September 4, 2001

Irene Stith-Coleman, Ph.D.
Office for Human Research Protections
200 Independence Avenue, S.W., Room 733-E
Washington, D.C. 20201

Dear Dr. Stith-Coleman:

The National Human Research Protections Advisory Committee (NHRPAC) of the Department of Health and Human Services is grateful for the opportunity to comment on the recently proposed amendment to the human subjects protections regulations, 45 CFR 46 Subpart B. This specific subpart of the regulations is intended to provide additional protections for pregnant women and human fetuses involved in research and also pertains to human in vitro fertilization. The goal of the proposed amendment as described in the summary is to make limited changes in terminology, clarify provisions for parental consent when research is conducted on fetuses, and clarify language concerning research on newborns of uncertain viability. Specifically the amendment proposes to:

> "*-require a father's consent (when the father is readily available) for participating in research that is directed solely at a fetus and that does not affect a mother's health;*
> *-add to the regulations the term 'neonate' to describe an infant that has been delivered but for which a viability determination has not been made; and*
> *-clarify the language that governs decisions regarding conduct of federally-supported research on neonates of uncertain viability*."

NHRPAC believes that the proposed amendment does not fulfill these goals and, in fact, is confusing and unclear in each of these areas. Although we understand and support the purpose of the amendment, NHRPAC harbors concerns about the somewhat artificial division between the interests of the pregnant woman and the fetus that this framework can be construed to represent. This letter is written to convey NHRPAC's specific concerns and to suggest language that might fulfill the intended goals with greater clarity while continuing to protect the common interests of pregnant women and human fetuses involved in research. NHRPAC believes that the regulations need to be substantially revised and would be prepared to assist the Department to accomplish this goal.

"Beneficial research"

NHRPAC is disturbed to note that this proposed amendment reinstates the illogical distinction between therapeutic (beneficial) and nontherapeutic (nonbeneficial) research. This distinction was in the original Subpart B as it was promulgated in 1975 but only because these regulations were issued before the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) completed its conceptual clarifications. No other federal regulations ever used this distinction again. When the earlier proposed revision of Subpart B was developed in 1998, this distinction was carefully removed. Thus, it seemed likely that our regulations would once and for all eliminate this problem. The current proposal would reinstate it.In the current proposal, the correct language may be found in 46.204(b) -- viz., "…interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus…." However, the proposal soon regresses to the language of the original 1975 version – language that the National Commission repudiated explicitly: "If the research holds out the prospect of direct benefit to pregnant woman…." Such language is found in other sections of the present proposal such as 46.204(d) and (e) as well as 46.205(b)(1)(i). We request correction. In each case it must be made clear that it is individual interventions or procedures that 'hold out' (or do not hold out) the prospect of direct benefit to the subject(s).

'Research' invariably consists of multiple interventions or procedures; by definition, some or all of them are must be 'nonbeneficial' or 'nontherapeutic'. In some cases, some component(s) of a research protocol may hold out the prospect of direct benefit to the subjects; this does not justify labeling the entire protocol 'beneficial' and having the entire protocol reviewed by an IRB according to the relatively permissive standards developed for 'beneficial research'.

NHRPAC recommends that the problematic language be replaced with the accurate language of the proposed amendment to Subpart B prepared in 1998 for the Secretary's signature or the language now found in Subpart D. In doing this, please note that this language applies to the standards for IRB approval when more than minimal risk is presented by interventions or procedures that 'hold out' (or do not hold out) the prospect of direct benefit to the subject(s).

Father's consent

NHRPAC concurs with the proposed amendment that requires only the mother's consent for participation in research in which [more than minimal] risk is related to interventions or procedures that hold out the prospect of direct benefit for both the pregnant woman and fetus. [Note that we recommend inserting 'more than minimal' in the preceding to conform with Subpart D as well as the earlier proposed amendment to Subpart B.] NHRPAC, however, is concerned about the proposed language concerning paternal

consent for research in which the risk is related to interventions or procedures that hold out the prospect of direct benefit solely to the fetus. The proposed Section 46.204 (e) reads:

> " If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that *the father's consent need not be obtained if he is unable to consent because* of *unavailability, incompetence, or temporary incapacity"* (italics added).

The proposed wording in italics replaces the following language in the original Subpart B Section 46.208 (b) in effect since the 1970s: "*the father's consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape."* NHRPAC believes that the proposed language does not fulfill the stated goal of requiring the father's consent when he is "readily available" and creates the unreasonable standard of "unavailability" which may require extraordinary efforts on the part of the investigator and the woman in an attempt to find a father who may be estranged or disaffected. In addition, NHRPAC believes that the consent of the father ought not be required in the case of a pregnancy that resulted from rape. Since the goal of these regulations is to protect the interests of pregnant women and human fetuses involved in research we can find no way in which seeking the consent of the father in the case of a pregnancy which resulted from rape fulfills those goals.

NHRPAC proposes the following change to the language of Section 46.204 (e): "*the father's consent need not be obtained if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not readily available, (3) he is incompetent or temporarily incapacitated, or (4)the pregnancy resulted from rape."*

<u>"Neonate"</u>

The term "neonate" is added to the title of Subpart B and inserted into the proposed regulations to clarify language that applies to research involving newborns of uncertain viability, particularly those for whom a viability determination has not yet been made. There are three definitions in the proposed regulations in Section 46.202 which relate to this issue:

> -*"(e) Neonate means a newborn."*
>
> -*"(a) Dead neonate means a neonate that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord."* and
> -*"(i) Viable as it pertains to the neonate, means being able, after delivery, to survive (given the benefits of available medical therapy) to the point of independently maintaining heartbeat and respiration."*

These definitions create unnecessary confusion and as used in the text of the regulations do not fulfill the stated goal of clarifying the status of newborns of uncertain viability. It is important to point out that a large number of newborns have "uncertain viability" by this definition. They require active resuscitation and intensive care for many days, weeks, or months until it can be known with any certainty that they will be able to maintain heartbeat and respiratory effort independent of technological support. Research involving these neonates is regulated in Subpart D of this part. Approved research over the last twenty years, using the standards of Subpart D, has enabled monumental breakthroughs in the treatment of premature neonates resulting in enhanced survival and quality of life for thousands of children. Using the term "neonate" in these regulations will create unnecessary conflict with extant standards in Subpart D and is unnecessary to fulfill the goals of the proposed amendment.

NHRPAC believes that the term "neonate" is unnecessary in Subpart B. We propose that the word "newborn" be used in its common language usage to describe a liveborn infant. The term "stillborn" can be used to describe what is now defined as "dead neonate".

We understand the need to clarify the definition of "viability" and the desire to clarify the language regarding research involving neonates of uncertain viability. To avoid conflicting standards for the same set of infants, the definition of viability could include language related to developmental capacity as it relates to extra-uterine survivability. Viability could be defined as: "*the developmental capacity of a fetus, once delivered, to have a reasonable likelihood of survival for a prolonged period of time given the benefits of available medical therapy.*"

NHRPAC believes that the entire Section 46.205 (Research involving neonates) is unnecessary, redundant, in conflict with extant regulations governing neonates in Subpart D, and will lead to confusion in implementation. Specifically, since a great number of neonates are of "uncertain viability" this section will impact on virtually all of the research presently being conducted that involves neonates.

Proposed Section 46.205 (b), Neonates of uncertain viability, requires that *"(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the neonate resulting from the research."* NHRPAC believes the imposition of a "no risk" standard is inappropriate. Regulation of research that directly involves human subjects should never impose a "no risk" standard since no study directly involving human subjects can meet that standard. We believe that Subpart D describes the standards for research involving all neonates, those of uncertain viability and those of likely viability, and that there is no need for additional clarification in Subpart B.

NHRPAC notes that proposed Section 46.205 (c) is also problematic. This section entitled "Nonviable neonates" states "After delivery, a non viable neonate may not be involved in research…" The words "after delivery" are unnecessary because, by definition, all neonates have already been delivered. The section could be clarified by being titled "Nonviable fetuses." Then the use of the language of "after delivery" makes sense. In addition, the "no risk" standard is invoked in this section. This standard is hard to comprehend in this context. All research directly involving human subjects, even simple observation, has the potential for some level of risk including the risk of discomfort or indignity. While understanding the intent of the proposed language, NHRPAC suggests the use of "minimal risk" as the standard to be invoked for research involving nonviable fetuses after delivery.

NHRPAC believes there are three groups of newborns to which these regulations apply. First are newborns who result from the delivery of a nonviable fetus. The allowable level of risk to which these dying infants ought to be subjected should be described as "minimal" and we agree that vital functions ought not be artificially maintained solely for the purpose of the research. The second group is those newborns who result from the delivery of a fetus of uncertain viability. With parental permission, these infants are generally resuscitated and provided with intensive medical intervention. Regulation of research should be covered under Subpart D of this part. Subpart B should not impose additional, conflicting or confusing standards might preclude important and needed research that might potentially enhance the outcome of these infants. The third group is those newborns who are clearly viable at delivery. Subpart D is the appropriate section of the regulations to cover research involving these infants.

Thank you for this opportunity to comment on the proposal to amend subpart B of the human subjects protection regulations. NHRPAC understands the desire of DHHS to clarify these important regulations without creating conflicting or confusing standards. NHRPAC is ready to assist the Department to create clear and appropriate standards to protect the interests of pregnant women and fetuses involved as the subjects of research. We look forward to working with you on this and other projects in the future.

Sincerely,

Mary Faith Marshall, Ph.D.
Chairman, NHRPAC

cc: Members, NHRPAC Committee
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