

Original Article

A New Era in the Ethics of Human Embryonic Stem Cell Research

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Abstract

Scientific progress in human embryonic stem cell (hESC) research and increased funding make it imperative to look ahead to the ethical issues generated by the expected use of hESC for transplantation. Several issues should be addressed now, even though Phase I clinical trials of hESC transplantation are still in the future. To minimize the risk of hESC transplantation, donors of materials used to derive hESC lines will need to be recontacted to update their medical history and screening. Because of privacy concerns, such recontact needs to be discussed and agreed to at the time of donation, before new hESC lines are derived. Informed consent for Phase I clinical trials of hESC transplantation also raises ethical concerns. In previous Phase I trials of highly innovative interventions, allegations that trial participants had not really understood the risk and benefits caused delays in subsequent trials. Thus researchers should consider what information needs to be discussed during the consent process for hESC clinical trials and how to verify that participants have a realistic understanding of the study. Lack of attention to the special ethical concerns raised by clinical trials of hESC transplantation and their implications for the derivation of new hESC lines may undermine or delay progress towards stem cell therapies.

Increased funding and continued scientific progress have opened a new era in the ethics of human embryonic stem cell (hESC) research. These developments will reframe the ethical debate, which to date has focused on the moral status of the embryo and the acceptability of using embryos for research purposes. Although such philosophical questions have not been resolved, the issue is no longer *if* hESC research should proceed, but rather *how* it should proceed. The rapid pace of research makes it imperative to look ahead to the ethical issues generated by the expected use of hESC for transplantation. Some of these issues should be addressed now, even though Phase I clinical trials of hESC transplantation are still in the future. Crucial issues concerning safety of hESC transplantation and the need to recontact donors of materials used to derive new hESC lines are best resolved when these materials are donated. In addition, informed consent for hESC transplantation Phase I clinical trials will present particular challenges, which will require modification of the usual consent process for clinical trials. Failure to address these ethical issues may delay or preclude clinical trials that will test whether interventions based on hESC are safe and effective.

The current scientific, ethical, and policy context of hESC research

New hESC lines are needed if hESCs or their products are to be used for transplantation into humans. The twenty or so hESC lines approved for federally funded studies in 2001 by President Bush were derived using nonhuman feeder cells and serum and express the nonhuman antigen Neu5Gc¹. Thus, they would probably be immunologically rejected by the recipients unless this problem was remedied.

Derivation of new hESC lines will be stimulated by the \$3 billion in funding for stem cell research authorized by California voters in 2004. This measure will give priority to funding research that cannot be funded by NIH, which is currently the case for derivation of new hESC lines. Other states and private funders have followed suit in providing nonfederal support for hESC research²⁻⁶. Outside of the U.S., hESC research is advancing vigorously. In May 2005, researchers from South Korea reported the derivation of 11 hESC lines using somatic cell nuclear transfer, demonstrating that technical obstacles to developing such stem cell lines can be overcome more readily than expected⁷. In turn, such findings will stimulate further research.

Current ethical and policy guidelines for hESC research focus on the derivation of new hESC lines. In May 2005, a National Academy of Sciences (NAS) panel called for voluntary adoption of ethical guidelines in hESC research⁸. Their recommendations included institutional oversight of hESC research protocols through Embryonic Stem Cell Research Oversight Committees (ESCROs), informed consent from donors of materials for new hESC lines, restrictions on payment to gamete donors, and guidelines for banking stem cells and documentation. The twenty-three NRC recommendations have been endorsed by academic and scientific organizations and adopted as interim regulations for research funded by the state of California. That same month, the FDA issued regulations on screening and testing donors of human cells, tissues, and cellular and tissue-based products (HCT/P)⁹. While valuable, these initial efforts do not address crucial ethical issues in clinical trials of hESC transplantation, which have important upstream implications for how hESC lines should be derived, as well as for the conduct of the trials themselves.

Our analysis begins with the need both to protect participants in Phase I trials of hESC transplantation and to respect the confidentiality of donors of materials used for derivation of hESC lines. These ethical responsibilities need to be addressed during the initial process of donating materials for new hESC lines. Next we consider challenges confronting informed consent for Phase I trials of hESC transplantation. We present specific recommendations for resolving these ethical issues.

Balancing the need to protect participants in Phase I clinical trials against the need to respect donors

The goal of Phase I clinical trials is to assess the safety and feasibility of the investigational intervention and to determine dosages for subsequent clinical trials^{10, 11}. Direct therapeutic benefit, although hoped for, is unlikely in early trials, particularly if the first participants receive low doses¹². The guiding ethical principle of Phase I studies should be “Do no harm.” This ethical responsibility to protect the subjects in Phase I trials has important implications for the derivation of hESC lines.

A major safety concern is transmission of infectious agents or serious genetic conditions through transplanted hESC cells or products. The public will expect strong protections against diseases transmitted through hESC transplantation, just as it demands that blood transfusions and

solid organ transplants be tested for very rare but serious communicable diseases^{13, 14}. The May 2005 FDA regulations addressed possible transmission of communicable diseases by cell-based therapies, setting standards for screening and testing at the time of donation and for tracking transplanted materials back to the original donors⁹. HCT/P must be linked through an identification code to the donor and to pertinent donor medical records⁹. Although these requirements are necessary to protect recipients, we contend that they are not sufficient to adequately protect them.

A broader perspective on protecting recipients of transplanted hESC materials is needed because of several clinical features of hESC transplantation. First, there is likely to be a considerable time period between donation of biological materials used to derive hESC lines and clinical trials involving transplantation of hESCs or products from them. During this period, new risks may become apparent in the donors whose gametes were used to derive the hESC lines. Emerging infectious diseases with long latency periods, such as Creutzfeldt-Jakob Disease (CJD), may be identified, for which testing and screening were not available at time of donation. Polymorphisms and biomarkers associated with risk for specific diseases are being defined at a rapid pace. Second, in hESC transplantation, serious genetic conditions might also be transmitted¹⁵, some of which may not have been apparent at the time the materials were donated. For instance, after donating, donors may develop cancer or a strong family history of cancer. Third, immunosuppressive drugs, which may be essential after cell transplantation to reduce rejection, will increase the risk of communicable diseases and cancer in recipients. Fourth, if hESC transplantation proves clinically effective, many patients may receive transplantation from a single hESC line over time. Hence many recipients may be at risk for diseases transmitted from donors. In order to safeguard recipients of hESC transplantation, researchers need to recontact persons whose gametes were used to derive the hESC lines at the time of clinical hESC transplantation trials to update information and perhaps do additional testing. Furthermore, if hESC transplantation becomes a proven clinical treatment, periodic updating of the clinical status of donors would be prudent.

How can screening and testing of donors of materials for hESC lines be updated in an ethically acceptable manner? The responsibility to protect hESC transplant recipients from harm must be balanced against a responsibility to respect donors and protect their confidentiality. To resolve these countervailing mandates, researchers will need to obtain permission to recontact

donors if hESC cells or materials derived from their gametes or embryos will be used for transplantation. Researchers need to tell donors about the kinds of information or testing that might be requested later and the reasons the information is needed. Such permission for recontact needs to be obtained when materials are donated for research. Without this permission, it would be a serious invasion of privacy to later recontact the donors. Also, donors who had not agreed to be recontacted might object strongly to a subsequent contact, refuse to provide information about their interim medical history, or undergo additional testing. Previous reports on the consent process for donating gametes and embryos for hESC research have not discussed the issue of recontact in depth^{8, 16, 17}. Obtaining permission to recontact will undoubtedly complicate the consent process for donating embryos for hESC research. However, permission for recontact will likely minimize the disqualification of hESC lines late in the development process for use in transplantation studies because of inadequate follow-up with donors. Recontacting donors presents logistical challenges because donors may move and contact may be lost. It would be desirable to ask donors to provide contact information for a relative or friends who will know their new address should they move.

Confidentiality must be carefully protected because breaches might subject donors to unwanted publicity or even harassment. Concerns that their identities will not be kept confidential may deter some individuals from agreeing to be recontacted. Because of the intense public interest in and contentiousness over hESC research, it would be prudent for researchers and research institutions to develop stringent mechanisms, extending beyond those employed in routine clinical care, in order to assure donors that their identity and contact information remain protected.

Recently, confidentiality of personal health care information has been violated through deliberate breaches by staff, through break-ins by computer hackers, and through loss or theft of laptop computers¹⁸. Files containing the identities of persons whose gametes were used to derive hESC lines should be protected against such breaches through additional security measures. Any computer storing such files should be locked down in a secure room and password protected, with access limited to a minimum number of individuals on a strict “need-to-know” basis. Entry to the computer storage room should also be restricted by means of a card-key, or equivalent system, that records each entry. Audit trails of access to the information should be routinely monitored for inappropriate access. The files with identifiers should be

copy-protected and double encrypted, with one of the keys held by a high-ranking institutional official who is not involved in stem cell research. The computer storing these data should not be connected to the Internet. To protect information from subpoena, investigators should obtain a federal Certificate of Confidentiality¹⁹. Human factors in breaches of confidentiality should also be considered. Personnel who have access to these identifiers might receive additional background checks, interviews, and training. The personnel responsible for maintaining this confidential database and contacting any donor should not be part of a hESC research team.

Funders of hESC research and IRBs or ESCROs that oversee hESC research should ensure that appropriate provisions for recontact and confidentiality are in place. The IRB should review and approve any requests for recontact of donors. The ethical reasons for these provisions are sufficiently compelling that materials donated without explicit permission for recontact should not be used to develop hESC lines for transplantation, lest the safety of recipients or privacy of the donors be compromised.

Informed consent for recipients of hESC transplantation in Phase I clinical trials

Current procedures for obtaining informed consent are likely to be inadequate to address particular issues faced by recipients of hESC transplantation in Phase I clinical trials. Because the matter is complex and any changes in policy will need careful consideration, discussions of the consent process need to begin now.

Problems with informed consent commonly occur in clinical trials. Participants in cancer clinical trials commonly expect that they will benefit personally from the trial, even though the primary purpose of Phase I trials is to test safety rather than efficacy²⁰. This tendency to view clinical research as providing a personal benefit has been termed the “therapeutic misconception²¹.” Analyses of consent forms suggest that such misunderstandings in cancer clinical trials do not reflect information in the consent forms²². Indeed, cancer patients seeking therapeutic benefit may decide to enroll in a clinical trial before they meet the research staff, before they learn about the risks and benefits of the study or read a consent form²³.

One study of the consent process in gene transfer clinical trials found that researchers’ descriptions of the direct benefit to participants in Phase I trials commonly were vague, ambiguous, and indeterminate²⁴. Some investigators try to balance hope and practical reality, for example believing that “if we’ve done our job right, they [subjects] don’t expect it, but they

hope for it²⁴.” This study concluded that “there is no clear resolution to the underlying normative question: what should investigators communicate about the potential for direct benefit to subjects in early phase clinical research²⁴?” The authors suggested that “this dilemma cannot be addressed by individual PIs alone, but must be acknowledged and openly discussed by the scientific community²⁴.” Investigators need to determine how to develop ways to present clearly to participants such issues as promising preclinical evidence, the lack of power to detect benefit in Phase I studies, and the clinical significance of surrogate endpoints. In Phase I trials of hESC transplantation, guidelines for describing the likely direct benefits to participants similarly would require wide discussion, not only by scientists but also by public representatives.

Participants receiving hESC transplantation in Phase I trials might overestimate the benefits and underestimate the risks for several reasons. The therapeutic misconception may be particularly prominent because the scientific rationale for hESC transplantation and preclinical results may seem compelling. In addition, press accounts of stem cell research, which typically have emphasized its potential to treat currently incurable diseases, may reinforce unrealistic hopes.

Participants in Phase I trials may not appreciate that there is a possibility that hESC transplantation might make their condition worse. In previous clinical trials of transplantation of fetal dopamine neurons into persons with Parkinson’s, transplanted cells failed to improve clinical outcomes^{25, 26}. Indeed, late disabling dyskinesias developed in about 15% of patients receiving transplantation, with some patients needing ablative surgery to relieve these adverse events^{25, 26}. Although the transplanted cells localized to the target areas of the brain, engrafted, and functioned to produce the intended neurotransmitters, appropriately regulated physiologic function was not achieved.

Several measures may reduce the therapeutic misconception in recipients of hESC transplantation in Phase I clinical trials. First, researchers should frame their discussions with participants in the context of publicity about the potential for hESC to treat serious diseases. Researchers need to communicate the distinction between the long-term hope for such effective treatments and the uncertainty inherent in any Phase I trial. Participants in Phase I studies need to understand that hESCs have never been tried before in humans for the specific study purposes, that researchers do not know whether they will work as hoped, and that in fact the great majority of participants in Phase I studies do not receive any direct benefit^{11, 27}.

Second, investigators in hESC clinical trials must discuss a broader range of information with potential participants than in other clinical trials. Informed consent requires researchers to discuss with potential participants information that is pertinent to their decision to volunteer for the clinical trial^{28, 29}. Generally, the relevant information concerns the nature of the intervention being studied and the medical risks and prospective benefits. However, in hESC transplantation, non-medical issues may be prominent or even decisive for some participants. Individuals who regard the embryo as having the moral status of a person would likely have strong objections to receiving hESC transplants. Even though this intervention might benefit them medically, these individuals might regard it as collaborating with or taking advantage of an immoral action, and thus tacitly supporting it. Researchers need to appreciate that views of hESC research are not monolithic and may change over time. Indeed, some individuals who are strong advocates of pro-life positions and opponents of abortion regard the blastocyst as a potential person, not an actual person³⁰⁻³². In this latter view, hESC transplantation is morally acceptable. Researchers in clinical trials of hESC transplantation should inform eligible participants that transplanted materials originated from human embryos and help them to think through the ethical implications and clarify their personal beliefs about this research. The therapeutic misconception and beliefs about the moral acceptability of hESC research may interact in complex ways. It is possible that persons who mistakenly believe that hESC Phase I clinical trials will benefit them medically may, in their eagerness to obtain treatment for a serious medical condition, overlook the origin of transplanted material. If they fail to gain clinical benefit from the clinical trial, they may then have second thoughts about their decision to accept such an intervention.

Third, and most importantly, researchers should verify that participants have a realistic understanding of the study. The crucial ethical issue about informed consent is not what researchers disclose in consent forms or discussions, but rather what the participants in clinical trials understand. In other contexts, some researchers have ensured that participants understand the key features of the trial by testing their comprehension. In controversial HIV clinical trials in developing countries, where it has been alleged that participants did not understand the trial, some researchers are now testing each participant in such trials to be sure he or she understands the essential features of the research as part of the consent process^{33, 34}. Direct assessment of participants' understanding of the study, in contexts where misunderstandings are likely, has also

been recommended by several national panels^{8, 28}. We urge that such tests of comprehension be routine in clinical trials of hESC transplantation.

Controversies about the consent process might lead to delays in clinical trials of cutting-edge interventions. In early clinical trials of organ transplantation, the implantable totally artificial heart, and gene transfer, the occurrence of serious adverse events led to allegations that study participants had not truly understood the nature of the research³⁵⁻³⁸. In turn, these concerns about consent contributed to delays in subsequent trials. Assessing the comprehension of participants would reduce or preclude post-hoc criticisms that hESC recipients did not understand the essential features of the Phase I trial.

To strengthen the informed consent process in trials of hESC transplantation, stakeholders should develop consensus best practice recommendations for informing potential participants about early hESC clinical trials and for assessing participants' comprehension of key features of these trials. These stakeholders include researchers, public representatives, advocacy groups, government officials, and members of institutional hESC oversight committees. Because such consensus guidelines need to be in place by the time such clinical trials are proposed, these stakeholder meetings should be convened now.

hESC clinical trials raise other important ethical questions. What kinds of in vitro studies must be done to characterize hESC and document karyotype, epigenetic status, cell cycle parameters, and differentiation potential? What kinds of preclinical and animal studies should be required before hESC transplantation is attempted in humans¹⁵? What long-term follow-up of participants should be carried out, and how can data on adverse events be pooled across different protocols? Who will pay for such long-term follow-up, since many Phase I trials will not lead to commercial products? To the extent that disagreements over these questions might delay clinical trials, these issues also need to be addressed in advance.

In conclusion, for hESC to fulfill its promise as therapy, a chain of activities needs to be established, including funding, basic science, and clinical trials. Recent events have increased funding and shown that the science may proceed rapidly. But a chain is only as strong as its weakest link. Attention to ethical issues raised by clinical trials is an essential part of the chain. The issues we have discussed are based on lessons from previous experience with related but not identical fields; invariably other unforeseeable issues will arise. Lack of attention to the special

ethical concerns raised by clinical trials of hESC transplantation and their implications for the derivation of new hESC lines may undermine or delay progress towards stem cell therapies.

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