POLICY FORUM: HUMAN GENETICS

# Ethical Considerations in Leaping from Bench to Bedside

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A critical step in developing interventions to ameliorate the course of human disease involves determining when it is safe and appropriate to initiate experimentation with human subjects. Self-experimentation by scientists was once used to determine whether it was ethical to make this step. As antivivisectionist opposition became less vigorous, this tradition gradually gave way to one favoring animal experimentation before undertaking human experimentation (*1*). Although animal experimentation and clinical research are replete with ethical issues that have received considerable discussion, the issues encountered in making the leap from bench to bedside have received surprisingly little public notice.

One exception has been proposals for human gene therapy, which undergo a more public process of review involving the Recombinant DNA Advisory Committee (RAC) (*2*). Submission of two preproposals to the RAC, involving severe combined immunodeficiency disease caused by adenosine deaminase deficiency (ADA-SCID) and α-thalassemia, has prompted considerable discussion (*3*). These discussions (*4, 5*) have dealt with the prospect of human in utero gene transfer experiments (IUGTEs), federal regulations regarding clinical studies for evaluating new drugs, and general ethical principles that must be addressed before initiating human experimentation (*5*). It is clear that several criteria should be addressed.

**Safety.** The safety of human subjects is of paramount concern. International codes of ethics, including the Declaration of Helsinki, indicate that laboratory and animal experiments must typically precede human experiments (*6*). Even so, there are unresolved issues about whether available laboratory data are sufficient or whether a particular animal model is appropriate. Nonetheless, accurate forecasting about safety in proposed human experimentation is essential, and there should be a high standard of consensus in the scientific community regarding its appropriateness.

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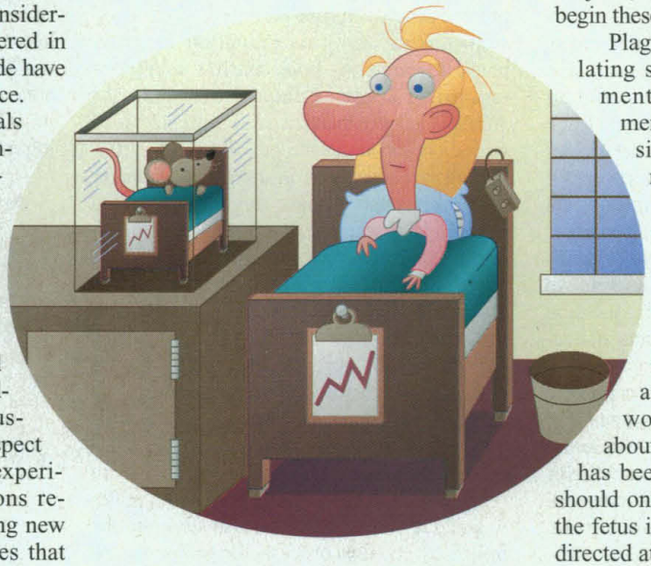
Safety must be considered in relation to the alternatives available in a particular situation. If there are no available treatments for a life-threatening condition, it seems reasonable to pursue experimental alternatives that may be somehow unsafe. In contrast, when alternatives exist or a condition is not life-threatening, it makes sense to be more guarded in pursuing potentially unsafe interventions. Moreover, determining safety is not simply an objective scientific judgment. Rather, something is safe not only on the basis of data but also as determined by communities and individuals.



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**"If it's good for you, is it good for me?"**—one issue to be resolved before human in utero gene transfer experiments could begin.

Different safety issues must be considered for different groups of subjects. When considering the possibility of human IUGTEs, it is imperative to examine matters of safety for the pregnant woman, the fetus, and future generations. For example, it is possible that an in utero intervention for α-thalassemia might be toxic to the pregnant woman should she carry the fetus to term, and there may be a risk of retroviral transmission to the mother in an intervention for ADA-SCID. The fetus itself may be harmed as a result of an in utero intervention (for example, by trauma from physical interventions that may cause the fetus to abort, as well as the unknown effects of in utero gene transfers, such as the possibility of mutagenesis). In other cases, a normal fetus might be harmed by an unnecessary intervention should prenatal genetic testing be inaccurate. Finally, the germ line might be affected "incidentally" in performing an in utero gene transfer, resulting in uncertain effects on future generations. Precisely because of the imprecision of these incidental effects, the potential for them compounds the already complex ethical considerations about safety and appropriateness attached to the prospect of directed germ line interventions in which a known deleterious gene might be corrected. In deliberations about the preproposals for IUGTEs, there was clearly a lack of consensus in the scientific community regarding the adequacy of existing data from laboratory and animal experimentation to assess safety in these different groups of human subjects, thereby making it inappropriate to begin these in utero human experiments.

Plagued by the difficulty of extrapolating safety data from animal experiments to proposed human experiments, Anderson (*3*) raised the possibility of performing initial human experiments in cases where a decision had already been made to abort a fetus. Despite the scientific appeal of the experiment, such a design raises unique ethical and regulatory concerns. For example, because of the possibility that following an experimental intervention a woman might change her mind about proceeding with an abortion, it has been argued that such experiments should only be conducted when the risk to the fetus is minimal and the intervention is directed at the health needs of the fetus (*7*). Existing data simply do not provide sufficient evidence that fetal risks are minimal in an IUGTE.

**The possibility of benefit.** Early-phase clinical trials are designed primarily to answer scientific questions; benefit to individual research subjects are a side benefit. For example, phase I studies in oncology are designed to test toxicity of experimental agents, and most subjects will not receive a dose that is expected to be in the therapeutic range. However, subjects may derive hope or meaning from the knowledge that they are contributing to scientific progress. Further, by participating in an early-phase trial they may have access to experienced clinical teams that provide emotional as well as physical support.

Regardless of such direct and indirect individual benefits, the central goals of early-phase research involving human sub-

jects typically relate to assessing safety rather than efficacy. In addition, provided that a proposed intervention shows reasonable promise as an effective intervention, it does not seem problematic if there is a lack of consensus in the scientific community concerning the possibility of individual benefit during early-phase experiments.

The possibility of direct benefit to the fetus was considered in deliberations about the two preproposals for human IUGTEs. Although there was not consensus about the likelihood of benefit, there seemed to be some support for the scientific concepts underlying the proposals if the very difficult questions regarding safety could be reconciled. However, the current U.S. regulatory approach for research with pregnant women requires that experimental interventions must hold the prospect of direct benefit to the fetus (*8*). This creates a paradox of permissibility for early-phase experiments, which by definition are primarily directed at assessing toxicity, not benefit (*5*).

**Experimental design.** Even if there is consensus regarding safety and there are good reasons to suppose that a proposed intervention might ultimately be shown to be effective, the experiment itself must be designed in such a way as to produce useful results. In short, it is unethical to conduct poorly designed experiments (*9*). Whether the results of the study are positive or negative, what matters is that they are useful in answering an important scientific question while not exposing human subjects unnecessarily to the risks of research.

Ethical questions accompany multiple steps in the design of such experiments. For example, justice would require considering carefully what conditions are selected for early experimentation when a particular intervention might have promise in several diseases (*10*). Should more common diseases be selected over rare diseases? Should diseases with an available cure be selected over those without a cure or vice versa? In addition, even though early-stage experimentation does not have a high likelihood of personal medical benefit for subjects, what can be done to maximize benefits and minimize risks? (*11*). These and related questions ought to be considered by Institutional Review Boards, as well as others charged with the prospective review and oversight of research with human subjects (*12*).

**Informed consent.** A now-accepted and crucial component of research with human subjects is obtaining valid informed consent for participation. To provide this consent, potential subjects must at first be competent to do so. This entails being able to understand and appreciate information about the proposed research and how participation will likely affect them and, when relevant, how this differs from usual care. Obtaining informed consent for early-phase clinical trials with patients suffering from a disease being studied can be particularly challenging, especially when good treatments are not available for the patient's disease. Patients may carry a "therapeutic misconception," whereby they assume that an experimental intervention is designed primarily as a means of providing direct medical benefit (*13, 14*). In addition, even the words selected by investigators to describe the protocol, such as "study" or "experiment," can greatly influence patients' understanding of what is involved, as a study is commonly understood to be virtually harmless while an experiment is believed to be risky (*15*). Similarly, referring to an IUGTE as "in utero gene therapy" might inadvertently create a misperception on the part of those being asked to serve as subjects (*16*).

The lack of therapeutic alternatives for certain conditions diagnosed in utero might put pressure on future parents in their decision-making about participation in early-phase research. As bone marrow transplantation is a known effective treatment for ADA-SCID postpartum (*17*), parents faced with a choice about the possibility of participating in early-phase in utero gene transfer research for this disease might be expected to be in a reasonable position to give meaningful informed consent. In contrast, since there is essentially no treatment for α-thalassemia and it is fatal in utero, faced with the near certain death of a fetus, informed consent might be especially difficult. Of note, such claims about what pressures may exist in the informed consent process for these experiments are largely based on related experience and conjecture. As yet, there are insufficient data from which to accurately guide decisions about how to structure the informed consent process for protocols for IUGTEs should a decision be made to begin experiments with human subjects.

Furthermore, in considering the informed consent process, attention must be paid to the tenability of "informed consent" for future children and, more problematically, for future generations. While there is obviously experience in having expectant parents give consent, or more accurately permission, for their future children, it is a unique notion to provide permission for future generations whose germ line might be affected by experimental interventions. What is the moral justification for providing intergenerational permission? What will be the durability of such agreements to adhere to long-term follow-up that might be required to assess whether in fact germ line changes have occurred?

**Concluding comments.** Safety, the possibility of benefit, experimental design, and informed consent are critical criteria to be considered as discussion and evaluation continues among scientists, regulators, and ethicists. Specifically, accepting the limits of preclinical models, the regulators and the scientific community should strive to reach consensus about the safety of proposed interventions. Even if consensus about safety is reached, there remains the therapeutic paradox of permissibility in the current regulatory apparatus for research on the fetus. Accordingly, whether it will be acceptable to do this research in the United States will depend on how the current regulations are ultimately changed. Should such research be acceptable, there needs to be broad public discussion and ethical analysis concerning whether the target conditions selected are fair and appropriate and how best to spend public resources dedicated to research. These tasks require open and explicit public input that could be facilitated by forums such as the Gene Therapy Policy Conferences conducted at different locations to enhance the likelihood of public input. Finally, if a decision is made to "leap" ahead, further conceptual work, guided by empirical study, must be directed at the possibility of obtaining meaningful informed consent.

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