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The Complex Ethics of First In Human Stem Cell Clinical Trials

Mark Yarborough, PhD [Bioethics Program],

University of California Davis

Teresa Tempkin, RNC, MSN, ANP,

Department of Neurology, University of California Davis

Jan Nolta, PhD [Director], and

Stem Cell Program and Institute for Regenerative Cures, University of California Davis

Nanette Joyce, D.O. [Staff Physician]

Department of Physical Medicine and Rehabilitation, University of California Davis

We applaud Dr. Hess for raising an issue of critical importance regarding Phase I clinical trials of novel stem cell (sc) transplants, which is the role that clinical efficacy endpoints should play in assuring the ethical design and conduct of such trials.¹ In what follows, we highlight significant considerations, all interrelated, that can challenge efforts to incorporate ethically appropriate clinical efficacy endpoints in Phase I sc trials. First and foremost is the need to preserve the principal aim of safety in such trials. Second is the degree of difficulty researchers can face in trying to minimize the risks that Phase I sc trials pose to clinical volunteers. Third is the difficulty of knowing what should count as adequate pre-clinical data that warrant the launch of Phase I trials with realistic expectations for clinical efficacy. Finally, there is the challenge of not permitting those clinical efficacy measures to introduce unrealistic expectations of therapeutic benefit into the informed consent process. Throughout we will draw from ongoing research, including research at our own institution, that targets sc therapies for both Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS).

A great service of the Hess article is that it shows the ways in which Phase I sc trials can differ from more traditional Phase I trials of molecular compounds. The degree of novelty and risk in some Phase I sc trials, combined with the desperation of trial participants, challenges the standard view that Phase I trials should be exclusively about safety. Therefore we appreciate his point that there is something unfair and unwarranted in asking people to volunteer for a clinical trial where there is no intention to look at the clinical effects of the new sc intervention. Having said that, however, the fact remains, and must remain, that safety should be the primary endpoint of Phase I trials of any new therapeutic substance, including novel stem cell transplants. The FDA is correct in its policy that one must first establish safety before exposing larger numbers of subjects to potentially dangerous substances. Biostatistics and clinical trial design further dictate what generalizable information can realistically be gained from a phase I trial. Phase I trials recruit a small sample size, are not powered to detect efficacy, do not randomize, and do not include a control. Therefore, efficacy cannot be adequately assessed and causation, even if efficacy is observed, must be left unassigned to the experimental treatment. Thus, questions about safety and tolerable cell dose are the only ones that can be answered at the completion of a Phase I trial. One can at best *learn about* clinical efficacy from a Phase I trial, but even this modest achievement is possible only if a trial is appropriately designed. As we show below, this can prove especially problematic for Phase I sc trials.

Since many experimental sc techniques are so novel, a first challenge to be confronted in proper trial design is deciding the degree to which clinical efficacy endpoints should influence safety considerations in a trial, if at all. The recent phase I trial initiated by

Neuralstem for treatment of ALS cited by Prof. Hess illustrates the degree to which trial design itself can significantly alter risk. That trial began with transplantation of neural stem cells (NSC) within the lumbar spinal cord, with treatment of the preferred clinical site at the cervical cord reserved to only the very last volunteers enrolled in the trial.² Given the novel nature of the trial, there was the very real prospect that the method of NSC transplant could have caused paralysis and paralysis in the lumbar region is much less life-threatening than paralysis in the cervical region. So, the trial initially explored whether the NSCs could be safely transplanted, in addition to assessing the safety of the cellular product. However, following the lead of Hess regarding the ethical necessity of looking for clinical efficacy in the earliest of trials, a strong case could have been made in support of using cervical spine transplantation earlier, or perhaps even at the start of the trial, as this site would have likely provided greater potential for benefit via the region's innervation of the diaphragm and the possibility of slowing progressive and typically lethal respiratory dysfunction if a beneficial clinical effect were to occur. This trial illustrates that if clinical endpoints are an ethical necessity of Phase I sc trials, it can prove difficult at times to know exactly how to incorporate them and many trials will require trade-offs between safety and efficacy in order to include endpoints we may learn very little about, given how the small number of trial participants will preclude any definitive understanding about therapeutic efficacy.

The Neuralstem ALS trial also illustrates our final point about safety in Phase I sc trials, which is that even though all Phase I sc trials are risky, they are not equally risky. Risks of sc transplants vary not only according to the site of implantation as we just discussed above, but also according to the type of sc to be implanted and the method of delivery used for transplantation. Many would consider embryonic (ESC) and induced pluripotent sc (iPSC) derived therapies to hold more risk than mesenchymal (MSC) therapies due to the defining capacity of ESC and iPSC to form teratomas. SC therapies that are transient, without the capacity for sustained engraftment, would theoretically be less risky than those that permanently engraft. Intracranial or intraspinal delivery of sc products has more potential for serious adverse consequences than intramuscular or even intra-arterial delivery. Thus, in contrast to more traditional Phase I trials, in sc research, a series of Phase I trials may be required to establish safety regarding type, method and site of sc transplants, many of which will likely entail trade-offs between safety and efficacy in trial design. While the need for tradeoffs is certainly not unique to sc Phase I trials, they are especially acute given both the lack of alternative interventions for many early sc trial participants and how, as Hess discusses, inclusion of clinical efficacy endpoints may represent more respectful treatment of trial volunteers.

The next challenge to be confronted when arguing for a more robust role for clinical efficacy endpoints in Phase I sc trials relates to pre-clinical data about both safety and efficacy. While the FDA insists upon rigorous data for both, questions remain about how to best target pre-clinical studies for many neurological disorders. For example, how does one use animal models to predict potential impact on human cognition and affect?³ Nor is it always clear what the most meaningful outcomes should be for a particular disease. Taking ALS as an example, should animal studies target functional improvement or prolonged survival?⁴

Those of us involved in HD research at our institution have overcome these challenges in our efforts to launch a Phase I HD MSC intracranial trial. We are performing all required IND enabling studies to ensure safety and efficacy in relevant non-human animal models. Research in rodent models of HD has shown efficacy while biosafety has been demonstrated by our research in a non-human primate model. Study personnel have been blinded at key points to assure accurate interpretation of data and the research findings and discussion have been published in peer-reviewed science journals.⁵⁻¹⁰ We have chosen to initially develop MSC transplants, due to the decades long record of their safe use in humans,^{11,12} as well as

recent Phase I and II trials that have utilized intracranial sc transplants without significant adverse events.¹³ In short, there are many years worth of targeted research in preparation for this trial that collectively establishes a reasonable prospect that the trial may safely progress to the Phase III stage and possibly FDA approval, thereby ethically justifying the initiation of human trials. So it is possible to design a Phase I sc trial that meets the requirements set forth by Hess.

There is one other potential complication to note about including clinical efficacy endpoints at the Phase I stage, however, and that is the need to include measures for those endpoints in the design of the trial. One way this is being done in the HD trial planned at our institution is through the use of a neuroimaging biomarker. It will be used at critical timepoints to monitor changes in the brain prior to therapy implantation and post implantation. This biomarker will address both safety measures and yield information about efficacy by producing data on changes in brain volume. Relevant measures will be a requirement for all Phase I sc trials that incorporate clinical efficacy endpoints. As Hess correctly notes, these measures may in some instances significantly increase the burden on trial volunteers due to the need for possibly invasive procedures to generate and document any clinical efficacy that may occur, further complicating a very difficult informed consent picture.

In that picture is a nest of challenges to overcome. First, no matter how extensive pre-clinical data may be or how well-established delivery techniques and procedures are, most novel sc approaches and applications entail unknown major risks that cannot be entirely quantified or minimized in advance. Hence the need for a Phase I study with the challenge of making sure potential volunteers understand the trial is only capable of definitively answering questions of safety. Second, most if not all prospective Phase I sc trials volunteers will lack meaningful treatment options. They will be eager, if not desperate, to participate in Phase I trials regardless of risks and trial design limitations. Third, and somewhat ironically, including clinical efficacy as an endpoint, even a secondary one, will increase the prospect for therapeutic misconception. If documenting any observable clinical effect is a study endpoint, so that information about risks and benefits can be documented, this will be referenced in the consent process and will of course be subject to great misunderstanding. The only hope for navigating this nest of challenges is to design an informed consent process with multiple safeguards to assure that prospective research participants understand the highly experimental nature of Phase I studies and that safety rather than subject benefit is the only question the study is designed to answer.

To sum up, we are supportive of Hess's contention that clinical efficacy endpoints deserve inclusion in Phase I sc trials. What we have tried to do is highlight the complex issues that need to be resolved in order to ethically include them. We worry, in closing, that many Institutional Review Boards and Stem Cell Research Oversight committees are currently ill equipped to understand and thus review and oversee the challenges that arise from the complexities.³ This is troubling given the essential ethical role that independent review plays in the research enterprise and the public's trust in it. Independent review and oversight of past gene therapy Phase I trials proved problematic, and the apparent lack of learning by the research oversight communities from those mishaps remains troubling.¹⁴ Further thought is needed at this time to explore how this can be avoided with sc Phase I trials, so that IRBs and SCROs can serve as knowledgeable and reasonable independent guardians of this vital research and the public's trust in it.

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