



1976

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: Research on the Fetus

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Recommended Citation

David W. Louisell, *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: Research on the Fetus*, 22 Vill. L. Rev. 300 (1976).

Available at: <http://digitalcommons.law.villanova.edu/vlr/vol22/iss2/3>

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NATIONAL COMMISSION FOR THE PROTECTION OF
HUMAN SUBJECTS OF BIOMEDICAL AND
BEHAVIORAL RESEARCH: RESEARCH
ON THE FETUS

DELIBERATIONS AND CONCLUSIONS

The charge to the Commission is to investigate and study research involving the living fetus and to make recommendations to the Secretary, DHEW, on "policies defining the circumstances (if any) under which such research may be conducted or supported." The Commission has attempted to fulfill that duty by conducting investigations into research on the fetus and by providing a public forum for the presentation and analysis of views on this subject. It must be recognized that the Commission was placed under severe limitations of time by its Congressional mandate. As a result, these considerations on research involving fetuses have necessarily been developed prior to the Commission's larger task of studying the nature of research, the basic ethical principles which should guide it, the problem of informed consent and the review process.

After the Commission identified the information that was required for adequate consideration of the charge, a compendium of pertinent scientific literature and medical experience was prepared by consultants and contractors. In addition, a broad range of views was presented in letters, reports and testimony by theologians, philosophers, physicians, scientists, lawyers, public officials and private citizens. The Commission then undertook critical analysis of the studies and presentations, and conducted public deliberations on the issues involved. Finally, the Commission formulated its Recommendations.

This section of the Commission's report summarizes the reasoning and conclusions that emerged during the deliberations. Section IX of the report sets forth the Commission's Recommendations to the Secretary, DHEW. These Recommendations arise from and are consistent with the Deliberations and Conclusions of the Commission. The Recommendations should be considered only within the context of the Deliberations that precede them.

A. Preface to Deliberations and Conclusions. Throughout the deliberations of the Commission, the belief has been affirmed that the fetus as a human subject is deserving of care and respect. Although the Commission has not addressed directly the issues of the personhood and the civil status of the fetus, the members of the Commission are

convinced that moral concern should extend to all who share human genetic heritage, and that the fetus, regardless of life prospects, should be treated respectfully and with dignity.

The members of the Commission are also convinced that medical research has resulted in significant improvements in the care of the unborn threatened by death or disease, and they recognize that further progress is anticipated. Within the broad category of medical research, however, public concern has been expressed with regard to the nature and necessity of research on the human fetus. The evidence presented to the Commission was based upon a comprehensive search of the world's literature and a review of more than 3000 communications in scientific periodicals. The preponderance of all research involved experimental procedures designed to benefit directly a fetus threatened by premature delivery, disease or death, or to elucidate normal processes or development. Some research constituted an element in the health care of pregnant women. Other research involved only observation or the use of noninvasive procedures bearing little or no risk. A final class of investigation (falling outside the present mandate of the Commission) has made use of tissues of the dead fetus, in accordance with accepted standards for treatment of the human cadaver. The Commission finds that, to the best of its knowledge, these types of research have not contravened accepted ethical standards.

Nonetheless, the Commission notes that there have been instances of abuse in the area of fetal research. Moreover, differences of opinion exist as to whether desired results could have been attained without the use of the human fetus in nontherapeutic research.

Concern has also been expressed that the poor and minority groups may bear an inequitable burden as research subjects. The Commission believes that those groups which are most vulnerable to inequitable treatment should receive special protection.

The Commission concludes that some information which is in the public interest and which provides significant advances in health care can be attained only through the use of the human fetus as a research subject. The Recommendations which follow express the Commission's belief that, while the exigencies of research and the moral imperatives of fair and respectful treatment may appear to be mutually limiting, they are not incompatible.

B. Ethical Principles and Requirements Governing Research on Human Subjects with Special Reference to the Fetus and the Pregnant Woman. The Commission has a mandate to develop the ethical principles underlying the conduct of all research involving human sub-

jects. Until it can adequately fulfill this charge, its statement of principles is necessarily limited. In the interim, it proposes the following as basic ethical principles for use of human subjects in general, and research involving the fetus and the pregnant woman in particular.

Scientific inquiry is a distinctly human endeavor. So, too, is the protection of individual integrity. Freedom of inquiry and the social benefits derived therefrom, as well as protection of the individual are valued highly and are to be encouraged. For the most part, they are compatible pursuits. When occasionally they appear to be in conflict, efforts must be made through public deliberation to effect a resolution.

In effecting this resolution, the integrity of the individual is pre-eminent. It is therefore the duty of the Commission to specify the boundaries that respect for the fetus must impose upon freedom of scientific inquiry. The Commission has considered the principles proposed by ethicists in relation to the exigencies of scientific inquiry, the requirements and present limitations of medical practice, and legal commentary. Among the general principles for research on human subjects judged to be valid and binding are: (1) to avoid harm whenever possible, or at least to minimize harm; (2) to provide for fair treatment by avoiding discrimination between classes or among members of the same class; and (3) to respect the integrity of human subjects by requiring informed consent. An additional principle pertinent to the issue at hand is to respect the human character of the fetus.

To this end, the Commission concludes that in order to be considered ethically acceptable, research involving the fetus should be determined by adequate review to meet certain general requirements:

(1) Appropriate prior investigations using animal models and nonpregnant humans must have been completed.

(2) The knowledge to be gained must be important and obtainable by no reasonable alternative means.

(3) Risks and benefits to both the mother and the fetus must have been fully evaluated and described.

(4) Informed consent must be sought and granted under proper conditions.

(5) Subjects must be selected so that risks and benefits will not fall inequitably among economic, racial, ethnic and social classes.

These requirements apply to all research on the human fetus. In the application of these principles, however, the Commission found it

helpful to consider the following distinctions: (1) therapeutic and nontherapeutic research; (2) research directed toward the pregnant woman and that directed toward the fetus; (3) research involving the fetus-going-to-term and the fetus-to-be-aborted; (4) research occurring before, during or after an abortion procedure; and (5) research which involves the nonviable fetus *ex utero* and that which involves the possibly viable infant. The first two distinctions encompass the entire period of the pregnancy through delivery; the latter three refer to different portions of the developmental continuum.

The Commission observes that the fetus is sometimes an unintended subject of research when a woman participating in an investigation is incorrectly presumed not to be pregnant. Care should be taken to minimize this possibility.

C. Application to Research Involving the Fetus. The application of the general principles enumerated above to the use of the human fetus as a research subject presents problems because the fetus cannot be a willing participant in experimentation. As with children, the comatose and other subjects unable to consent, difficult questions arise regarding the balance of risk and benefit and the validity of proxy consent.

In particular, some would question whether subjects unable to consent should ever be subjected to risk in scientific research. However, there is general agreement that where the benefits as well as the risks of research accrue to the subject, proxy consent may be presumed adequate to protect the subject's interests. The more difficult case is that where the subject must bear risks without direct benefit.

The Commission has not yet studied the issues surrounding informed consent and the validity of proxy consent for nontherapeutic research (including the difficult issue of consent by a pregnant minor). These problems will be explored under the broader mandate of the Commission. In the interim, the Commission has taken various perspectives into consideration in its deliberations about the use of the fetus as a subject in different research settings. The Deliberations and Conclusions of the Commission regarding the application of general principles to the use of the fetus as a human subject in scientific research are as follows:

1. In therapeutic research directed toward the fetus, the fetal subject is selected on the basis of its health condition, benefits and risks accrue to that fetus, and proxy consent is directed toward that subject's own welfare. Hence, with adequate review to assess scientific merit, prior research, the balance of risks and benefits, and the sufficiency of the consent process, such research conforms with all relevant principles

and is both ethically acceptable and laudable. In view of the necessary involvement of the woman in such research, her consent is considered mandatory; in view of the father's possible ongoing responsibility, his objection is considered sufficient to veto.

2. Therapeutic research directed toward the pregnant woman may expose the fetus to risk for the benefit of another subject and thus is at first glance more problematic. Recognizing the woman's priority regarding her own health care, however, the Commission concludes that such research is ethically acceptable provided that the woman has been fully informed of the possible impact on the fetus and that other general requirements have been met. Protection for the fetus is further provided by requiring that research put the fetus at minimum risk consistent with the provision of health care for the woman. Moreover, therapeutic research directed toward the pregnant woman frequently benefits the fetus, though it need not necessarily do so. In view of the woman's right to privacy regarding her own health care, the Commission concludes that the informed consent of the woman is both necessary and sufficient.

In general, the Commission concludes that therapeutic research directed toward the health condition of either the fetus or the pregnant woman is, in principle, ethical. Such research benefits not only the individual woman or fetus but also women and fetuses as a class, and should therefore be encouraged actively.

The Commission, in making recommendations on therapeutic and nontherapeutic research directed toward the pregnant woman, (Recommendations (2) and (3)), in no way intends to preclude research on improving abortion techniques otherwise permitted by law and government regulation.

3. Nontherapeutic research directed toward the fetus *in utero* or toward the pregnant woman poses difficult problems because the fetus may be exposed to risk for the benefit of others.

Here, the Commission concludes that where no additional risks are imposed on the fetus (e.g., where fluid withdrawn during the course of treatment is used additionally for nontherapeutic research), or where risks are so minimal as to be negligible, proxy consent by the parent(s) is sufficient to provide protection. (Hence, the consent of the woman is sufficient provided the father does not object.) The Commission recognizes that the term "minimal" involves a value judgment and acknowledges that medical opinion will differ regarding what constitutes "minimal risk." Determination of acceptable minimal risk is a function of the review process.

When the risks cannot be fully assessed, or are more than minimal, the situation is more problematic. The Commission affirms as a general principle that manifest risks imposed upon nonconsenting subjects cannot be tolerated. Therefore, the Commission concludes that only minimal risk can be accepted as permissible for nonconsenting subjects in nontherapeutic research.

The Commission affirms that the woman's decision for abortion does not, in itself, change the status of the fetus for purposes of protection. Thus, the same principles apply whether or not abortion is contemplated; in both cases, only minimal risk is acceptable.

Differences of opinion have arisen in the Commission, however, regarding the interpretation of risk to the fetus-to-be-aborted and thus whether some experiments that would not be permissible on a fetus-going-to-term might be permissible on a fetus-to-be-aborted. Some members hold that no procedures should be applied to a fetus-to-be-aborted that would not be applied to a fetus-going-to-term. Indeed, it was also suggested that any research involving fetuses-to-be-aborted must also involve fetuses-going-to-term. Others argue that, while a woman's decision for abortion does not change the status of the fetus *per se*, it does make a significant difference in one respect — namely, in the risk of harm to the fetus. For example, the injection of a drug which crosses the placenta may not injure the fetus which is aborted within two weeks of injection, where it might injure the fetus two months after injection. There is always, of course, the possibility that a woman might change her mind about the abortion. Even taking this into account, however, some members argue that risks to the fetus-to-be-aborted may be considered "minimal" in research which would entail more than minimal risk for a fetus-going-to-term.

There is basic agreement among Commission members as to the validity of the equality principle. There is disagreement as to its application to individual fetuses and classes of fetuses. Anticipating that differences of interpretation will arise over the application of the basic principles of equality and the determination of "minimal risk," the Commission recommends review at the national level. The Commission believes that such review would provide the appropriate forum for determination of the scientific and public merit of such research. In addition, such review would facilitate public discussion of the sensitive issues surrounding the use of vulnerable nonconsenting subjects in research.

The question of consent is a complicated one in this area of research. The Commission holds that procedures that are part of the research design should be fully disclosed and clearly distinguished from

those which are dictated by the health care needs of the pregnant woman or her fetus. Questions have been raised regarding the validity of parental proxy consent where the parent(s) have made a decision for abortion. The Commission recognizes that unresolved problems both of law and of fact surround this question. It is the considered opinion, however, that women who have decided to abort should not be presumed to abandon thereby all interest in and concern for the fetus. In view of the close relationship between the woman and the fetus, therefore, and the necessary involvement of the woman in the research process, the woman's consent is considered necessary. The Commission is divided on the question of whether her consent alone is sufficient. Assignment of an advocate for the fetus was proposed as an additional safeguard; this issue will be thoroughly explored in connection with the Commission's review of the consent process. Most of the Commissioners agree that in view of the father's possible responsibility for the child, should it be brought to term, the objection of the father should be sufficient to veto. Several Commissioners, however, hold that for nontherapeutic research directed toward the pregnant woman, the woman's consent alone should be sufficient and the father should have no veto.

4. Research on the fetus during the abortion procedure or on the nonviable fetus *ex utero* raises sensitive problems because such a fetus must be considered a dying subject. By definition, therefore, the research is nontherapeutic in that the benefits will not accrue to the subject. Moreover, the question of consent is complicated because of the special vulnerability of the dying subject.

The Commission considers that the status of the fetus as dying alters the situation in two ways. First, the question of risk becomes less relevant, since the dying fetus cannot be "harmed" in the sense of "injured for life." Once the abortion procedure has begun, or after it is completed, there is no chance of a change of mind on the woman's part which will result in a living, injured subject. Second, however, while questions of risk become less relevant, considerations of respect for the dignity of the fetus continue to be of paramount importance, and require that the fetus be treated with the respect due to dying subjects. While dying subjects may not be "harmed" in the sense of "injured for life," issues of violation of integrity are nonetheless central. The Commission concludes, therefore, that out of respect for the dying subjects, no nontherapeutic interventions are permissible which would alter the duration of life of the nonviable fetus *ex utero*.

Additional protection is provided by requiring that no significant changes are made in the abortion procedure strictly for purposes of research. The Commission was divided on the question of whether a woman has a right to accept modifications in the timing or method of the abortion procedure in the interest of research, and whether the investigator could ethically request her to do so. Some Commission members desired that neither the research nor the investigator in any way influence the abortion procedure; others felt that modifications in timing or method of abortion were acceptable provided no new elements of risk were introduced. Still others held that even if modifications increased the risk, they would be acceptable provided the woman had been fully informed of all risk, and provided such modifications did not postpone the abortion beyond the twentieth week of gestational age (five lunar months, four and one-half calendar months). Despite this division of opinion, the Recommendation of the Commission on this matter is that the design and conduct of a nontherapeutic research protocol should not determine the recommendations by a physician regarding the advisability, timing or method of abortion. No members of the Commission desired less stringent measures.

Furthermore, it is possible that, due to mistaken estimation of gestational age, an abortion may issue in a possibly viable infant. If there is any danger that this might happen, research which would entail more than minimal risk would be absolutely prohibited. In order to avoid that possibility the Commission recommends that, should research during abortion be approved by national review, it be always on condition that estimated gestational age be below 20 weeks. There is, of course, a moral and legal obligation to attempt to save the life of a possibly viable infant.

Finally, the Commission has been made aware that certain research, particularly that involving the living nonviable fetus, has disturbed the moral sensitivity of many persons. While it believes that its Recommendations would preclude objectionable research by adherence to strict review processes, problems of interpretation or application of the Commission's Recommendations may still arise. In that event, the Commission proposes ethical review on a national level in which informed public disclosure and assessment of the problems, the type of proposed research and the scientific and public importance of the expected results can take place.

D. Review Procedures. The Commission will conduct comprehensive studies of existing review mechanisms in connection with its broad mandate to develop guidelines and make recommendations con-

cerning ethical issues involved in research on human subjects. Until the Commission has completed these studies, it can offer only tentative conclusions and recommendations regarding review mechanisms.

In the interim, the Commission finds that existing review procedures required by statute (P.L. 93-348) and DHEW regulations (45 C.F.R. 46) suffice for all therapeutic research involving the pregnant woman and the fetus, and for all nontherapeutic research which imposes minimal or no risk and which would be acceptable for conduct of a fetus *in utero* to be carried to term or on an infant. Guidelines to be employed under the existing review procedures include: (1) importance of the knowledge to be gained; (2) completion of appropriate studies on animal models and nonpregnant humans and existence of no reasonable alternative; (3) full evaluation and disclosure of the risks and benefits that are involved; and (4) supervision of the conditions under which consent is sought and granted, and of the information that is disclosed during that process.

The case is different, however, for nontherapeutic research directed toward a pregnant woman or a fetus if it involves more than minimal risk or would not be acceptable for application to an infant. Questions may arise concerning the definition of risk or the assessment of scientific and public importance of the research. In such cases, the Commission considers current review procedures insufficient. It recommends these categories be reviewed by a national review body to determine whether the proposed research could be conducted within the spirit of the Commission's recommendations. It would interpret these recommendations and apply them to the proposed research, and in addition, assess the scientific and public value of the anticipated results of the investigation.

The national review panel should be composed of individuals having diverse backgrounds, experience and interests, and be so constituted as to be able to deal with the legal, ethical, and medical issues involved in research on the human fetus. In addition to the professions of law, medicine, and the research sciences, there should be adequate representation of women, members of minority groups, and individuals conversant with the various ethical persuasions of the general community.

Inasmuch as even such a panel cannot always judge public attitudes, panel meetings should be open to the public, and, in addition, public participation through written and oral submissions should be sought.

E. Compensation. The Commission expressed a strong conviction that considerable attention be given to the issue of provision of compensation to those who may be injured as a consequence of their participation as research subjects.

Concerns regarding the use of inducements for participation in research are only partially met by the Commission's Recommendation (14) on the prohibition of the procurement of an abortion for research purposes. Compensation not only for injury from research but for participation in research as a normal volunteer or in a therapeutic situation will be part of later Commission deliberations.

F. Research Conducted Outside the United States. The Commission has considered the advisability of modifying its standards for research which is supported by the Secretary, DHEW, and is conducted outside the United States. It has concluded that its recommendations should apply as a simple minimal standard, but that research should also comply with any more stringent limitations imposed by statutes or standards of the country in which the research will be conducted.

G. The Moratorium on Fetal Research. The Commission notes that the restrictions on fetal research (imposed by Section 213 of P.L. 93-348) have been construed broadly throughout the research community, with the result that ethically acceptable research, which might yield important biomedical information, has been halted. For this reason, it is considered in the public interest that the moratorium be lifted immediately, that the Secretary take special care thereafter that the Commission's concerns for the protection of the fetus as a research subject are met, and appropriate regulations based upon the Commission's recommendations be implemented within a year from the date of submission of this report to the Secretary, DHEW. Until final regulations are published, the existing review panels at the agency and institutional levels should utilize the Deliberations and Recommendations of the Commission in evaluating the acceptability of all grant and contract proposals submitted for funding.

H. Synthesis. The Commission concludes that certain prior conditions apply broadly to all research involving the fetus, if ethical considerations are to be met. These requirements include evidence of pertinent investigations in animal models and nonpregnant humans, lack of alternative means to obtain the information, careful assessment of the risks and benefits of the research, and procedures to ensure that informed consent has been sought and granted under proper conditions. Determinations as to whether these essential requirements have been met may be made under existing review procedures, pending study by the Commission of the entire review process.

In the judgment of the Commission, therapeutic research directed toward the health care of the pregnant woman or the fetus raises little

concern, provided it meets the essential requirements for research involving the fetus, and is conducted under appropriate medical and legal safeguards.

For the most part, nontherapeutic research involving the fetus to be carried to term or the fetus before, during or after abortion is acceptable so long as it imposes minimal or no risk to the fetus and, when abortion is involved, imposes no change in the timing or procedure for terminating pregnancy which would add any significant risk. When a research protocol or procedure presents special problems of interpretation or application of these guidelines, it should be subject to national ethical review; and it should be approved only if the knowledge to be gained is of medical importance, can be obtained in no other way, and the research proposal does not offend community sensibilities.