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# *SACHRP Recommendations for Review of Children's Research Requiring DHHS Secretary's Approval*

Federal regulations for research involving human subjects include special protections for children under 45 CFR 46 Subpart D.[1] Unlike other sections outlining protections for the general population and other vulnerable groups, Subpart D delineates three risk-benefit classifications for research that can be independently approved by a local Institutional Review Board (IRB) and a fourth classification that requires Department of Health and Human Services (DHHS) review. IRBs can independently approve research with children

> 1) that does not involve greater than minimal risk if the IRB finds that adequate provisions have been made for parental permission and child assent (46.404).
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> 2) that presents greater than minimal risk but offers a potential for direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, if the IRB determines (a) the risk is justified by the anticipated benefit to the subject; (b) the risk benefit assessment is at least as favorable as available alternative approaches; and (c) adequate provisions are made for soliciting parental/guardian permission and child assent (46.405).
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> 3) that presents greater than minimal risk but offers no potential for direct benefit for the individual subject if the IRB determines: (a) the risk to subjects is a minor increase over minimal risk; (b) the intervention and procedures present subjects with experiences that are reasonably commensurate with those inherent in their actual or expected situations; (c) the research is likely to yield generalizable knowledge of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) adequate provisions are made for soliciting parental/guardian permission and child assent.

If an IRB determines that the proposed research does not meet one of the requirements described in the sections above, and it presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, an IRB may submit the protocol to DHHS's Office for Human Research Protections (OHRP) for determination whether the research can go forward. The 46.407 review process involves consultation with experts and public comment on the proposed research.

In 2003 the Secretary's Advisory Committee on Human Research Protections (SACHRP) undertook a review of the process for conducting a 46.407 review of pediatric research proposals. SACHRP developed recommendations for this review process and forwarded them to the DHHS Secretary; in late 2004 the Secretary approved the recommendations for implementation by OHRP.

## SACHRP Endorsement of the 46.407 Process and Procedural Goals

SACHRP endorsed the 46.407 process for the following reasons: 1) a national perspective that includes scientific experts, bioethicists, and the public is required for research that an IRB believes is worthy but that does not satisfy the criteria for approval under 46.404, 46.405, and 46.406; 2) the 46.407 process provides a critical forum for protocols in which the risk level requires special scrutiny or no clear national consensus exists on the ethical matters under consideration; and 3) adequate transparency in the 46.407 process provides the public and IRB community with a body of case examples that can inform future deliberations.

Although research reviewed to date under the 46.407 review process represents a very small minority of pediatric studies conducted under the jurisdiction of DHHS, SACHRP members considered it important to have a well-developed 46.407 review process based upon the following factors:

- The expectation that research involving children not

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otherwise approvable will increase in light of the Children's Health Act directing the DHHS Secretary to require all research involving children (including clinical investigations involving products regulated by the Food and Drug Administration [FDA]) to be in compliance with subpart D (Public Law 106-310, October 14, 2000) and the Best Pharmaceuticals for Children Act re-authorizing pediatric exclusivity incentives for drug products (January 4, 2002).

• Institutions that have submitted protocols and experts who have provided consultation for individual 46.407 reviews have voiced concern about the process in terms of clarity of IRB responsibilities, length of time from application to Secretary's decision, public and expert input, transparency, and OHRP/FDA harmonization.[2]

In enhancing the 46.407 review process, SACHRP sought to recommend modifications that would help ensure that 1) research essential to the welfare of children is not delayed, 2) stakeholders in the 46.407 review process (the IRB community, the prospective subject population and their families, investigators, funders, and the public) are fully informed in a timely manner about studies under 46.407 review, 3) the Secretary will have available the perspectives of the public and a range of expert opinion, and 4) steps and responsibilities of the process are clear to all stakeholders to ensure consistent, informed, and fair protocol evaluations.

In the remainder of this article we summarize SACHRP recommendations that have immediate implications for local IRB review of protocols deemed to be eligible for the 46.407 review process. Transcripts of SACHRP meetings and detailed summaries of these recommendations can be obtained from OHRP's website.[5]

## IRB Responsibilities and the OHRP 46.407 Screening Process

IRBs may forward to DHHS only those protocols funded by DHHS or under the jurisdiction of the FDA that are not approvable under 45 CFR 46.404-406 or 21 CFR 50.51-53.[3] To fulfill this responsibility, SACHRP recommended that IRBs must provide separate justification and document why the protocol fails to meet each of the 46.404-406 classifications and a rationale for why the research is ethically valid and possesses sufficient scientific and societal promise to warrant consideration from a wider perspective. When OHRP receives the request for a 46.407 review it will screen the application and materials and then either accept the request for a review or send it back to the IRB with feedback that insufficient detail or materials were provided or that the protocol may fall under a 46.404-406 or 21 CFR 50.51-53 classification.

## Model for Obtaining Expert Consultation and Public Input

SACHRP recommended the following panel model for protocols accepted for 46.407 review:

• After it has determined that a 46.407 review is appropriate OHRP will select a panel with at least one public member representing family or child population's interests and consultants with expertise in the science and ethics relevant to the specific protocol.

• Prior to the expert panel meeting, a notice will be posted in the Federal Registrar to permit public review of and comment on documents associated with the study.

• The panel will meet in person to review both the application materials and the written public comments. The meeting will be open for the public to attend and provide additional comment.

• The panel members will discuss their views, but a panel consensus document will not be created. Each consultant will write an independent recommendation.[4]

• The consultants' recommendations will be posted on the OHRP website.

• OHRP will develop its own recommendation based on the materials, panel discussions, and public and expert opinions and forward its recommendation to the Secretary for consideration.

• OHRP will communicate to the IRB the Secretary's decision, and at the Secretary's discretion post the decision on the OHRP website.

• As described in regulations the Secretary may approve the protocol as is, approve with stipulations, or disapprove.

• OHRP will provide advice and assistance to the institution on any modifications that may need to be implemented before the research can begin.

• Final approval of the modifications rests with OHRP.

## SACHRP Recommendations for 46. 407 Review of Multi-Site Research Protocols

SACHRP considered the unique challenges of conducting ethically responsible 45 CFR 46.407 procedures for multiple site studies. Under the National Institutes of Health (NIH) streamlined grant review process, investi-

gators submit proposals to their local IRBs only after scientific peer review and sponsor commitment to funding. Consequently, the timing of participant enrollment will vary across sites. In addition, there is no guarantee that IRBs at the different sites will evaluate the protocol in the same way. This raises the likelihood that for some studies an IRB at one site may conclude that a protocol requires a 46.407 review when IRBs at other sites approved the protocol under 46.404, 46.405, or 46.406. Finally, some sites with IRB approval may have already begun subject enrollment. To address these complicated scenarios SACHRP recommended that:

- OHRP initiate the screening process described above any time a local IRB associated with a multi-site study requests a 46.407 review regardless of whether other centers arrived at a different risk/benefit classification.
- OHRP notify the funding agency and the Principal Investigator of the IRB's application for a 46.407 review, and when appropriate seek information from other participating site IRBs regarding their Subpart D classification of the protocol.
- OHRP provide feedback to the IRB and determine whether a 46.407 review should be commenced.
- OHRP and the local IRB may use the following criteria to determine whether enrollments should be suspended or terminated pending a 46.407 review: 1) a study approved under 46.406 by the local IRB may pose more than a minor increment over minimal risk, or 2) a study approved under 46.405 may not offer the prospect of direct benefit.
- Participating families should be informed if enrollments are suspended or terminated.
- Information about the 46.407 review should be provided to families if enrollments are not suspended or terminated pending a 46.407 review if it is reasonable to assume that knowledge about such a review being conducted would raise legitimate family concerns about participation in light of a recalculation of risk and prospective benefits.
- At the conclusion of the 46.407 review process the IRB should seek re-consent from families currently enrolled in the study if the Secretary has ruled that 1) the risk-benefit calculus has significantly changed from that described in the original consent protocol, or 2) the study should be terminated, but previously enrolled participants are permitted to continue in the study.
- Families who have completed participation in the study prior to the Secretary's ruling should be notified about the ruling if the 46.407 review produced new information pertinent to the continued welfare of the child.

## Monitoring

SACHRP asked that as these new 46.407 procedures are implemented, OHRP and SACHRP continually evaluate the process to identify aspects that are successful and those that can be improved further.

### Disclaimer

The authors are Co-Chairs of the SACHRP Subcommittee on Pediatric Research. The summary of SACHRP recommendations highlighted in this article is the sole responsibility of the authors and does not necessarily represent how they would be summarized by other SACHRP members.

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### References

1. 45 CFR 46 Subpart D. Additional DHHS Protections for Children Involved as Subjects in Research.
2. Nelson RM, Prentice ED, Hammerschmidt DE. The process of federal panel review of research protocols involving children. *Medical Research Law & Policy Report* 2002;1:613-615.
3. FDA regulations 21 CFR 50.51-54 for the protection of children parallel 46.404-407 classifications; see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.
4. Under federal statute, non-Federal Advisory Committees are not permitted to submit a consensus document. Protocols jointly reviewed by OHRP and FDA may issue a consensus report if reviewed by the FDA Federal Advisory Committee.
5. Available at http://www.hhs.gov/ohrp/sachrp/index.html.