Regulatory and Ethical Issues for Phase I *In Utero* Gene Transfer Studies

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Abstract

Clinical gene transfer research has involved adult and child subjects, and it is expected that gene transfer in fetal subjects will occur in the future. Some genetic diseases have serious adverse effects on the fetus before birth, and there is hope that prenatal gene therapy could prevent such disease progression. Research in animal models of prenatal gene transfer is actively being pursued. The prospect of human phase I *in utero* gene transfer studies raises important regulatory and ethical issues. One issue not previously addressed arises in applying U.S. research regulations to such studies. Specifically, current regulations state that research involving greater than minimal risk to the fetus and no prospect of direct benefit to the fetus or pregnant woman is not permitted. Phase I studies will involve interventions such as needle insertions through the uterus, which carry risks to the fetus including spontaneous abortion and preterm birth. It is possible that these risks will be regarded as exceeding minimal. Also, some regard the probability of therapeutic benefit in phase I studies to be so low that these studies do not satisfy the regulatory requirement that they “hold out the prospect of direct benefit” to subjects. On the basis of these considerations, investigators and institutional review boards might reasonably conclude that some phase I *in utero* studies are not to be permitted. This paper identifies considerations that are relevant to such judgments and explores ethically acceptable ways in which phase I studies can be designed so that they are permitted by the regulations.

Introduction

RESEARCH ON *IN UTERO* GENE TRANSFER with animal models currently is under way, in an attempt to lay groundwork for clinical studies (Han *et al.*, 2007; Gubbels *et al.*, 2008; Niiya *et al.*, 2009; Tarantal *et al.*, 2010). If progress in this area continues, one can expect clinical research that initially will involve phase I studies. Such studies will be needed to determine the extent to which vectors reach target tissues, to identify appropriate dosages, and to assess toxicity. The current U.S. federal regulations on human subjects research contain requirements that have a bearing on these future phase I trials. Specifically, the regulations state that research involving greater than minimal risk to the fetus and no prospect of direct benefit to the fetus or pregnant woman is not permitted (Code of Federal Regulations, 2005, Title 45, Part 46, Section 204). *In utero* phase I studies will involve interventions such as needle insertions through the uterus and into the fetus. The risks involved in such interventions include spontaneous abortion and premature birth, among others (Blakemore, 1999). Moreover, the primary purpose of phase I studies would not be to benefit the fetus or pregnant woman, but to establish dosages and toxicities. These considerations raise a number of regulatory and ethical questions:

1. What level of risk should be regarded as “minimal risk” in regard to fetuses?
2. Are the risks associated with needle insertions through the uterine wall greater than minimal?
3. Can phase I studies reasonably be regarded as offering direct benefit to the fetus or pregnant woman?
4. Will it be possible to conduct phase I *in utero* gene transfer studies within the framework of the current U.S. regulations?

The answer to question 4 depends in part on the answers to questions 1–3. This paper explores the various considerations that are relevant to answering all four questions. If the risk of needle insertions exceeds the level of risk permitted for fetuses by the regulations, then this would be a potential obstacle to the conduct of phase I trials. This paper also discusses some justifiable ways to overcome this possible regulatory obstacle to phase I *in utero* gene transfer studies.

Background

Somatic cell gene transfer holds great promise for treating a variety of human diseases. There have been notable successes in gene therapy, perhaps the best examples being

treatment for several types of severe combined immunodeficiency (SCID) (Cavazzana-Calvo *et al.*, 2000; Hacein-Bey-Abina *et al.*, 2002; Aiuti *et al.*, 2009). There also have been unsuccessful attempts at gene therapy and serious harmful effects in some cases (Hacein-Bey-Abina, 2003; Raper, 2003). Gene transfer research is a developing field, and we have much to learn before we can carry out such therapy safely and effectively. A number of requirements for successful gene therapy have been identified (Somia and Verma, 2000; Coutelle *et al.*, 2003). For gene therapy to work, normal DNA must reach the appropriate target cells. That DNA must become integrated into those cells in such a way as to express the protein for which it is coded. It must do so in a way that does not interfere with the normal functioning of other genes. It must reach enough target cells so that it can produce its protein in sufficient quantities to make a difference in the course of the disease. It must remain in those target cells, producing protein for a sustained period, to prevent the effects of the disease from reappearing. And it must avoid creating significant toxic effects. There are a number of scientific and technical problems to be solved before the accomplishment of these requirements (Somia and Verma, 2000). One of the main problems is an immune response directed against the vector and transgenic protein, which can prevent success of the attempted therapy. More needs to be known about how to deal with this problem.

There is growing interest in prenatal gene therapy, for several reasons (Coutelle and Rodeck, 2002; Waddington *et al.*, 2005; David and Peebles, 2008; Wagner *et al.*, 2009). First, some diseases begin to have pathological effects even before birth. Examples include α -thalassemia and SCID. For some diseases, such as α -thalassemia, postnatal therapy would be too late to reverse these harmful effects. Second, during early gestation the fetal immune system is undeveloped, and it is hoped that there is a window during which vectors can be introduced without encountering the immune response problem. Third, there is hope that the fetus could become permanently "tolerant" to the new protein if it is introduced early in gestation, so that rejection will not occur after the immune system develops. Fourth, there may be a greater uptake of DNA in the fetus compared with the infant, particularly when retroviral vectors are used, because retroviral vectors integrate into dividing cells, and cell division is high during gestation. Given these potential advantages, various diseases are being considered for prenatal gene therapy, including hemophilia, cystic fibrosis, muscular dystrophy, and sickle cell anemia, among others (Coutelle *et al.*, 2003; Waddington *et al.*, 2005).

Prenatal gene transfer will involve risks to the pregnant woman and fetus. Some of the risks are related to procedures used to gain access to the fetus, such as needle insertions through the uterus and into the fetus. These risks include spontaneous abortion, fetal demise, fetal trauma or bleeding, intrauterine infection, rupture of membranes, preterm labor, and preterm delivery (Blakemore, 1999). Other risks are specific to gene transfer. These include a risk of malignant tumor formation caused by disruption of the subject's DNA by viral vectors. Also, there is a risk of toxic effects caused by gene transfer to, and expression in, somatic cells in the fetus and pregnant woman that are not targeted for gene transfer. In addition, if there are any progeny of the fetus, there is a possibility of harm to those future individuals caused by unintended genetic alteration of fetal germ cells.

In 1999, the Recombinant DNA Advisory Committee (RAC) sponsored a national conference to examine the scientific, medical, and ethical issues raised by fetal gene therapy. Subsequently, the RAC issued a conference report stating a number of conclusions, including the following: candidate diseases should be serious genetic diseases that do not have an effective postnatal therapy; candidate diseases should be ones for which *in utero* diagnosis is definitive and the genotype-phenotype relationship is well defined; and the likelihood of germline integration should be minimized. A main conclusion was that there were insufficient preclinical and clinical data to support the initiation of clinical trials involving prenatal gene transfer. The report stated that significant additional preclinical and clinical studies addressing vector transduction efficacy, biodistribution, and toxicity are required before a human *in utero* gene transfer protocol should proceed (Recombinant DNA Advisory Committee, 2000).

Gene transfer research, both in prenatal animal models and clinical studies involving children and adults, is ongoing for a variety of diseases being considered for future fetal gene transfer (Alton, 2007a,b). Given the fact that such research is in progress, it is worthwhile to continue discussing the ethical and regulatory aspects of human prenatal gene transfer in advance of its anticipated feasibility.

U.S. Regulatory Framework

To explore these issues, it will be helpful to review the current U.S. regulatory framework. In the United States there is a special process for review and approval of gene therapy research in human subjects. All such protocols to be carried out in institutions receiving federal funding must be submitted jointly to the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA). The FDA has jurisdiction over human cells, tissues, and cellular and tissue-based products intended for use in humans. Submission to the OBA results in a determination as to whether public review by the RAC is needed. At present, public RAC review is carried out only for protocols that "represent novel characteristics deserving of public discussion" (Office of Biotechnology Activities, 2002). Because human prenatal gene transfer will have novel features, compared with studies involving children or adults, RAC review can be expected, particularly during the early stages of such clinical research. FDA review addresses topics such as manufacturing process and quality control, whereas RAC review deals with subject selection, confidentiality, and informed consent, among other issues. These differences reflect the different missions of these two bodies (Brody, 1998, p. 84).

In addition to FDA and RAC review, each clinical protocol must be approved by the research institution's Institutional Biosafety Committee and Institutional Review Board (IRB). The federal regulations pertaining to IRB review include rules that must be satisfied for approval of research protocols. These regulations include rules for selection of research subjects, obtaining the informed consent of subjects, and assessing the comparative risks and benefits to subjects. Of particular relevance are the rules pertaining to research involving pregnant women and fetuses. These are stated in Subpart B of the regulations and include the following

requirement (Code of Federal Regulations, 2005, Title 45, Part 46, Section 204):

The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

The concept of minimal risk is defined in the regulations as follows:

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (Code of Federal Regulations, 2005, Title 45, Part 46, Section 102).

What Is “Minimal Risk” for Fetuses?

What would it mean to speak of risks ordinarily encountered in daily life by a fetus? And how is the concept of risks during the performance of routine physical or psychological examinations or tests to be applied to fetuses? Surprisingly, there has been little discussion of these questions. There is, after all, a substantial amount of published work addressing the question of how “minimal risk” should be interpreted. Similarly, there is a large body of literature on the ethics of research involving pregnant women and fetuses, particularly maternal–fetal surgery. However, in neither of these bodies of work can one find an analysis of minimal risk regarding fetuses or pregnant women.

The extensive literature on minimal risk arose in response to a need to clarify the regulatory definition. A serious shortcoming of the definition is that it leaves unanswered the question of *whose* daily life IRBs are to consider in comparing the risks of daily life with the risks in a research protocol. A number of views about this have been put forward, in discussions focusing primarily on research involving children. To answer the question of how the definition should be interpreted regarding fetuses, it will be helpful to consider the views on minimal risk in that literature.

In the literature, a distinction is made between an “absolute” and “relative” interpretation of the regulatory definition (National Bioethics Advisory Commission, 2001, p. 83). According to an absolute standard, the level of risk that is considered to be minimal should be the same for all research subjects. From this view, minimal risk is regarded as the risk ordinarily encountered in daily life or during routine examinations by *healthy* individuals, and this level of risk is taken as the standard for all research subjects, healthy or not. By contrast, a relative standard considers minimal risk to be relative to the subject population for a given research protocol. Several professional commissions that have considered the merits of these two views have concluded that an absolute standard is ethically preferable (National Bioethics Advisory Commission, 2001, p. 83; National Human Research Protections Advisory Committee, 2001, p. 5; Institute of Medicine, 2004, pp. 121–122; Secretary’s Advisory Committee

on Human Research Protections, 2005). A main argument against a relative standard is that it would permit ill subjects to be exposed to greater risks than healthy subjects. This would occur because some ill subjects encounter in their daily lives the risks associated with their diseases, medical treatments, and institutional environments. Another argument is that a relative standard would permit subjects living in unsafe neighborhoods to be exposed to higher research risks than subjects living in safe locations because their risks of daily life are greater. In the regulations, the requirement that risk be no greater than minimal applies only when there is no prospect of direct benefit to subjects. When there is no such prospect of benefit, it is considered unjust to permit some subjects to be exposed to greater research risks because of their particular medical or home situation. On the basis of these considerations, a consensus has developed among the various commissions that have considered this issue, according to which an absolute standard should be used.

Regarding the risks “ordinarily encountered in daily life” by healthy individuals, it has been pointed out that some healthy people encounter greater risks in daily life than others (Kopelman, 1981, p. 2). This gives rise to several ways to interpret an absolute standard. In one interpretation, the standard includes the risks ordinarily encountered by the most risk-prone individuals. However, this standard, which includes the risks of fire-fighting and hang-gliding, for example, would permit research risks that are unacceptably high when there is no prospect of direct benefit to subjects. A preferable interpretation is that the standard refers to the risks of daily life that all healthy individuals *have in common* (Kopelman, 1981, p. 4). From this point of view, the standard refers to risks involved in common daily activities such as crossing the street, driving or riding in a car, taking a shower, or walking down stairs, among others. It is worth noting that in the literature this standard is consistently interpreted as *not* including the risks of acquiring common diseases, but rather as risks in day-to-day activities.

Given this analysis of minimal risk, the relevant risks of daily life for pregnant women are the ones they have in common with other healthy adults. In applying the concept of minimal risk to fetuses, it is worth noting that there are fetal risks associated with the risks of daily life that pregnant women have in common with other healthy adults. For example, when a pregnant woman is injured in a motor vehicle accident, there can be fetal injury or even miscarriage. These considerations suggest the following interpretation of minimal risk to fetuses:

In regard to fetuses, “minimal risk” is a level of risk that is not greater than the fetal risks associated with the risks that healthy pregnant women ordinarily encounter in daily life and have in common with other healthy adults or the risks fetuses encounter during routine prenatal examinations or tests of healthy women with healthy fetuses.

The routine prenatal examinations and tests for healthy women with healthy fetuses include maternal blood and urine tests, Pap smears to check for cancer and certain sexually transmitted infections, vaginal and anal swabs to check for group B *Streptococcus*, and ultrasound examinations (American College of Obstetricians and Gynecologists, 2009). These procedures involve very low risks to the fetus. There are no known

harmful effects to the fetus from routine diagnostic ultrasound (American College of Obstetricians and Gynecologists, 2004; American Institute of Ultrasound in Medicine, 2007). This proposed definition of minimal risk for fetuses is consistent with the level of risk implied by the term “minimal risk.” This term connotes a low level of risk—indeed, a risk that is *minimal*.

Would *In Utero* Gene Transfer Exceed Minimal Risk?

Assuming that this interpretation of minimal risk for fetuses is reasonable, would the risks involved in needle insertions into the fetus for gene transfer exceed minimal? At present, we lack data that would provide a precise quantitative description of these risks. Perhaps the closest analogy for which data are available is pregnancy loss after amniocentesis. One review of the literature identified 10 controlled studies comparing fetal loss rates in pregnancies with and without amniocentesis performed. The combined data yielded a pregnancy loss rate attributable to amniocentesis of 0.6% (Seeds, 2004). The study found that the background rate of pregnancy loss, based on combined data from all control subjects, was 1.08%. Another systematic review using pooled data yielded a 1.9% pregnancy loss rate after amniocentesis, including the background rate (Mujezinovic and Alfirevic, 2007). Assuming a background rate of 1.08%, this would give a loss rate attributable to amniocentesis of 0.82%. It is possible that pregnancy loss rates associated with *in utero* gene transfer would differ from those of amniocentesis because of several factors. If needles smaller than the 20-gauge needles commonly used for amniocentesis were used, it is possible that this would lower the loss rate. On the other hand, if gene transfer is performed earlier than many amniocenteses, it is possible that this would increase the loss rate, as there is evidence suggesting that earlier interventions might have a greater loss rate, even after correcting for spontaneous losses (Saltvedt and Almström, 1999; Alfirevic *et al.*, 2009). Pre-clinical studies may provide additional information, keeping in mind that animal models may not duplicate human response. Even if results from animal studies were to suggest lower risks, extrapolating such results to humans would involve uncertainty. To err on the side of caution, one should not assume that human risks would be as low. If the loss rate for gene transfer were assumed to be in the range associated with amniocentesis, 0.6 to 0.82%, then it would be reasonable to claim that it exceeds minimal risk. One death in every 167 subjects (a loss rate of 0.6%) would exceed what is generally regarded as minimal risk. These considerations suggest, at the very least, that the question of whether *in utero* gene transfer would exceed minimal risk needs to be explored further and that there is a genuine possibility that we will reasonably regard it as exceeding minimal.

Do Phase I Studies Offer the “Prospect of Direct Benefit”?

The primary purpose of a phase I study is to characterize the toxicities of the experimental agent and to establish the maximally tolerated dose, in preparation for phase II evaluations of efficacy. In the context of gene transfer, some phase I studies might also seek to determine the uptake of transgenes or levels of their gene products in various tissues. In a phase I study, an initial dose believed to be below the maximally tolerated dose is given to a cohort, typically one to three

subjects, and the toxicity is observed. Each subsequent cohort is given a higher dose than the previous cohort until unacceptably severe toxicities occur. The dose previous to that one is then considered to be the maximally tolerated dose. Because starting dosages are relatively low, typically it is unlikely for there to be therapeutic benefit, particularly for subjects in relatively early cohorts. Also, if the duration of administration of the experimental agent is short, compared with a phase II study, this can diminish the likelihood of therapeutic benefit.

There is controversy over the meaning of the regulatory language, “holds out the prospect of direct benefit to subjects.” As a result, there is disagreement over whether phase I studies hold out such a prospect. Some maintain that a low probability of benefit is sufficient to justify the claim that there is “the prospect of direct benefit” (Ackerman, 1995; Anderson *et al.*, 2004). In opposition to this view, one commentator states, “To classify research as offering the prospect of direct benefit suggests a certain probability of success, and not the mere possibility of benefit” (Ross, 2006, p. S22). It is also argued that phase I trials should not be described as offering the prospect of direct benefit because doing so would promote the “therapeutic misconception” (Ross, 2006), which is a tendency of research subjects to overestimate a study’s potential for therapeutic benefit (Appelbaum *et al.*, 1987; Daugherty *et al.*, 1995). On the basis of concern about the therapeutic misconception, one bioethics panel recommended that all phase I consent forms include the statement, prominently displayed in boldface type on the first page, “This medical research project is not expected to benefit you” (Moreno *et al.*, 1998, p. 1954). Given this controversy, we should acknowledge the possibility that IRBs will have differing views concerning whether phase I *in utero* gene transfer protocols “hold out the prospect of direct benefit.”

It might be objected that, even if phase I trials do not offer a prospect of direct benefit to the fetus, the pregnant woman could benefit. For example, the pregnant woman could obtain benefits such as satisfying a desire for altruism by participating in a phase I study to help others. It might be claimed that this would make a phase I trial permissible according to the regulations. In reply, it should be noted that the regulations use the term “direct benefit,” not simply “benefit.” The implication is that direct benefit is a particular type of benefit. Here, too, there is a question concerning how the regulatory term should be interpreted. Discussions of this term make a distinction between direct and indirect benefit. Direct benefit refers to medical benefit caused by the research intervention. In contrast, indirect benefit refers to collateral benefits such as the gratification of altruism, receiving free physical examinations, and greater access to professional care and support (National Bioethics Advisory Commission, 1998; King, 2000, p. 333). In phase I *in utero* trials, the pregnant woman can receive indirect benefits, such as fulfilling a desire to be altruistic. However, she does not receive a direct medical benefit because the intervention is directed toward the fetus. Some might respond that a direct benefit to the fetus should be regarded as a direct benefit to the woman, given the intimate relationship between the pregnant woman and fetus. In reply, even if one were to agree with this point, it would not support the objection. From the view in question, there would not be a direct benefit to the woman unless there were a direct benefit to the fetus. So, the issue ultimately hinges on whether there is the prospect of direct benefit to the fetus.

Some Ethically Justifiable Ways to Meet These Regulatory Requirements

The considerations discussed previously suggest that some IRBs might regard phase I *in utero* gene transfer studies as having greater than minimal risk and not offering a prospect of direct benefit. Other IRBs might not draw one or both of these conclusions, but might nevertheless regard the balance of risks and benefits to the fetus to be ethically unacceptable in some phase I studies, given the risk of pregnancy loss and the low probability of therapeutic benefit. Assuming that these serious concerns would be held by at least some investigators and IRBs, would it be possible to design phase I trials that deal with these concerns in an ethically acceptable way?

It can be argued that there are several acceptable ways to address these concerns. One approach would be to recruit pregnant women whose fetuses have diseases that invariably are fatal during gestation or soon after birth. As an example, a phase I trial involving α -thalassemia would recruit women whose fetuses have α -thalassemia, a uniformly lethal condition. This would be an ethically justifiable approach because the assessment of research risks to the fetus differs, depending on whether the fetus has such a fatal condition. For example, in the absence of such lethal conditions, a risk of premature birth and the handicaps that might be associated with it would be serious concerns regarding fetuses and the children into which they would develop. By contrast, for fetuses with such fatal conditions, there would be no surviving child to be injured by premature birth. Similarly, a risk of pregnancy loss would be a serious concern for fetuses that have a prognosis consistent with survival, but for fetuses with a lethal condition the outcome of death would occur anyway. Because of these considerations, a given research procedure such as needle insertion into the uterus can reasonably be regarded as posing lower risks for fetuses that are expected to die relatively soon, compared with fetuses that are not. This difference in risks can make research acceptable involving fetuses with a lethal disease that would not be acceptable for fetuses without such a condition. Risks that exceed minimal for fetuses with a prognosis consistent with survival could be regarded as minimal for fetuses with a lethal condition.

A second approach that avoids the regulatory and ethical problems in question is to recruit pregnant women who have decided to terminate pregnancy. A similar argument can be given in this scenario; the assessment of risks differs, depending on whether the woman intends to carry the fetus to term or to have an abortion (Lebacqz, 1979; Steinbock, 1994). The risks of pregnancy loss and premature birth would be major concerns regarding fetuses to be carried to term and the children into which they would develop. But for fetuses to be aborted, the outcome of death would occur anyway, and there would be no future child to be injured by premature birth. Risks that exceed minimal for fetuses to be carried to term could be regarded as minimal for fetuses to be aborted.

The research design of certain types of phase I studies might also support recruiting women who plan to terminate pregnancy. Some studies will have as one of their purposes assessing the uptake of a vector in fetal organs and tissues. End points might include the measurement of levels of the transgene or gene products in target tissue. Phase I studies

might also examine cells and tissues for evidence of toxicity. Examination of fetal tissue after pregnancy termination would be one way to carry out such assessments.

Restricting research participation to women who have decided to terminate pregnancy is an accepted approach when risks would outweigh benefits for fetuses to be carried to term. In the early stages of development of procedures such as amniocentesis, chorionic villus biopsy, fetoscopy, and umbilical cord blood sampling, trials were carried out in which these procedures were performed before the initiation of abortions (Mahoney, 1975; Levine, 1988, p. 302). For example, the Ethics Advisory Board of the U.S. Department of Health, Education, and Welfare approved a research protocol designed to test the safety of fetoscopy. In that study, the new technique of fetoscopy was carried out on pregnant women at 16 to 20 weeks' gestational age who had elected to undergo abortion (Anonymous, 1979, p. 8).

Several objections have been raised against having a woman's decision to terminate pregnancy as an inclusion criterion in research studies, and these should be addressed. One objection is that such inclusion criteria take away the woman's right to change her mind about having an abortion (Recombinant DNA Advisory Committee, 2000, p. 1222). In reply, this objection rests on a misunderstanding concerning inclusion criteria. They are criteria that must be satisfied for a subject to *enter* a study but do not require that a subject remain in the study. Subjects retain their right to withdraw from a study at any time. For trials in which a decision to terminate pregnancy is an inclusion criterion, a woman who enters the study does not waive her right to change her mind about having an abortion, and it is important for the pregnant woman and investigator to have an explicit understanding about this. Also, it is necessary that her abortion decision be made before any discussion of the research project, to prevent the abortion decision from being influenced by a request to participate in research.

A closely related objection might claim that a woman's agreement to participate in research would put pressure on her not to change her mind about terminating the pregnancy. The concern is that this would be an infringement of her freedom to make her own decision concerning abortion. In reply, the objection assumes that we should prevent people from entering into agreements when doing so might influence other decisions they might make. Presumably, the idea is that preventing such agreements would promote autonomy. But it seems that autonomy would be better promoted by permitting people to enter into such agreements and helping them understand that doing so might influence other decisions. Thus, as part of the informed consent process, it could be pointed out to the woman that her decision to participate in the research might possibly influence her not to change her mind about terminating pregnancy. With this consideration in mind, she can then decide for herself whether to enter the study. Also, emphasizing to the woman that she is free to withdraw from the study would help diminish the force of the objection.

Another objection is that after the research intervention the woman could change her mind about having an abortion. In that event, a future child could suffer harm as a result of the research (Green, 2008). In reply, there are at least two ways to design research in order to reduce the likelihood of potential harms associated with the woman's changing her

mind. One approach is to have the research intervention take place as part of a single operative procedure that will conclude with the abortion (Toulmin, 1975, pp. 10-10 to 10-11). This method might be feasible for research in which there is no need for a delay between the research intervention and the examination of fetal tissues. On the other hand, some studies might require a longer period of time for the effects of the research intervention to appear in fetal tissue. For this category of research, there are steps that can be taken in an attempt to recruit only women who are unlikely to change their minds. Investigators could recruit only women who state a firm intention to terminate pregnancy. Whether the woman would state such an intent could be explored in an interview in which she is invited to discuss her intention to terminate the pregnancy. Expressions of ambivalence by the woman concerning abortion would indicate that she does not meet the inclusion criterion in question. In addition, the informed consent process should inform the woman concerning the risks to the fetus if the research intervention is carried out and the woman then changes her mind about having an abortion. The woman could then take such risks into account in deciding whether to enter the study.

Yet another objection is based on concepts such as dignity and respect. This objection holds that, to avoid an affront to the dignity of the fetus, or to the respect owed to the fetus, we should not perform procedures on fetuses to be aborted that we would not perform on fetuses to be carried to term (Louisell, 1975). A reply to this objection consists of two points. First, although we can identify cases in which it is clear that there is an affront to dignity or respect, nevertheless there is a certain amount of vagueness in the meaning of these terms. Those who put forward this argument typically do not define or analyze the terms. Second, whether the fetus is treated in a disrespectful manner depends on the nature of the research intervention. Research procedures that do not exceed minimal risk would generally not seem to be disrespectful toward the fetus. Thus, the mere fact that a research procedure is performed on women planning to terminate pregnancy but not on women planning to carry the pregnancy to term does not make the procedure disrespectful toward the fetus.

In summary, none of the objections to having a decision to terminate pregnancy as an inclusion criterion withstands critical examination.

Conclusion

In the literature, there has been no discussion concerning how the regulatory definition of minimal risk should be interpreted regarding fetuses. This paper offers such an analysis, according to which minimal risk is understood as risk that is not greater than the fetal risks associated with the risks that healthy pregnant women ordinarily encounter in daily life and have in common with other healthy adults or the risks fetuses encounter during routine prenatal examinations or tests of healthy women with healthy fetuses. Such risks are relatively low, and this is consistent with the connotation of the term "minimal risk."

In consideration of the risks associated with amniocentesis, we should be open to the possibility that in the future it will be reasonable to regard the fetal risks of *in utero* gene transfer to exceed minimal for fetuses to be carried to term.

Although there is controversy over whether phase I trials "hold out the prospect of direct benefit to subjects," the view that they should not be regarded as doing so is supported by reasonable arguments. Given these considerations, some IRBs may conclude that phase I *in utero* studies do not meet the requirements of Subpart B of the regulations regarding fetuses to be carried to term. Alternatively, some IRBs may find that the balance of risks and benefits for fetuses to be carried to term makes such studies ethically unacceptable. Moreover, phase I trials recruiting women who plan to carry the pregnancy to term make the therapeutic misconception possible. As one group of commentators pointed out, this creates a risk that there will be disappointment in research subjects and a diminished trust in gene transfer (Recombinant DNA Advisory Committee, 2000, p. 1223).

In response to these concerns, there are at least three ways to design phase I *in utero* studies so that ethical and regulatory requirements are met. First, recruitment can be restricted to women whose fetus has a disease that uniformly is fatal during gestation or soon after birth. This could include cases in which the woman has decided to have an abortion or cases in which she plans to continue the pregnancy. Depending on the objectives of the research, recruitment could focus on either or both of these types of situations. In a second approach, the woman has decided to terminate pregnancy and the research intervention is part of a single operative procedure that will conclude with the abortion. A third approach would recruit women who have decided to terminate pregnancy and concerning whom it is reasonable to conclude that their intent to do so is firm. In this paper, arguments have been given in support of the ethical permissibility of these three types of research design. This discussion has included identifying and responding to objections to having a potential subject's decision to terminate pregnancy as an inclusion criterion.

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