

WEDNESDAY, JANUARY 11, 1978
PART III



**DEPARTMENT OF
HEALTH,
EDUCATION,
AND WELFARE**



**ADDITIONAL
PROTECTIONS
PERTAINING
TO RESEARCH,
DEVELOPMENT AND
RELATED ACTIVITIES
INVOLVING FETUSES,
PREGNANT WOMEN
AND IN VITRO
FERTILIZATION**



[4110-08]

Title 45—Public Welfare

SUBTITLE A—DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, GENERAL ADMINISTRATION

PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart B—Additional Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women and In Vitro Fertilization

MISCELLANEOUS AMENDMENTS

AGENCY: Department of Health, Education, and Welfare.

ACTION: Final rule.

SUMMARY: These amendments clarify the definitions of "Pregnancy" and "Fetus" as used in the original rule, modify provisions governing establishment of Ethical Advisory Boards, and delete provisions which would have permitted artificial maintenance of the vital functions of nonviable fetuses when the purpose of the research was to develop new methods for enabling fetuses to survive to the point of viability.

EFFECTIVE DATE: These amendments shall become effective on January 11, 1978.

FOR FURTHER INFORMATION CONTACT:

D. T. Chalkley, Ph. D., Director, Office for Protection from Research Risks, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014, 301-496-7005.

SUPPLEMENTARY INFORMATION: Proposed amendments were published in the FEDERAL REGISTER on Thursday, January 13, 1977. In addition, some 5,000 copies of the amendments were distributed to research institutions, to public interest organizations concerned with research and other activities related to human reproduction, and to other persons who had shown concern with these issues by commenting on earlier proposed rulemakings and on the Report and Recommendations on Research on the Fetus of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (40 FR 33530). Interested persons, institutions and organizations were given until March 13, 1977, to submit comments and criticism. A total of 130 comments were received. None were addressed to the proposed additions in policy (§ 46.102) concerning steps to be taken to avoid involvement of pregnant women in research or to proposed changes in provisions regarding the Ethical Advisory Boards (§ 46.204).

One commentator suggested that § 46.209(a) as written seemed to imply that experimentation with a fetus ex

utero would be permissible if an investigator decided that it was not medically viable. Since 1,000 grams is the accepted medical boundary of viability, this would permit otherwise prohibited experimentation on smaller fetuses, even though fetuses weighing far less than 1,000 grams have been known to survive.

Response. Section 46.209(b) substantially limits the kinds of research that may be performed on nonviable fetuses. In addition, in a notice published at 40 FR 33530, the Secretary determined that any fetus ex utero, other than a dead fetus, weighing 500 grams or more and having a gestational age of 20 weeks or more is to be considered viable and a premature infant for the purposes of these regulations. (This determination reflects the finding of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research that no fetus weighing less than 600 grams and of less than 24 weeks gestational age has been reliably reported to have survived.) A simple determination by a physician that a particular fetus ex utero is medically nonviable would not automatically permit involvement of that fetus in research under these regulations. The Secretary is awaiting the National Commission's report on research involving children before proposing regulations regarding research with and for premature and term infants.

This same commentator noted that the definition of fetus as amended at § 46.201(c) was "something of an improvement" but expressed continued concern that the definition of the life span of the fetus as beginning at implantation would allow time for research between fertilization and implantation without the informed consent of the pregnant woman.

Response. Basic DHEW regulations contained in Subpart A of 45 CFR Part 46 require at § 46.109 that any institution proposing to place any subject at risk is obligated to obtain legally effective informed consent. The provisions of Subpart B, including those relating to consent, are additional protections pertaining to research activities involving fetuses and pregnant women and do not substitute for the basic protections available to all classes of subjects.

Approximately 128 comments were directed almost entirely to aspects of the definitions of the terms "fetus" and "pregnancy" in § 46.203(b) and (c), which are not changed by the proposed amendments. Usually, they addressed issues discussed both in the preamble to the final regulations published on August 8, 1975 (40 FR 33526), and in the preamble to the notice of proposed rulemaking published in the FEDERAL REGISTER on August 23, 1974 (39 FR 30648), which

preceded the final regulations. There seems no reason to repeat these discussions here. Certain criticisms explored new ground. These centered on the following issues: (i) There had been inadequate prior notice of the definitions, (ii) particularly, there had been inadequate prior notice to medical practitioners, (iii) the definitions were inconsistent with existing dictionary definitions and were medically incorrect in that they did not define pregnancy and fetal life to begin at fertilization.

Response. The criticisms are not sound. (i) The basic definitions of "fetus" and "pregnancy" to be amended as described in the proposed rulemaking are essentially the same definitions that appeared in a draft proposed rulemaking on November 16, 1973 (38 FR 31738), in a formal notice of proposed rulemaking on August 23, 1974 (39 FR 30648), and in a final rule issued August 8, 1975 (40 FR 33526). (ii) Added notice to practitioners per se is inappropriate and unnecessary since the regulations are concerned solely with research, development and related activities conducted or supported by the Department of Health, Education, and Welfare, not with the practice of medicine. Practitioners must be in compliance with applicable State or local laws bearing upon activities involving the fetus including laws concerning consent and the provision of due care. (iii) The term fetus is variously defined in popular and medical dictionaries as the product of conception from the eighth or ninth week, the latter part of the third month or "from the time the embryo is formed" until birth. The definitions of "fetus" and "pregnancy" employed in § 46.203 cover the period of gestation from the time of implantation, about seven days after fertilization, until termination of pregnancy. The definitions of "fetus" and "pregnancy" agree in essence with those of the American College of Obstetrics and Gynecology, in *Obstetric-Gynecologic Terminology*, Edward C. Hughes, ED., Philadelphia (1972) and that employed in the most recently issued medical dictionary, *Stedman's Medical Dictionary*, 23d Edition (1976). Both of these authorities define "fetus" and "pregnancy" to begin at conception and define conception to coincide with implantation.

Two commentators noted that the definition of "fetus" was at variance with the findings of the First International Conference on Abortion held in 1967. The medical group assembled at the Conference is quoted as stating that "The majority of our group could find no point of time between the union of sperm and egg, or at least the blastocyst stage, and the birth of the infant at which point we could say that this was not a human life. The changes occurring between implanta-

tion and * * * a mature adult are mere stages of development and maturation" (emphases added).

Response. Since implantation occurs at the blastocyst stage, the proposed definition of fetus is within the scope of the findings of the Conference.

One commentator suggested that the terms "fetus" and "pregnancy" must of necessity include all or part of the period between fertilization and implantation, citing the work of Saxena, B. B. et al. (Science, 184:794) and Landsman, R., and Saxena, B. B. (Fertil. and Steril. 27:357, 1976), describing results obtained with a pregnancy test dependent upon radioreceptor assay for human chorionic gonadotropin. The data presented in these articles suggested that the presence of the fertilized and developing ovum could be confirmed as early as four days following fertilization, and three days prior to implantation, while the developing ovum is still in a free-floating state.

Response. As stated in the prior notice of proposed rulemaking (42 FR 2792), designation of a precise time for the start of the fetal period is a matter of practical and regulatory necessity. The regulations impose additional duties and responsibilities on investigators and research institutions over and above those generally imposed by statute and common law on medical practitioners and medical institutions. As of the time of drafting of the proposed rule, it appeared that the time of implantation not only coincided with the onset of fetal life as defined by the medical profession, but also with the first point in the course of human development which could be medically confirmed by existing pregnancy tests. This still appears to be the case. Saxena's suggestion that the developing ovum might be detected prior to implantation has not been supported (Catt, K. J. et al., Jour. Clin. End. Met., 40:537, 1975) and is not repeated by him in a more recent publication (Saxena, B. B. et al., Fertil. and Steril. 28:163, 1977). Since the radioreceptor assay fails to distinguish between luteinizing hormone levels, which peak sharply at the time of ovulation, and human chorionic gonadotropin levels, which rise shortly after implantation, some confusion in assay is inevitable. Identification of the confirmation of pregnancy as the point at which these additional protections must be imposed appears to be scientifically sound.

While no comments were received on the proposed changes in provisions regarding the Ethical Advisory Board

(§ 46.204), the Secretary has determined that the prohibition in this section against the appointment as a member of the Board of any full-time employee of the Federal Government is unnecessarily restrictive and denies to the Board expertise available elsewhere within the Federal Government. Therefore, the last sentence of this section is changed to read, "No board member may be a regular, full-time employee of the Department of Health, Education, and Welfare." With the exception of this change and the correction of typographical errors, the proposed amendments are adopted as published in 42 FR 2792.

NOTE.—The Department of Health, Education, and Welfare has determined that this document does not contain a major proposal requiring preparation of an Inflation Impact Statement as required by Executive Order 11821 and by OMB Circular A-107.

Dated: July 29, 1977.

JAMES F. DICKSON,
*Acting Assistant Secretary
for Health.*

Approved: December 29, 1977.

JOSEPH A. CALIFANO, Jr.,
Secretary.

Accordingly, Part 46 of 45 CFR, Subtitle A, is amended by:

1. Revising § 46.102(c) to read:

§ 46.102 Policy.

* * * * *

(c) Unless the activity is covered by subpart B of this part, if it involves as subjects women who could become pregnant, the Board shall also determine as part of its review that adequate and appropriate steps will be taken to avoid involvement of women who are in fact pregnant (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), when such activity would involve risk to a fetus.

2. Revising §§ 46.203(b) and 46.203(c) to read:

§ 46.203 Definitions.

* * * * *

(b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the pre-

sumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

§ 46.201 [Amended].

3. Revising § 46.204(a) to read:

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health, Education, and Welfare.

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4. Deleting § 46.204(b) and redesignating §§ 46.204(c) through 46.204(e) as §§ 46.204(b) through 46.204(d).

5. Amending § 46.204(b), as so redesignated, by deleting the word "appropriate" wherever it occurs.

6. Amending §§ 46.209(a) and 46.209(b) to read:

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained.

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

[FR Doc. 78-662 Filed 1-10-78; 8:45 am]