

Cell-based interventions for neurologic conditions

Ethical challenges for early human trials



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ABSTRACT

Background: Attempts to translate basic stem cell research into treatments for neurologic diseases and injury are well under way. With a clinical trial for one such treatment approved and in progress in the United States, and additional proposals under review, we must begin to address the ethical issues raised by such early forays into human clinical trials for cell-based interventions for neurologic conditions.

Methods: An interdisciplinary working group composed of experts in neuroscience, cell biology, bioethics, law, and transplantation, along with leading disease researchers, was convened twice over 2 years to identify and deliberate on the scientific and ethical issues raised by the transition from preclinical to clinical research of cell-based interventions for neurologic conditions.

Results: While the relevant ethical issues are in many respects standard challenges of human subjects research, they are heightened in complexity by the novelty of the science, the focus on the CNS, and the political climate in which the science is proceeding.

Conclusions: Distinctive challenges confronting US scientists, administrators, institutional review boards, stem cell research oversight committees, and others who will need to make decisions about work involving stem cells and their derivatives and evaluate the ethics of early human trials include evaluating the risks, safety, and benefits of these trials, determining and evaluating cell line provenance, and determining inclusion criteria, informed consent, and the ethics of conducting early human trials in the public spotlight. Further study and deliberation by stakeholders is required to move toward professional and institutional policies and practices governing this research. *Neurology*® 2008;71:288-293

GLOSSARY

CBI-NCs = cell-based interventions for neurologic conditions; **ESCROs** = embryonic stem cell research oversight committees; **FDA** = Food and Drug Administration; **hESCs** = human embryonic stem cells; **IND** = Investigational New Drug; **IRBs** = institutional review boards.

Attempts to translate basic stem cell research into treatments for neurologic diseases and injury are well under way. In the United States, the Food and Drug Administration (FDA) has approved an Investigational New Drug application (IND) for using human CNS stem cells, isolated from fetal brain tissue, in clinical trials as a potential treatment for Batten disease,¹ a fatal inherited disorder of the nervous system.² In addition, there are reports of at least five additional human trials for cell-based interventions for neurologic conditions (CBI-NCs) being planned, involving a wide variety of human stem cells derived from embryonic and adult sources.³⁻⁷ These trials will target neurologic conditions such as spinal cord injury, Hurler syndrome, stroke, and Huntington disease. Outside the United States, there are unpublished, but publicized, reports of cell-based treatments for spinal cord injury, stroke, and many other neurologic conditions (e.g., www.stem-cells.com/case.php, www.nrrft.com, www.emcell.com).

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Arguably, this science is proceeding faster than the social debate concerning the ethical integrity of and the protection of human subjects in the research. Although national-level review is required in a few countries (e.g., by the Human Fertilization and Embryology Authority in the United Kingdom), in the United States, the idea of national review is still under consideration and no national ethics oversight group exists. As a consequence, the oversight of the ethics of these first human trials remains the responsibility of local institutional review boards (IRBs), nascent embryonic stem cell research oversight committees (ESCROs), and the FDA. Although in many respects the ethical issues these local groups will address are standard challenges of human subjects research, they are heightened in complexity by the novelty of the science, the focus on the CNS, and the political climate in which the science is proceeding.

This article identifies some of the distinctive challenges confronting US scientists, administrators, IRBs, ESCROs, and others who will need to make decisions about work involving stem cells and their derivatives and evaluate the ethics of the first forays into human clinical trials for CBI-NCs. The US experience represents one example of how the challenges will likely be defined and addressed; however, versions of these challenges will be faced by all countries seeking to regulate such trials. These trials will raise many of the same questions about risk, benefit, and safety, regardless of the type of cell used (e.g., human embryonic stem cells [hESCs] vs adult stem cells); as such, our discussion applies to trials of cell-based interventions generally.

RISKS, BENEFITS, AND SAFETY IN NEUROLOGIC TRIALS Clinical trials for neurologic conditions raise unique concerns about risk, and the use of stem cells and their derivatives add considerable uncertainty to those risks. Risks may include development of abnormalities in brain function (including changes in cognition or affect) and motor or sensory function, as well as changes in other systems. While we cannot predict a priori the full spectrum of possible risks, prior research⁸⁻¹⁵ suggests that we evaluate research subjects for at least those risks listed above, in addition to potential risks of cell-based interventions generally, including tumor formation, misdif-

ferentiation, and mistargeting.¹⁶ Oversight bodies must consider how they will assess the probability and magnitude of both risks and benefits to human subjects. Since some of the risks are unknown and may take time to manifest, investigators and oversight bodies should also consider whether to require long-term monitoring of research participants, and (if so) what that monitoring should include.

Importantly, many of the risks involved in trials for neurologic conditions, such as undesirable changes in cognition and affect, are not easily evaluated in animal models. This is part of a broader set of challenges raised by the use of animal models for preclinical studies, including concerns related to human-nonhuman primate neurologic chimeras.¹⁷ For example, there is no animal model for the cerebral version of adrenoleukodystrophy,^{18,19} the animal model for multiple sclerosis is limited,^{20,21} and though many preclinical studies of pharmacologic agents have shown promise in nonhuman animal models of stroke, none has so far been successful in humans.²² Even for those risks that can practically be evaluated in nonhuman animals (e.g., neoplasm development), the predictive utility of animal models for human disease is often unknown. That said, animal model data are frequently crucial and oversight bodies should ask investigators for all relevant nonhuman animal data. Oversight bodies will need to determine what constitutes “adequate” animal data in this new field, and if there are cases where extensive nonhuman animal data ought not be required before moving forward in humans (e.g., when no appropriate nonhuman animal model exists).

The stem cells themselves pose an additional unknown risk. The longer cells are grown in culture, the more likely they are to acquire genetic and epigenetic changes,²³⁻²⁵ such that later passages may not be genetically identical to earlier passages. Several institutions have begun developing procedures for evaluating stem cell lines.²⁶ However, it is unclear which tests (e.g., DNA sequencing, expression analysis) provide meaningful data in terms of risk to human subjects. As in other types of stem cell transplantation,^{27,28} the risk of transfer of a donor’s genetic disease via stem cells must be considered. The health risks associated with, for example, a cell-based treatment for stroke that uses cells carrying the mutation for Huntington disease is unclear. Scientists and oversight bodies will need to determine which disease-causing genetic mutations should bar human materials from use in deriving stem cell lines. However, this may create a conflict between maintaining the confidentiality of the personal health information of the donor and the need of scientists and patients

to know the potential genetic risks and disorders associated with a cell line.

Assessing benefits to human subjects can be as difficult as assessing risks. IRBs must, for example, judge the relative benefits not only to the patient, but also to future patients and the broader society. Such judgments about a specific cell-based trial may be difficult for IRB and ESCRO members whose expertise falls outside neurology or stem cell science. The varying etiologies (e.g., genetic vs environmental) and courses (e.g., rapid and certain decline vs chronic, stable disability) of these conditions raise different concerns both in terms of risk and in likelihood of benefit to the research subject and the broader patient community. Such complexities, along with unique risks such as the unknown implications of genetic mutations in cell lines or the risk of undesirable changes in cognition, underscore the need to involve relevant experts in the review process, even if this causes some delay.

PROVENANCE OF STEM CELL LINES The manufacture of a drug or device and the generation, growth, and maintenance of a cell line are quite different processes. While new drugs used in US clinical trials must meet rigorous FDA standards for production, the process of deriving cell lines does not map neatly to concepts of good manufacturing practices. For example, hESCs are derived following fertilization (involving cells of varying genetic make-up), manipulation and destruction of the blastocyst, and subsequent cell culture, all of which have less predictability than combining precise quantities of known chemical products.

The US National Academies has issued guidelines for research involving human embryonic stem cells.²⁹ One of the primary recommendations of the Academies was for research institutions to establish ESCROs to work alongside IRBs, animal care and use committees, and others to provide oversight for research involving human embryonic stem cells.

Since the provenance of a stem cell line has scientific and ethical implications, how IRBs and ESCROs determine and document provenance will be important for any use of these cells in human trials or in any FDA-approved intervention. For example, are local IRBs and ESCROs obligated to evaluate and approve as ethically acceptable the original derivation of stem cell lines to be used? In the case of hESCs, does this include evaluation of the consent process for human materials donors?

In terms of the scientific integrity of the research, IRBs and ESCROs may also be interested in the training and experience of the person or laboratory that isolated the tissue, as this may have implications

for safety. They should also consider how many passages a line has been through, the types of media and other cells to which it has been exposed, and quality control measures employed throughout its lifetime.

Evaluation and documentation of provenance is further complicated for cell lines derived in other nations. What constitutes due diligence on the part of scientists and oversight bodies when consent forms are in a foreign language and local standards for research oversight are quite different than those in the United States, or entirely unknown to those reviewing a protocol at a US university? Research institutions have begun establishing ESCROs, but it remains to be seen what, if any, consensus will emerge regarding the standards and procedures for oversight. However, such standards will have significant scientific and ethical implications for downstream use of embryonic and other stem cells in human trials.

TRIAL DESIGN AND SELECTION OF HUMAN SUBJECTS Decisions about inclusion and exclusion of human subjects for early trials of CBI-NCs must be ethically defensible. The presence of unknown risks suggests that caution and stringent inclusion criteria be employed, while patients affected with these often devastating conditions may understandably clamor for access to trials. Though each condition will require independent deliberation and reasoning, all will face a similar set of critical decisions.

For example, should initial trials of an intervention be designed as phase I or combined phase I/IIa trials? Different trial designs come with different risk/benefit ratios that must be weighed to achieve the best balance. Recently, a small literature on “futility” designs has emerged, which may be one model for consideration.^{30,31} Futility studies are designed not to test efficacy, but to quickly and inexpensively weed out those treatments that are not likely to show significant benefit, the further testing of which is expected to be futile.

Scientists and oversight bodies must wrestle with the question of placebo use in early trials. While placebo controls may not be required for phase I trials, they will likely be considered necessary for later-stage trials.³²⁻³⁴ It is worth noting that while the placebo-controlled, double-blinded study is the gold standard in the United States, placebo use is considered unethical by many and is highly restricted in the recent revisions of the Declaration of Helsinki.³⁵ While the US FDA has apparently rejected these revisions,³⁶ others have embraced them. While these cultural differences may not much affect US trials, they may

affect how US scientists and oversight bodies view data generated in non-US trials.

With regard to patient selection, while there is likely no justification for using healthy volunteers in early trials of CBI-NCs, scientists, IRBs, and ESCROs must determine whether it is scientifically and ethically preferable to enroll seriously ill patients or comparatively “healthier” patients in early trials. Alternatively, it may be that the primary inclusion criterion simply should be that no other treatment is available. While there may be scientific and ethical justification for going to the sickest patients first, the sickest are also likely those with the fewest (if any) other options, and therefore may be more susceptible to therapeutic misconception and least able to give valid informed consent. This group may also be the least likely to benefit, with their inclusion leading to the false impression that the trial intervention provides no benefit. However, excluding the sickest patients may unjustly deny them a last chance. And as we have seen, inclusion of comparatively “healthier” patients comes with risks, as well.³⁷

Different neurologic conditions will clearly require the weighing of different factors according to disease etiology, symptoms, natural history, and prognosis. One morally justifiable exclusion criterion across all early trials may be the distance between a potential subject’s primary residence and the trial site. Due to the nature of cells, oversight bodies may insist that all participants live within a certain distance of the trial site to facilitate long-term follow-up or monitoring for neoplasm development and maintenance of cell function.

Scientists and oversight bodies must also decide under what conditions, if any, it would be ethically appropriate to include children in early human trials. There is certainly significant interest—from scientists, parents of sick children, and the FDA—in enrolling children in earlier phase trials; however, beyond the general concerns of conducting research in children,^{38–40} they may face additional risks by participating in early cell-based trials. For example, following an early trial—from which he or she will likely receive no benefit—a child (vs an adult) may face many more years of life during which he or she is excluded from more advanced trials. Furthermore, a trial may decrease mortality, but not morbidity, resulting in a prolonged period of grievous disability for a child. However, it is also the case that the still-developing brain of a child may be better able to incorporate and direct the differentiation of stem cells into neuronal circuits than the adult brain, making children, perhaps, ideal participants for early human trials.

INFORMED CONSENT Once inclusion criteria are determined, scientists, IRBs, and ESCROs will need to grapple with issues related to informed consent for early human trials of CBI-NCs. While many of these questions are familiar, the stakes in these early trials are likely to be so high—scientifically, socially, and politically—that the importance of a thorough and continuing informed consent process for trial participants should be stressed.

The consent process for this research will take a considerable amount of time. The science is complex, the risk of therapeutic misconception high, and the neurologic conditions grave; it will likely take many hours for a potential subject to be meaningfully educated and informed about the details, risks, and benefits of a trial. The question of how fairly to characterize the risks and benefits of trial participation is in itself daunting.^{41,42} However, it seems clear that it will need to be emphasized that early trials are not designed to establish or provide therapeutic benefit. Additionally, many of these neurologic conditions involve cognitive or mood impairments that compromise a subject’s ability to make free and informed choices, requiring the inclusion of a surrogate decision-maker. Given the complex issues involved, consideration should be given to using formalized measures to assess understanding, such as interviews or questionnaires. Similarly, the unique social and political circumstances surrounding stem cell research suggest the need for special mechanisms—above and beyond what would normally be required—to ensure the voluntariness of consent and to improve subjects’ understanding of the protocol (e.g., consent monitors, potentially novel approaches for those impaired by the neurologic condition under study).

Researchers and oversight bodies should ensure that the informed consent process is demonstrably above reproach, and that it provides as few opportunities as possible for even misguided criticism. Special attention should be paid to avoiding bias, or perceived bias, in the presentation of information. Additionally, oversight bodies should carefully consider how potential participants should be informed of study scientists’ financial and other conflicts of interest, so that they can make a more informed choice about participation.

SCIENCE IN THE LIMELIGHT Stem cell research is not just another new area of research of intense interest to scientists, but little more than a blip on the screen of non-specialists. Stem cell research has become a flash point in both social and political debate. Given the high stakes of such a controversial and intensely public area of science, special attention must be paid to the ethics of communication be-

tween and relationships among scientists, research subjects, the public, and policy makers.

Stem cell research is not the first example of cutting-edge medical science in the spotlight. In December 1982, hundreds of reporters waited at the University of Utah Medical Center, in Salt Lake City, for news of Barney Clark and the first artificial heart transplant. This first-of-its-kind medical experiment was highly controversial, highly publicized, and intensely scrutinized by the public and the press.⁴³⁻⁴⁵ It is not unreasonable to expect that a similar atmosphere and significant media attention will come with early human trials of cell-based interventions.

In light of this potential for intense public scrutiny, scientists, IRBs, and ESCROs will have the additional challenge of managing how and when information on the conduct, progress, and results of early human trials of CBI-NCs will be relayed to the public. How early should investigators go public with information on a trial? More than likely, subjects enrolled in a trial will talk with each other and with their communities about the trial and the results insofar as they know them. Therefore, it may be more prudent for scientists to be open from the beginning. Nevertheless, balancing accuracy with enthusiasm will be difficult in the spotlight. Further, this may bring unwanted attention to the research participants themselves. However, if transparency is the choice, research institutions should provide scientists with guidance on how to respond to pressures from the press, disease advocacy groups, and political advocates for information about trial progress. There will be failures in early trials, and scientists must be prepared to discuss them.

Finally, given that companies will have intellectual property concerns and may eschew publicity and carefully guard research results, universities and research institutions running the trials may want to consider steps to manage carefully their relationship with companies involved in early trials of CBI-NCs they are running.

CONCLUSIONS Despite being socially and politically contentious, stem cell research and cell-based trials are not discontinuous with prior research. Solid organ transplant, blood product use, fetal cell transplants for Parkinson disease, and microchimerism all provide information and lessons that we can draw on as this new area of biomedical research progresses. The social and political environment surrounding stem cell research argues that scientists, IRBs, and ESCROs will be faced with an array of ethical issues and heightened awareness and scrutiny as they engage in controversial research. Stakeholders within research, policy, and the public must begin to consider and deliberate the issues now, in an effort to

establish professional and institutional policies and practices for leading edge research such as early stage human trials of CBI-NCs.

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