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Department of Health and Human Services

45 CFR Part 46

Protection of Human Research Subjects; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

RIN 0925–AA14

Protection of Human Research Subjects

AGENCY: Department of Health and Human Services (HHS).

ACTION: Notice of Proposed rulemaking.

SUMMARY: The Department of Health and Human Services (HHS) is proposing to amend its human subjects protection regulations applicable to research conducted or supported by HHS, by replacing the existing Subpart B of the regulations entitled ''Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization'' with new regulations entitled ''Additional DHHS Protections for Pregnant Women, Human Fetuses, and Newborns Involved as Subjects in Research, and Pertaining to Human In Vitro Fertilization.'' This revision continues the Department's recognition of the need to provide special protections for the human fetus and newborn in research, while eliminating unnecessary barriers to consent to research that can benefit fetuses or newborns.

Additionally, consistent with recent practices and statutory changes, this proposed regulation provides a mechanism for special ethical reviews on an ad hoc basis as may be deemed appropriate by the Secretary, HHS.

DATES: Comments on the proposed regulation must be received on or before August 18, 1998.

ADDRESSES: Comments must be mailed to: Carol Wigglesworth, Senior Policy Analyst, Office for Protection from Research Risks, 6100 Executive Boulevard, Suite 3B01, MSC–7507, Rockville, MD 20892–7507. The Department invites written comments on the proposed regulations and requests that comments identify the specific regulatory provisions to which they relate.

FOR FURTHER INFORMATION CONTACT: Carol Wigglesworth, Senior Policy Analyst, Office for Protection from Research Risks, 6100 Executive Boulevard, Suite 3B01, MSC–7507, Rockville, MD 20892–7507, (301) 402–5913 (not a toll-free number). Interested persons may obtain a fax copy of the current regulations for the protection of human research subjects (45 CFR 46), including Subpart B as well as Subparts A, C, and D, by telephoning (301) 594–0464 (not a toll free number) and requesting document number 1004.

SUPPLEMENTARY INFORMATION:

Background

On August 8, 1975, The Department of Health and Human Services (HHS) [then the Department of Health, Education, and Welfare (HEW)] published regulations pertaining to research involving fetuses, pregnant women, and human in vitro fertilization. Those regulations were consistent with the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) and were codified at Subpart B of Title 45, Part 46, of the Code of Federal Regulations. Along with subsequent secondary changes, incorporated on January 11, 1978 and June 1, 1994, these regulations remain in force today. Both the 1975 Report of the National Commission and the 1975 regulations were published in the **Federal Register** on August 8, 1975 (40 FR 33526 (1975)).

During the last four years, the following pertinent events involving research covered by the 1975 regulations occurred:

- The enactment on June 10, 1993 of the ''National Institutes of Health (NIH) Revitalization Act of 1993'' (Pub. L. 103–43) nullifying the HHS regulatory requirement for Ethical Advisory Board review of research involving in vitro fertilization of human ova at 45 CFR 46.204(d) (59 FR 28276 (1994)).
- The 1994 recommendations of the Institute of Medicine Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies urging the Office for Protection from Research Risks (OPRR), HHS, to ''* * * revise and reissue subpart B * * *'' of the human subject protection regulations consistent with the Committee's recommendations for enhanced inclusion of women in research studies (*Women and Health Research:* Ethical and Legal Issues of Including Women in Clinical Studies, National Academy Press, 1994).
- The issuance of a Food and Drug Administration ''Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs'' on July 22, 1993 (58 FR 39406 (1993)), the issuance of NIH ''Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research'' on March 28, 1994 (59 FR 14508 (1994)), and the issuance of a Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry ''Policy on the Inclusion of Women and Racial and Ethic Minorities in Externally Awarded Research'' on September 15, 1995 (60 FR 47947 (1995)), each designed, in part, to improve the opportunity for women to be included as human subjects in research.
- The enactment on September 30, 1996, of the ''Omnibus Consolidated Fiscal Year 1997 Appropriations Act'' (Pub. L. 104–208) prohibiting HHS from using funds appropriated by the act for (i) the creation of a human embryo or embryos for research purposes, or (ii) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). On January 26, 1996, identical language pertinent to FY 1996 funds had been enacted in Pub. L. 104–99.

The impact of these events on research involving pregnant women, fetuses, and in vitro fertilization and the fact that there had been no major review of the regulations applicable to these subjects for nearly two decades, presented a forceful argument for a contemporaneous review of these regulations.

The OPRR, located at NIH, has HHS-wide responsibility for the development, implementation, and compliance oversight of these regulations. The Director, OPRR, convened the Public Health Service Human Subject Regulation Drafting Committee, a committee of representatives of the heads of the pertinent operating components within the Public Health Service, to evaluate Subpart B of 45 CFR Part 46 and to consider if revisions were in order. Beginning in May 1994, this committee met twice monthly over the next 14 months to review the regulations and to make recommendations for any needed revisions.

The Drafting Committee found that the regulations provide adequate protections for women and fetuses. In light of the IOM Report and the NIH guidelines on the Inclusion of Women and Minorities as subjects in Clinical Research, the Drafting Committee concluded that women ought not be unnecessarily excluded from research on the basis of pregnancy.

Accordingly, this proposed rule institutes a policy of presumed opportunity for inclusion of pregnant women in research in place of one of presumed exclusion. Similarly, the proposed rule modifies the consent requirements for fetal research to remove potential barriers to therapeutic research that might provide medical

benefit to a fetus. The Drafting Committee also found that nonsubstantive technical, formatting, and clarifying changes are in order.

In the midst of the Drafting Committee's evaluation and discussion, the National Task Force on AIDS Drug Development, chaired by the Assistant Secretary for Health, recommended that the regulations applicable to pregnant subjects of research be amended to remove any requirement that permission or consent of the father of the fetus be obtained before the woman could become a research subject. The Drafting Committee carefully reviewed the issue of a ''paternal consent'' requirement for participation of pregnant women and has incorporated into this proposed rule changes which are responsive to the recommendation of the Task Force. The Presidential Advisory Council on HIV/AIDS subsequently addressed the matter of paternal consent during their December 1995 meeting, and recommended that the Secretary, HHS publish for public comment proposed regulations regarding participation of pregnant women in clinical trials, with a revision which will provide that the lack of a written consent from the father of the fetus will not disqualify a pregnant woman from participation in a federally funded clinical trial.

The Drafting Committee approved a proposed rule and recommended that the Assistant Secretary for Health and the Secretary, HHS, publish the proposal for public comment. The notice of proposed rulemaking fulfills that recommendation.

Proposed Changes to Subpart B

See Figure 1 and Table 1.

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Figure 1. Relationships Among Selected Terms Employed in Proposed Subpart B.

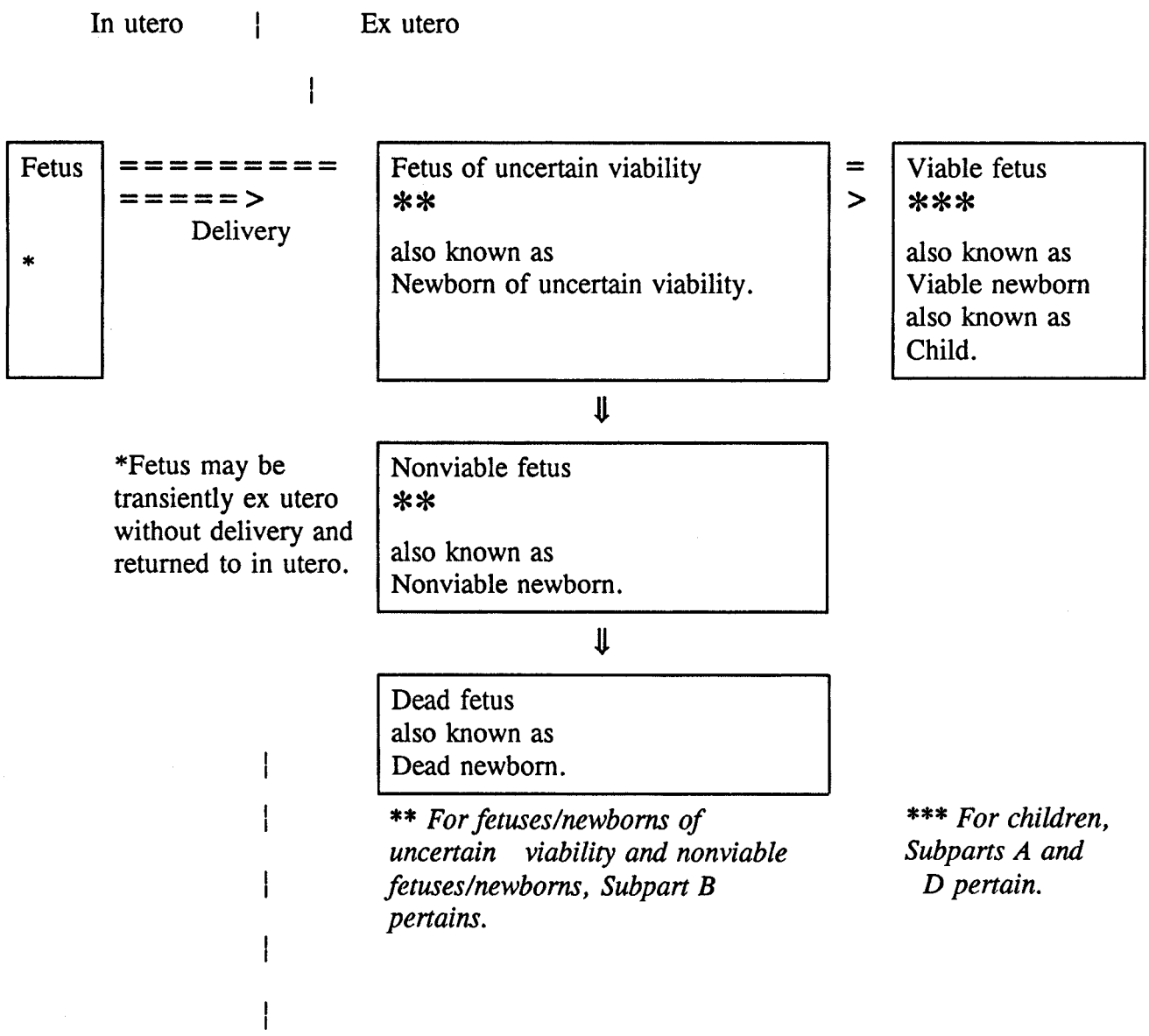

TABLE 1 - Current and Proposed 45CFR46, Subpart B

Content	Current Regulations	Proposed Changes
General limitations.	Appropriate studies on animals and nonpregnant individuals must have been completed. Individuals engaged in research will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy, and in determining the viability of the fetus at the termination of the pregnancy. Inducements, monetary or otherwise, may not be offered to abort pregnancy.	*No substantive change.* Language is more explicit about preclinical and clinical studies and resulting data to assess potential risks. *No substantive change.* Redundant language deleted.
Regulatory presumption.	Presumption of *exclusion* of pregnant women from research. Language states "No activity... may be undertaken unless...".	Presumption of *inclusion* of pregnant women in research. Language states "Pregnant women may be involved if all the following conditions are met...".
Definitions:		
"Pregnancy"	From confirmation of implantation until expulsion or extraction of the fetus.	*No substantive change.* Defined as implantation until delivery.
"Fetus"	The product of conception from implantation to an ex utero determination of viability.	*No substantive change.* "[F]rom implantation" replaced with "during pregnancy." "[P]regnancy" defined as implantation until delivery.
"Newborn"	No definition in current rule.	Defined as a fetus after delivery.
"Viable" (current rule) = "viable fetus" or "viable newborn" (proposed)	A fetus that is able to survive, ex utero, to the point of independently maintaining heart beat and respiration.	*No substantive change.* Reference to "newborn" added and reference to "infant" deleted.
"Nonviable fetus" (current rule) = "nonviable fetus" or "nonviable newborn" (proposed)	A fetus, ex utero, which, although living, is not viable.	*No substantive change.* Reference to "newborn" added.
"Dead fetus" (current rule) = "dead fetus" or "dead newborn" (proposed)	A fetus ex utero which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if attached).	*No substantive change.* Reference to "newborn" added.
"Children"	No definition in current rule.	Defined as persons who have not attained the legal age for consent, consistent with 45CFR46, Subpart D.
"In vitro fertilization"	Fertilization of human ova outside of the body.	*No change.*
Research involving in vitro fertilization.	IRB review and approval required.	*No change.*
Exempt research.	No categories of research are exempt.	Exemptions at 46.101(b)(1)-(6) pertain.

Research involving pregnant women.	Any risk to the fetus must be the least possible risk for achieving the objectives of the research. Either (1) the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal. Consent of the mother and consent of the father are required unless the purpose is to meet the health needs of the mother, or the father is unknown, unavailable, or the pregnancy resulted from rape.	***No substantive change.*** This section combined with section on research involving fetuses. ***No substantive change.*** The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by activities designed to meet the health needs of the mother or her fetus. Consent of the father is not required. Consent of the mother ***or*** her legally authorized representative is required. Mother must be informed of the reasonably foreseeable impact of the research on the fetus.
Research involving fetuses.	Any risk to the fetus must be the least possible risk for achieving the objectives of the research. Either (1) the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. Consent of the mother ***and*** consent of the father are required unless the father is unknown, unavailable, or the pregnancy resulted from rape.	***No substantive change.*** This section combined with section on research involving pregnant women. ***No substantive change.*** The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by activities designed to meet the health needs of the mother or her fetus. The requirement for IRB determination about purpose of activity is obviated by new requirement for mother's determination about participation in the activity after being informed about risk to fetus. Consent of the father is not required. Consent of the mother ***or*** her legally authorized representative is required. Mother must be informed of the reasonably foreseeable impact of the research on the fetus.
Research involving newborns of uncertain viability.	There may be no added risk from the research activity unless the purpose of the research is to enhance the possibility of survival of the particular fetus to the point of viability. Purpose must be the development of important biomedical knowledge which cannot be obtained by other means. Consent of legally competent mother and consent of legally competent father are required, unless the father is unknown, unavailable, or the pregnancy resulted from rape.	*No change.* Consent of the mother ***or*** the father is required, ***or*** that of a legally authorized representative of the mother ***or*** father if both parents are unavailable, temporarily incapacitated, or incompetent.
Research involving nonviable newborns.	The vital functions of the newborn may not be artificially maintained, the research may not terminate the heartbeat or respiration, and there may be no added risk of injury or death. Purpose must be the development of important biomedical knowledge which cannot be obtained by other means. Consent of legally competent mother and consent of legally competent father are required, unless the father is unknown, unavailable, or the pregnancy resulted from rape.	*No change.* Consent of the mother and father are required, ***unless*** one is unavailable, incompetent, or temporarily incapacitated. Consent of a legally authorized representative is prohibited.
Research involving viable newborns.	Requires that the research be conducted in accord with requirements of other Subparts.	***No substantive change.*** An explicit reference to Subpart D, Additional Protections for Children, is added.

Provision for special review by experts.	Requires one or more HHS Ethical Review Boards (EAB) to render advice on issues raised by applications or proposals. Secretary has authority to establish classes of research that must be reviewed by the EAB.	Requirement for EAB deleted. Provides Secretary, HHS, with the discretion, after consulting, as needed with a panel of experts, to modify or waive requirements for specific projects or classes of research.

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Section 46.201 To what do these regulations apply?

Paragraph (a)—There is no substantive change to this paragraph. Consistent with recent revisions of other subparts of Part 46, references to grants and contracts are deleted to demonstrate that these regulations apply to all activities, intramural and extramural, which are conducted or supported by the Department.

Paragraph (b)—It is now proposed that the exemptions at § 46.101(b)(1)–(6) of Subpart A be applicable to Subpart B. These exemptions were proposed, discussed, and promulgated subsequent to the last substantive revision of Subpart B. The proposals, discussions, and promulgations of these exemptions were published in the **Federal Register** on: August 14, 1979 (exemptions first proposed, 44 FR 47688); January 26, 1981 (exemptions first promulgated, 46 FR 8366); March 22, 1982 (new exemption proposed, 47 FR 12276); March 4, 1993 (new exemption promulgated, 48 FR 9276); March 8, 1983 (exemptions added to Subpart D of 45 CFR 46, 48 FR 9814); June 3, 1986 (exemptions proposed for proposed Model Federal Policy for the Protection of Human Subjects, 51 FR 20204); November 10, 1988 (exemptions proposed in revised proposed Federal Policy for the Protection of Human Subjects, 53 FR 45661); and June 18, 1991 (exemptions revised in promulgation of Federal Policy for the Protection of Human Subjects, 56 FR 28003). The Department is particularly interested in comment on the inclusion of these exemptions.

Paragraph (c)—This provision extends the additions, exceptions, and provisions for waiver, as set forth in paragraphs (c) through (i) of § 46.101 of Subpart A of Part 46, to the regulations at Subpart B. The provision is identical to § 46.401(c) of the regulations providing additional protection for research involving children. It does not appear in the existing Subpart B only because the additions, exceptions, and provisions for waiver were not included in Subpart A at the time Subpart B was promulgated.

Paragraphs (c) through (i) of § 46.101 address: the authority of Department and Agency heads to determine the applicability of the regulations to specific research activities or classes of research activities (paragraphs (c), (d), and (i)); the relationship of the regulations to any Federal laws or regulations providing additional protection for human subjects (paragraph (e)); the relationship of the regulations to any state or local laws or regulations which provide additional protection for human subjects (paragraph (f)); the relationship of the regulations to foreign laws or regulations which provide additional protection for human subjects (paragraph (g)); and the authority of Department and Agency heads to determine the applicability of foreign procedures for the protection of human subjects which differ from the requirements of the regulations (paragraph (h)). Note that the proposed § 46.201(c) clarifies that the reference to State or local laws is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

The authority for determinations by Department and Agency heads under those provisions and the recognition of Federal, State, local, and foreign laws and regulations that provide additional protection for human subjects can and should be applied to the research covered by Subpart B in the same manner as they apply to other research involving human subjects.

Section 46.202 Definitions

The text of the existing § 46.202, ''Purpose,'' is unnecessary because it does not provide any substantive guidance. It is deleted in the proposed regulation. The absence of a ''purpose'' section is consistent with Subparts A and D of 45 CFR Part 46.

Definitions in existing § 46.203 are moved to § 46.202 in the proposed regulation. The definitions in the proposed regulation are substantively the same as those in the existing regulation; some language has been clarified or simplified and definitions of ''newborn'' and ''children'' are provided.

Paragraph (a) *''Secretary''*—no change

Paragraph (b) *''Pregnancy''*—The definition conforms with the standard medical definition of pregnancy. The phrase ''expulsion or extraction of the fetus'' has been replaced by the commonly used term ''delivery'' here and throughout Subpart B. The word ''confirmation'' of implantation has been deleted as unnecessary. (If a woman shows any presumptive sign of pregnancy, such as missed menses, she is considered pregnant until the results of a pregnancy test are negative or until delivery.)

Paragraph (c) *Fetus*—the definition has been simplified by adding the phrase ''during pregnancy'' and deleting reference to ex utero.

Paragraph (d) *Newborn*—the definition is new and equates to a fetus after delivery.

Paragraph (e) *Nonviable fetus or nonviable newborn*—the definition replaces the current definition of ''nonviable fetus'' which refers to fetuses ex utero. Both terms (fetus and newborn) are provided because some persons may prefer one term to the other depending on the length of the gestational period. No substantive change is intended.

Paragraph (f) *Dead fetus or dead newborn*—the definition replaces the definition of dead fetus which pertains to a fetus ex utero. Both terms (fetus and newborn) are provided because some persons may prefer one term to the other depending on the length of the gestational period. No substantive change is intended.

Paragraph (g) *Viable fetus or viable newborn*—the definition refers to fetuses after delivery and replaces the current definition which refers to fetuses ex utero. A viable fetus or a viable newborn is a child. Both terms (fetus and newborn) are provided because some persons may prefer one term to the other depending on the length of the gestational period. The meaning of viability is unchanged, and a reference to Subpart D is added.

Paragraph (h) ''Children''—the definition in Subpart D is repeated in this subpart for ease of reference.

Paragraph (i) *''In vitro fertilization''*—no change.

Section 46.203 Duties of IRBs in Connection With Research Involving Pregnant Women, Human Fetuses, Newborns and Human in Vitro Fertilization

Definitions in existing § 46.203 are found in § 46.202 in the proposed regulation.

Definitions in existing § 46.203 are found in § 46.202 in the proposed regulation. There is no substantive change to this section; the language is more concise. The proposed § 46.203 would replace the existing § 46.205 regarding IRB duties, which is duplicative of language in Subpart A.

In assessing research involving pregnant women, IRBs must be attentive to the Department's objective that research it supports include pregnant women unless there are compelling reasons to exclude them. In other words, the presumption is one of inclusion, not exclusion.

Pregnant women are not a vulnerable population solely by virtue of pregnancy. IRBs should consider if proposed research has the potential to diminish or interfere with this population's ability to make a decision. That is, in its review, the IRB should note that the intent of ''vulnerable'' in Subpart A, section 46.111(a)(3) and (b) of these regulations, when applied to pregnant women, is not that pregnant women have less capacity to make autonomous decisions than men or non-pregnant women, but that sometimes the medical management of pregnancy has the potential to apply coercion to a woman due to her concerns for the health of the fetus. This may be particularly relevant in the case where a researcher views a planned research activity as potentially highly beneficial to a pregnant woman with a life-threatening illness or to a fetus and, therefore, the researcher believes that the potential benefit of the planned research should override the autonomy of a pregnant woman. The 1978 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the *Belmont Report*), and the resulting regulations in 45 CFR 46, stand in direct contrast to that position. *The Belmont Report* shall guide the interpretation of the regulations in section 46.203 so that a pregnant woman's decisionmaking autonomy is always preeminent.

Section 46.204 Research Involving Pregnant Women or Fetuses

The existing § 46.204 entitled ''Ethical Advisory Boards'' calls for the establishment of one or more standing EABs by the Secretary, HHS. These EABs were to have had broad expertise and advise the Secretary with regard to ethical issues raised by research activities covered by Subpart B. This proposed regulation deletes the text of existing § 46.204 (a)–(c) and proposes a provision for convening an ad hoc panel of expert consultants to review proposals for modification or waiver of the regulation which are raised by individual research proposals. (See proposed § 46.207). An EAB has not existed within the Department since 1980, and § 46.204(d), which required EAB review prior to HHS funding of human in vitro fertilization, was nullified June 10, 1993, by the NIH Revitalization Act of 1993, Pub. L. 103–43.

The obligations and requirements in existing §§ 46.206 (General limitations), 46.207 (Activities directed toward pregnant women as subjects) and 46.208 (Activities directed toward fetuses in utero as subjects), are combined into a single section in the proposed rule, § 46.204, for ease of reference.

From the standpoint of risk to mother or fetus, it is irrelevant whether research is ''directed toward'' the woman or directed toward the fetus, because research on either affects both. Thus, if a pregnant woman and her fetus are involved in research, regardless of whether she or her fetus is the object of the research, the protections should be essentially identical. Accordingly, the proposed regulation combines all relevant protections for pregnant women and fetuses into a single section and deletes any reference to the object of the research.

The proposed rule adds specificity to the current requirement for preclinical studies on animals and nonpregnant individuals, by calling for ''scientifically'' appropriate studies, including studies on pregnant animals, that provide data to assess potential risks (proposed § 46.204(a)).

The proposed risk threshold is unchanged. Pregnant women or fetuses may not be involved in research unless the risk to the fetus is not greater than minimal, except when the risk to the fetus is caused solely by research designed to meet the health needs of the mother or the fetus (proposed § 46.204(b)). The existing requirement that any risk be the least possible risk for achieving the objectives of the research is also unchanged in the proposed regulation.

The proposed regulation includes a reminder (proposed § 46.204(f)) that research involving pregnant children is subject to the requirements for research involving children in 45 CFR Part 46, Subpart D, Additional DHHS Protections for Children Involved as Subjects in Research.

The existing prohibition on the involvement of research personnel in decisions regarding the timing, method, or procedures to terminate a pregnancy, and in determinations of viability is unchanged (proposed § 46.204(g)). The phrase ''terminate the pregnancy'' is replaced by ''abort'' in the proposed rule. The existing prohibition on inducements to terminate pregnancy is strengthened by deleting the phrase ''for purposes of the activity'' (i.e., research), thus barring any inducement to abortion regardless of the purpose (proposed § 46.204(h)).

The proposed regulation strengthens the existing requirements for informed consent by requiring that the pregnant woman be informed of the reasonably foreseeable impact on the fetus, irrespective of the focus of the research (proposed § 46.204(d)).

Current regulations require, in most instances, that both parents consent and be legally competent. The Department concurs with recent recommendations of the Presidential Advisory Council on HIV/AIDS and the National Task Force on AIDS Drug Development regarding paternal consent and finds that the fetus is best served by eliminating unnecessary barriers to consent for research that has the possibility of benefitting the fetus. Therefore, the proposed regulation modifies the parental consent requirements by permitting research based on the consent of the mother or her legally authorized representative (proposed § 46.204(e)).

The existing regulation (§§ 46.207(b) and 46.208(b)) permits research involving pregnant women and fetuses only if the mother and father are legally competent and have given their informed consent. The father's consent is not required under certain circumstances: if his identity or whereabouts cannot reasonably be ascertained, if he is not reasonably available, or if the pregnancy resulted from rape. Nor is the father's consent required if the purpose of the research is to meet the health needs of the mother.

When research is directed toward the health needs of the fetus, there is currently no exception to the paternal consent requirement equivalent to the one for the health needs of the mother. Thus, under the existing regulation, there are instances in which research intended to benefit the fetus may not occur because one parent refuses, or because one parent is not legally competent.

The parental consent rules in the existing regulation are based in part on the studies and recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The history of the Commission's consideration of the issue and the resulting regulation is pertinent to the proposed modification. In its Research on the Fetus: Report and Recommendations (May 1975), the Commission proposed that: (1) only the woman's consent be required when the research was directed toward her health needs; and (2) in the other kinds of research, the woman's consent be required and be sufficient if the father does not object (page 73). The final rule published on August 8, 1975 as 45 CFR Part 46, Subpart B, Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization (the existing rule) incorporated the first part of this recommendation, but with respect to research not directed toward the mother's needs it went beyond the recommendation by requiring explicit consent from the father (with the exceptions described above). The rationale was one of practical implementation: the most effective way of determining that the father did not object was to request his consent (40 FR 33526–33527 (1975)).

The Commission looked again at the role of parental consent in its 1976 report, Research Involving Children: Report and Recommendations. It recommended that: (1) the permission [1] of only one parent be required for research involving children that either was not greater than minimal risk, or presented the prospect of direct benefit to the child; and (2) the permission of both parents be required for any other, more problematic, research (pages 12–14). This recommendation was incorporated into 45 CFR Part 46, Subpart D, Additional DHHS Protections for Children Involved as Subjects in Research.

The Commission's recommendations regarding parental consent differ for fetuses and for children despite the similarities when they are subjects of research. The similarities are striking: neither the fetus nor the child (especially an infant) can give consent; the fetus and the child are both vulnerable; both the mother and father have an interest in and legal responsibility for their fetus or their child. Yet the existing requirements for parental consent, based largely on the Commission's recommendations, treat children and fetuses differently. The Commission did not examine or explain the inconsistency. It acknowledged that its report about the fetus was hurried, was its first task, and was done out of sequence (before first examining research in general) (page 61).

In actual experience, one approach to parental consent has presented no problems, the other several problems. Since the regulation for research on children (Subpart D) was issued in 1983, there has been no reported abuse resulting from the policy of requiring only one parent's permission for a child's participation in research that presents no greater than minimal risk or may be of direct benefit to the child or infant. Although both parents have an interest in and responsibility for their child, no parent has been reported to object that research may be conducted with only one parent's permission. Since the regulation governing research on the fetus (Subpart B) was issued in 1975, however, the required consent of both parents for fetal research has posed some difficulties. For example, in the recent trial of the drug zidovudine (AZT) in pregnant women with HIV infection (showing that the drug reduced the percentage of newborns infected with HIV), the requirement to obtain the father's consent was an obstacle to the participation of some women. Some fathers, while ''available'' in some literal sense, did not wish to be involved with the woman or her pregnancy in any way. In some situations, asking for the father's consent introduced the possibility of retaliation against the pregnant woman by the father. The result in some instances was that fetuses who could benefit from participating in research were excluded when the paternal consent required by the existing regulation could not be obtained.

The barriers to participation posed by the requirement that both parents consent, and the experience with consent by one parent under the regulation for research on children, suggest that accepting consent by one parent provides effective protection for the interests of the fetus and enhances the opportunities for the fetus to benefit from research. In light of the physical realities of pregnancy, any research involving or directed toward the fetus necessarily involves the pregnant woman, and her consent must be sought. Absent her consent, the research could not take place even if the father did consent. Thus, if the consent of one parent is to be sufficient, that parent must be the mother.

The Department recognizes the father's likely interest in and responsibility for the fetus and strongly encourages paternal involvement in decision-making with respect to offspring. The father can normally be assumed to have as much interest, feeling, and concern for the future well-being of the fetus as the mother.

The basic requirements for consent to research in Subpart A offer a framework for participation of the father. Consent may be sought only under circumstances that provide sufficient opportunity to consider whether or not to participate (§ 46.116). In considering whether to participate, many women would wish to consult with the father. In other situations, to seek the consent of the father could be detrimental to the mother or could be an obstacle to a potential therapy for a fetus. The pregnant woman is in the best situation to determine whether she should consult with the father.

Thus, the Department proposes to modify the regulation to accept consent from the mother alone as a sufficient basis for participation of the fetus in the limited classes of research permitted under this subpart, i.e., minimal risk research or research designed to meet the health needs of the mother or her fetus.

A similar barrier to participation is created by the requirement that both parents be legally competent before their consent can be accepted for a fetus to participate in research. Under the other subparts of 45 CFR Part 46 (including the provisions governing research on children (§ 46.408(b))) consent from a legally authorized representative is adequate for participation in research. Thus, it is proposed that consent from a legally authorized representative of the mother could be used as a substitute for the mother's consent (proposed § 46.204(e)). This permits participation in research, including research directed towards the health needs of the pregnant woman or her fetus, even though the pregnant woman is a minor but not emancipated under state law, or is legally incompetent for other reasons. The authorized representative could in many instances be the father.

The proposed changes would establish a consent process that has choice about the best interests of the fetus as its principal objective. The rights and responsibilities of parents and families are recognized by requiring appropriate review and parental involvement.

[1] The term ''permission'' as used by the Commission and in Subpart D has the same meaning as ''consent'' for the purposes of this discussion.

Section 46.205 Research Involving Newborns of Uncertain Viability, Nonviable Newborns, and Viable Newborns

It is proposed that the existing § 46.209 be replaced by this section. A number of clarifications are made and the consent requirement is modified to remove barriers to potentially therapeutic research. The proposed title refers to newborns, rather than ''fetuses ex utero,'' and reflects more clearly the three types of situations that may arise after delivery: (a) Viability of the newborn may not be known, (b) the newborn may be known to be nonviable, or (c) the newborn may be known to be viable. The term ''activity'' is changed to ''research'' for consistency with other portions of the subpart and to reflect that the regulation addresses risks associated with research activities in contrast to those associated with therapeutic activities that are part of the accepted standard of care.

a. Proposed § 46.205(a) acknowledges that there is sometimes a period of uncertainty about the viability of a newborn. In accordance with section 498 of the Public Health Service Act, 42 U.S.C. 289g, the proposed section limits research during this period to either research that evaluates activities designed to enhance the probability of survival of that particular newborn to viability or risk free research, the purpose of which is the development of important biomedical knowledge which cannot be obtained by other means. As has been the case under the existing regulations, the application of this condition will permit research activities that, in and of themselves, pose no risk to the newborn, such as observational research using monitors or other devices that are already in place as part of normal therapeutic practice, if the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means.

It is proposed that the consent requirement for research activities on newborns of uncertain viability be changed from the consent of both parents to the consent of either parent, and that the competency requirement for mother and father, in the existing § 46.209(d), be deleted. It is further proposed that if neither parent is able to consent for the reasons given, then the consent of a legally authorized representative of either is sufficient. This less restrictive consent requirement is appropriate for the limited scope of research activities that either must enhance the possibility of survival to viability or pose no risk and be directed toward the development of important biomedical knowledge that cannot be obtained by other means.

The existing regulation, while generally requiring consent from both parents, also recognizes that there may be circumstances when it is not reasonable to require the father's consent; in those circumstances, it allows consent from only one parent, the mother. For research involving the fetus, the mother must clearly be the one to consent. After delivery, however, if consent is to be required from only one parent, HHS proposes that it is appropriate to allow for consent from either the mother or the father. In formulating the new requirement, it is recognized that there may also be circumstances when it is not possible to obtain the mother's consent, (e.g., the mother is under general anesthesia as a result of a surgical delivery). Because of the critical nature of life-saving interventions performed on newborns of uncertain viability, and the limited time available to make decisions regarding participation in potentially beneficial research to enhance the possibility of their survival, the proposed regulation also allows for consent by a legally authorized representative, if needed.

b. With regard to research on nonviable newborns, the proposed regulation is more restrictive. It does not permit a legally authorized representative to consent, and the provisions for IRB waiver of informed consent in Subpart A of 45 CFR Part 46 are not authorized. Research involving nonviable newborns will continue to be strictly limited (i.e., the proposed regulation retains the requirement that the proposed research poses no added risk to the fetus of suffering injury or death and the purpose of the research activity be the ''development of important biomedical knowledge that cannot be obtained by other means,'' and the prohibition against the use of artificial life support or research that would terminate heartbeat or respiration).

In the existing regulation, the consent of both parents is required for research on the nonviable newborn unless, for the reasons given, consent of the father cannot reasonably be obtained then the mother's consent will suffice. In the proposed regulation, the consent of both parents is also required, but if either parent is unable to consent, then the legally effective consent of the other parent will suffice.

The requirement in the existing regulation that both parents be legally competent is replaced by a requirement that at least one parent be competent and provide consent. If neither parent is able to give consent, whether it is because of incompetence or because of some other reason, the research will not be allowed.

c. No substantive changes are proposed to the existing provisions addressing research involving viable newborns. A reference to Subpart D is included.

Section 46.206 Research Involving, After Delivery, the Placenta, the Dead Newborn, or Fetal Material

It is proposed that the existing § 46.210 be replaced by this section. No substantive changes are proposed to the current provisions. The intent of the existing regulation, that *all* placentas after delivery are covered by this section, is clarified.

The Department notes that for cultural reasons, many ascribe special value and significance to the placenta. Further, State, local, or tribal jurisdictions that have laws or regulations concerning research involving the placenta do not necessarily distinguish between the placentas of living or dead fetuses or newborns.

Paragraph (b) of § 46.206 is proposed as a reminder that if, in the course of using the placenta, the dead newborn, or fetal material, a living person (e.g., the mother) is identified in the research, then that living person (e.g., the mother) is a research subject (see definition of human subject at 45 CFR 46.102(f)). In that case, the other subparts of 45 CFR Part 46 are applicable and the researcher is responsible for obtaining any necessary review, assurance, approval, and informed consent.

Section 46.207 Modification or Waiver of Specific Requirements

This proposed section, to replace the existing § 46.211, is parallel to the waiver provisions of Subpart C at § 46.306(a)(2)(C) and (D) and Subpart D at § 46.407. This provision allows the Secretary, HHS, to modify or waive requirements after consultation with appropriate experts and opportunity for public review and comment. In making such a decision, the Secretary must consider whether the risks to the subjects are so outweighed by the sum of the benefits to the subjects and the importance of the knowledge to be gained as to warrant the modification or waiver.

The proposed rule removes the requirement for an EAB, consistent with the NIH Revitalization Act of 1993 (Public Law 103–43).

The following statements are provided for the information of the public.

Executive Order 12866

Executive Order 12866 requires that all regulatory actions reflect consideration of the costs and benefits they generate, and that they meet certain standards, such as avoiding the imposition of unnecessary burdens on the affected public. If a regulatory action is deemed to fall within the scope of the definition of the term ''significant regulatory action'' contained in § 3 (f) of the Order, pre-publication review by the Office of Management and Budget's (OMB's) Office of Information and Regulatory Affairs (OIRA) is necessary. OMB deemed this proposed rule a ''significant regulatory action,'' as defined under Executive order 12866. Therefore, the proposed rule was submitted to OIRA for review prior to its publication in the **Federal Register**.

Regulatory Flexibility Act

This proposed rule primarily affects individual persons. None of the changes proposed will have the effect of imposing costs on universities, other research institutions, or other small entities. Therefore, the Secretary certifies that this rule will not have significant impact on a substantial number of small entities and that preparation of an initial regulatory flexibility analysis is not required.

Paperwork Reduction Act

This proposed rule does not contain any new information collection requirements which are subject to Office of Management and Budget (OMB) approval under the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35).

List of Subjects in 42 CFR Part 46

Health—clinical research, Medical research.

Dated: April 3, 1997.

Harold E. Varmus,

Director, National Institutes of Health.

Approved: September 16, 1997.

Donna E. Shalala,

Secretary.

Editorial Note: This document was received at the Office of The Federal Register May 13, 1998.

For reasons presented in the preamble, it is proposed to amend part 46 of title 45 of the Code of Federal Regulations as set forth below.

PART 46—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 45 CFR part 46 would be revised to read as follows:

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

2. Subpart B of 45 CFR part 46 would be revised to read as follows:

Subpart B—Additional DHHS Protections for Pregnant Women, Human Fetuses, and Newborns Involved as Subjects in Research, and Pertaining to Human In Vitro Fertilization

Sec.

§ 46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, and newborns as subjects, and to all research involving the in vitro fertilization of human ova, conducted or supported by the Department of Health and Human Services. This includes all research conducted in Department facilities by any person and all research conducted in any facility by Department employees.

(b) The exemptions at § 46.101(b) (1) through (6) are applicable to this subpart.

(c) The additions, exceptions, and provisions for waiver as they appear in § 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in § 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

§ 46.202 Definitions.

The definitions in § 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services (DHHS) to whom authority has been delegated.

(b) *Pregnancy* encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(c) *Fetus* means the product of conception during pregnancy until a determination is made after delivery that it is viable.

(d) *Newborn* is a fetus after delivery.

(e) *Nonviable fetus* or *nonviable newborn* means a newborn or fetus after delivery that, although living, is not viable.

(f) *Dead fetus* or *dead newborn* means a newborn or fetus after delivery which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) *Viable fetus* or *viable newborn* means a newborn that is able to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the **Federal Register** guidelines to assist in determining whether a fetus or newborn is viable for purposes of this subpart. If a newborn is viable then it is a child, and subpart D of this part is applicable.

(h) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. (See definition of ''viable fetus'' or ''viable newborn'' at § 46.202 (g)).

(i) *In vitro fertilization* means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

§ 46.203 Duties of IRBs in connection with research involving pregnant women, human fetuses, newborns, and human in vitro fertilization.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§ 46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by activities designed to meet the health needs of the mother or her fetus;

(c) Any risk is the least possible for achieving the objectives of the research.

(d) The woman is fully informed regarding the reasonably foreseeable impact of the research on the fetus (or a resultant child);

(e) The woman's consent or the consent of her legally authorized representative is obtained in accord with the informed consent provisions of subpart A of this part;

(f) For pregnant children, assent and permission are obtained in accord with the provisions of subpart D of this part;

(g) Individuals engaged in the research will have no part in:

(1) Any decisions as to the timing, method, or procedures used to abort a pregnancy, or

(2) Determining the viability of a newborn; and

(h) No inducements, monetary or otherwise, will be offered to abort a pregnancy.

§ 46.205 Research involving newborns of uncertain viability, nonviable newborns, and viable newborns.

(a) *Newborns of uncertain viability.* After delivery and until it has been ascertained whether or not a newborn is viable, a newborn may not be involved as a subject in research covered by this subpart unless both of the conditions in paragraphs (a)(1) and (2) of this section are met:

(1) The purpose of the research is:

(i) To enhance the possibility of survival of the particular newborn to the point of viability, or

(ii) The development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the newborn resulting from the research, and

(2) The legally effective informed consent of the mother or the father of the newborn or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of the mother's or the father's legally authorized representative is obtained in accord with Subpart A of this part.

(b) *Nonviable newborns.* After delivery, a nonviable newborn may not be involved as a subject in research covered by this subpart unless all of the following conditions are met:

(1) Vital functions of the newborn will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the newborn;

(3) There will be no added risk to the fetus of suffering injury or death resulting from the research and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(4) The legally effective informed consents of both the mother and the father of the newborn are obtained in accord with subpart A of this part, except that the waiver and alteration provisions of § 46.116 (c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of the other parent of a nonviable newborn will suffice to meet the informed consent requirement of this paragraph (b)(4). The consent of a legally authorized representative of either or both of the parents of a nonviable newborn will not suffice to meet the requirements of this paragraph (b)(4).

(c) *Viable newborns.* A viable newborn is a child and may be included as a subject in research only to the extent permitted by and in accord with the requirements of Subparts A and D of this part.

§ 46.206 Research involving, after delivery, the placenta, the dead newborn, or fetal material.

(a) Research involving, after delivery, the placenta; the dead newborn; macerated fetal material; or cells, tissue, or organs excised from a dead newborn shall be conducted only in accord with any applicable Federal, State or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living persons can be identified, directly or through identifiers linked to those persons, those persons are research subjects and all pertinent subparts of this part are applicable.

§ 46.207 Modification or waiver of specific requirements.

The Secretary may modify or waive specific requirements of this subpart for specific research projects or classes of research, after consultation with a panel of experts in pertinent disciplines and after opportunity for public review and comment, including a public meeting. In making a decision to modify or waive, the Secretary will consider whether the risks to the subjects are so outweighed by the sum of the benefits to the subjects and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the **Federal Register**.

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