consent in stem cell clinical trials in neurodegenerative diseases. Neural Regen Res 11(1):83-85.*

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