DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Secretary's Advisory Committee on
Human Research Protections
Washington DC 20201

NOV - 9 2006

The Honorable Michael O. Leavitt
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Leavitt:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), the following is a list of recommendations relative to the regulatory protections for research involving children, that exist under the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46). The enclosure at Appendix A provides additional discussion of the Committee's recommendations. These recommendations represent the fourth in a series of recommendations from SACHRP; two letters containing SACHRP recommendations on research involving children and research involving children and prisoners, respectively, were presented to Secretary Tommy G. Thompson, and a single previous letter on the Health Insurance Portability and Accountability Act was presented to you. This report also contains a brief description of on-going SACHRP work projects and those in the immediate planning stage.

Recommendations Relative to Research Involving Children

HHS regulations at 45 CFR part 46 include subpart D—Additional Protections for Children Involved as Subjects in Research. On July 23, 2003, SACHRP recommended the creation of the Subcommittee on Research Involving Children to review HHS regulations that govern research in children. SACHRP's charge to the Subcommittee on Research Involving Children was to provide recommendations for consideration by SACHRP on interpretations of the requirements of subpart D in order to help ensure that children who participate in research are neither under protected, nor overprotected. To that end, the following recommendations were approved by SACHRP over a period of three meetings (November 1, 2005, March 14, 2006 and August 1, 2006).

Recommendations related to 45 CFR 46.402 and Assent:

1. When an institutional review board (IRB) determines that the subject population is capable of assent, it should ensure that the protocol describes how assent procedures will meet the requirements of 45 CFR 46.402(b).

2. When the child's views may not ultimately be determinative, the investigator or parent/guardian should solicit the child's perspective without promising to follow his or her wishes. Investigators should only invite a child's decision about study participation when they intend to honor that decision. The practice of asking a child for a decision, then disregarding that decision if it conflicts with what the investigator or parents/guardians wish, is unacceptable.

3. Relative to documentation discretion for assent:
   a. When the IRB determines that assent is required, it should also determine whether and how it should be documented. Often, IRBs require children's signatures because they think they have to; however, in many instances these signatures are developmentally inappropriate and therefore meaningless.
   b. IRBs should use the discretion permitted in federal regulations for different documentation procedures (e.g., child's signature or documentation in investigator notes that assent was granted verbally) taking into account relevant state and local law.
   c. To make such determinations, the IRBs should draw upon knowledge of the developmental level of the subject population and how different documentation procedures will best serve the goals of assent for particular research protocols and populations.

Recommendations related to 45 CFR 46.408:

4. In considering parent/guardian waiver under 45 CFR 408 (c), IRBs should consider justifications for "not a reasonable requirement" beyond the example of "neglected or abused children" given within the regulation and include instances in which parental/guardian permission would jeopardize subject welfare or fail to provide additional subject protection.

5. Assuming that an appropriate mechanism for protecting the children is provided, the IRB may waive parental/guardian permission under 45 CFR 46.408(c) by applying the following three criteria:
   a. The investigator has provided a reasonable argument that informing parents/guardians may result in harm to the child, or
   b. The investigator has provided a reasonable argument that parental/guardian permission may not be in the child's best interest

because of conflicts in parental/guardian role as it relates to the research, or

c. The research involves adolescents and:
   i. it is important to population health
   ii. subjects have consent capacity
   iii. participation is voluntary, and
   iv. procedures are commensurate with State law.

6. SACHRP reaffirms the following:
   a. Passive consent (in which parents/guardians are sent forms describing the research and asked to respond only if they do not want their child to participate) is not an approvable mechanism for satisfying the parent/guardian requirement under 45 CFR 46.116 or 45 CFR 46.408.
   b. When parental/guardian permission meets the requirement for waiver under 45 CFR 46.116(d) and 45 CFR 46.408(c), an IRB should consider whether parental/guardian notification and right of refusal is appropriate.

Recommendations related to 45 CFR 46.409:

7. A ward should be defined as a child who is placed in the legal custody of the State or other agency, institution, or entity consistent with Federal, State or local law.

8. In approving the advocate for a specific protocol the IRB should take into consideration whether the advocate:
   a. has appropriate education and training, in order to take into consideration the nature of the research and the expectations of the advocacy role.
   b. has the ability to make a determination regarding each ward's participation in research that is independent and free of any contractual requirements or financial gains or other conflicts that depend upon the number or types of subjects required for recruitment, enrollment, and ongoing participation.
   c. has independence from the research for the entire period of the advocacy role.
   d. can act in the interests of protecting the safety and welfare of the ward by assuming an intermediary role between the child, investigator, guardians, and the IRB. This may include, as appropriate, meeting with wards, biological parents, foster parents, and researchers as deemed necessary, having the time and ability to become familiar with the child's health, behavior, social and physical environment, and notifying the investigator and IRB of any concerns about the child's participation in research.

9. In reviewing research that falls within category §46.404 and §46.405 and includes or will potentially include wards, the IRBs should consider the inclusion of additional safeguards to protect the rights and welfare of these subjects in accordance with the provisions of subpart A section §46.111(b). This may include actions such as the appointment of an advocate or any other safeguard deemed necessary to protect the safety and welfare of the ward taking into consideration the nature of the research.

10. Two parts:
    a. If an individual child/adolescent becomes a ward while participating in research that falls under category §46.406 or §46.407, the requirements of section §46.409 must be implemented in order for the ward to continue participation.
    b. If an individual child/adolescent becomes a ward while participating in research that falls under category §46.404 or §46.405, the IRB may consider requiring additional safeguards to protect the safety and welfare of the ward as specified in subpart A section §46.111(b).

11. If an IRB reviews a protocol for which the investigator may reasonably anticipate that some subjects may become wards during the course of the research and the research falls into category §46.406 or §46.407, the IRB may consider reviewing and approving the protocol in accordance with §46.409. This would include identifying a potential advocate in the event one were needed.

12. Institutions and their IRBs, in collaboration with other operating units (e.g., office of legal counsel or legal counsel), should provide guidance and education to investigators and the associated research personnel regarding:
    a. who is defined as a ward of the State in accordance with state regulation
    b. specific State regulations and requirements if they exist.
    c. the need to notify the IRB when a ward is initially considered for research in category §46.406 and §46.407 research.
    d. the need to notify the IRB when a child/adolescent already participating in research categorized as §46.406 and §46.407 becomes a ward of the state.

Recommendations related to Subpart A:

13. To determine that a parent/guardian waiver "will not adversely affect the rights and welfare of the subjects" under §46.116(d) the IRB should consider:
    a. Federal, State or local laws pertaining to parental/guardian permission
    b. alternative mechanisms to protect the rights and welfare of child participants, and

c. when appropriate, whether the investigator has adequately considered the norms of the community from which the subjects will be drawn.

14. To determine whether parental/guardian permission can be waived under §46.116(d)(3) because the research cannot be "practicably carried out", the IRB should require the investigators to provide :
    a. a reasonable argument that scientific validity would be compromised if parental/guardian permission was required
    b. a reasonable argument that alternative methods to obtain parental/guardian permission are not feasible, and
    c. a rationale for why the research could not be conducted with a population for whom parental/guardian permission could be practicably carried out.

15. Parental/guardian permission should never be waived under §46.116(d)(3) for convenience nor waived solely for reasons of cost or speed or other expedient measures if doing so weakens protection of subjects' rights and welfare.

16. In evaluating whether assent should be waived under §46.116(d) for research involving no greater than minimal risk, the IRB may consider the following:
    a. research involves no greater than minimal risk
    b. requirements for parental/guardian permission have been met,
    c. waiver of assent does not violate Federal, State, or local law,
    d. the study could not be practicably conducted (e.g. scientific validity would be compromised without the waiver), and
    e. the investigator has presented evidence that alternative methods to obtain assent are not feasible.

    Note: Even when child assent is waived, the IRB should consider explaining the research to the child and the right of refusal.

SACHRP On-Going Work Projects or Projects in the Planning Stage

1. SACHRP continues to address problems and issues associated with the application of the Federal Policy for the Protection of Human Subjects (codified by HHS at 45 CFR part 46, subpart A and known as the Common Rule), particularly with respect to behavioral and social science research. Deliberative efforts and recommendations from the Subpart A Subcommittee, formed to consider these issues, were presented at the November 1-2, 2006 meeting held in Arlington, VA.
2. SACHRP and OHRP will continue to work closely on the issue of alternative IRB review mechanisms for human subjects research. Plans are in place for a national conference on alternatives to local IRBs and related issues, to be held on November 20-21, 2006 in Washington D.C.

3. SACHRP will continue to be briefed on the progress of the Federal Adverse Event Task Force.
4. SACHRP hosted a panel, consisting of representatives from multiple patient advocacy organizations, to address issues related to subjects who are decisionally impaired at its November 1-2, 2006 meeting in Arlington, VA.
5. SACHRP and OHRP are actively working on the development of a new subcommittee to evaluate the unique concerns and vulnerabilities of decisionally-impaired subjects participating in research.
6. SACHRP and OHRP will continue to work closely together to address the concerns and recommendations relative to research involving prisoners presented in the Institute of Medicine's report entitled "Ethical Considerations for Research Involving Prisoners."

Mr. Secretary, I trust you will find this report acceptable. Your committee members and SACHRP subcommittee members have worked hard in their pursuit of the charges contained in the charter. SACHRP has also worked closely with Dr. Bernard Schwetz and the rest of the OHRP staff and has benefitted greatly from their expertise and leadership. We look forward to continuing our work and providing you with recommendations that will enhance human subject protections and advance science for the benefit of all Americans.

Sincerely,

Catherine Slatinshek for

Ernest D. Prentice, Ph.D.
Chair Secretary's Advisory Committee
on Human Research Protections

Enclosure

cc: Bernard A. Schwetz, D.V.M., Ph.D., Executive Secretary, SACHRP
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