DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

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

JUL - 8 2004

The Honorable Tommy G. Thompson
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Thompson:

In accordance with the provisions of the charter of the Secretary's Advisory Committee on Human Research Protections (SACHRP), the following is a list of recommendations classified by topic for your consideration. These recommendations represent the first in a series which will be presented to you as the committee continues to pursue its responsibilities as specified in the charter with particular emphasis on research involving vulnerable subject populations. This report also contains a brief description of on-going SACHRP work projects and those in the immediate planning stage.

Research Involving Children

Department of Health and Human Services (HHS) regulations at 45 CFR part 46 include subpart D – Additional Protections for Children Involved as Subjects in Research. SACHRP's initial efforts relative to research involving children have been directed towards examination of the review process at the level of the HHS Secretary provided for under HHS regulations at 45 CFR 46.407 (the 407 process). The 407 process is required when an Institutional Review Board (IRB) determines that an HHS - conducted or supported study involving children does not meet the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406, but does believe that the research is important to the health or welfare of children. SACHRP views the 407 process as an important safeguard that provides a national perspective to the ethical evaluation and approvability of research involving children. The following recommendations are designed to enhance the validity, clarity, efficiency, consistency, and transparency of the 407 process, as well as the harmonization of any 407 process conducted jointly by the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA):

Recommendation I: OHRP should continue to screen requests from IRBs for review under the 407 process and ensure the following:

- Clear guidance is provided to IRBs concerning the submission requirements for a request for review under the 407 process.
- The algorithm for analysis under the 407 process (Appendix A) should be distributed by OHRP to IRBs as guidance.
- OHRP should promptly screen any request for review under the 407 process and either return it with guidance to the referring IRB for reconsideration under HHS regulations at 45 CFR 46.404, 405, 406, or forward it to a panel of expert consultants for further review in accordance with HHS regulations at 45 CFR 46.407(b).

Recommendation II: OHRP should adopt a non-Federal Advisory Committee (FAC), publicly open-panel model for the expert panel consultation required under the 407 process that includes the elements specified in Appendix B.

Recommendation III: Each panel of expert consultants convened under the 407 process should include at least one public member who meets one or more of the following criteria as appropriate:

- The public member is identified as an effective advocate for the interests of children who would likely become subjects of the research and is self-identified with those interests.
- In the case of children with a specific, defined disorder or condition, a family member or guardian of such a child should be appointed as a public member on the panel of expert consultants.
- If there is no such family member or guardian to voice the interests of children, one public member who is identified as an effective advocate for the interests of children should be appointed to the panel of expert consultants.

Recommendation IV: Any 407 process conducted jointly by OHRP and FDA should strive for harmonization in accordance with the following principles:

- The goals of transparency, public and expert input, timeliness, clarity, and consistency endorsed by SACHRP for adoption by OHRP must be at the forefront for any joint 407 process.
- Harmonization should be a priority where and whenever possible.
- As the FDA process is developing, OHRP should have decisional flexibility to select procedures to best meet a harmonized process goal.

Recommendation V: OHRP should follow the procedures specified in Appendix C for any request for review under the 407 process which involves multi-site research in order to ensure adequate and consistent protection of human subjects across study sites.

Recommendation VI: The 407 process should be monitored in accordance with the following:

- OHRP should provide a yearly report to SACHRP on 407 process activity related to transparency; timeliness; expert opinion; public opinion; clarity, consistency, and consensus; and OHRP/FDA harmonization.
- During the year, OHRP should keep SACHRP informed about the number of protocols received for review under the 407 process and the number of reviews in progress.
- A SACHRP designated subcommittee should work with OHRP to identify aspects of the 407 process that are successful and those that can be improved.
- The designated Subcommittee should issue an annual report and recommendations (if necessary) to SACHRP on the monitoring.

Accreditation of Human Research Protection Programs

Because the two current human research protection program accrediting organizations grew out of publicity surrounding deficiencies uncovered during a series of high profile research shutdowns by OHRP and FDA, SACHRP decided to examine accreditation of Human Research Protection Programs (HRPP's). After considerable study, SACHRP supports the concept of accreditation of HRPPs. Accreditation promises to be a useful mechanism for all organizations involved in human research that, like education and certification for individuals, can lead to self improvement of systems and outcomes. However, since accreditation of HRPPs is relatively new, limited existing data does not allow valid conclusions to be drawn at this time concerning the efficiency of HRPP accreditation as a guarantor of quality research and subject safety. Therefore, the following SACHRP recommendations are based upon the perceived promise and current status of HRPP accreditation:

Recommendation I: It is premature for OHRP, FDA, or other government agencies to offer incentives to research institutions to seek HRPP accreditation. Natural market pressures should push institutions toward seeking accreditation, particularly if research sponsors gravitate to placement of research in those institutions that have achieved accreditation.

Recommendation II: Building on the Centers for Disease Control and Prevention grant awarded to the Association for the Accreditation of Human Research Protection Programs (AAHRPP), there should, in the future, be a systematic evaluation of HRPP accreditation as an assurance of quality research and human subject protections. There also may be value in evaluating the process and procedures used by accrediting bodies in accredited institutions. In addition, current practices used by regulatory agencies to

collect data on IRBs and institutions could be further developed to measure the impact accreditation has on accredited institutions. SACHRP intends to keep abreast of the status nationally of HRPP accreditation and may, at the appropriate time, address the timing of an evaluation and the approach which should be used.

Recommendation III: The government should have no role in endorsing one accrediting organization over another. However, any HRPP accrediting body should have a strong self-assessment for institutions undergoing the accreditation process.

Recommendation IV: After the assessment of the impact of accreditation occurs (assuming a positive outcome) appropriate government agencies should develop, if warranted, a list of incentives for research institutions that seek accreditation.

Recommendation V: A conference should be organized under the purview of HHS with involvement of OHRP, FDA, and others. This conference should include all of the major stakeholders and be designed to offer an opportunity to examine a wide range of self-regulatory initiatives that have been undertaken by responsible parties over the last four years, of which certification of IRB professionals is the most structured and furthest along.

Adverse Event Reporting

Many research institutions and independent IRBs are attempting to cope with an overwhelming workload problem which is associated with IRB review of an extremely large number of IND safety reports (external AERs) which are generated during multi-center IND trials. Some institutions are receiving in excess of 12,000 IND safety reports per year. These reports seldom contain adequate information, and IRBs are not constituted to act as Data Safety Monitoring Boards. The problem continues to escalate as the amount of clinical research increases and fear of litigation grows. The net effect is to consume already strained IRB resources.

Recommendation: OHRP and FDA should promptly issue clear and consistent joint guidance on IRB review of both internal and external AERs which will best serve to protect human subjects and effectively reduce regulatory burden.

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

1. SACHRP is in the process of evaluating the adequacy of HHS regulations at 45 CFR part 46, subpart C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) and will continue to develop recommendations on the interpretation and application of subpart D of 45 CFR part 46.

2. SACHRP is continuing its examination of the HIPAA Privacy Rule and its impact on clinical research and IRBs. Recommendations will be forthcoming shortly.

3. SACHRP will begin shortly to address problems and issues associated with application of the Federal Policy for the Protection of Human Subjects (codified by HHS at 45 CFR part 46, subpart A) to behavioral and social science research.

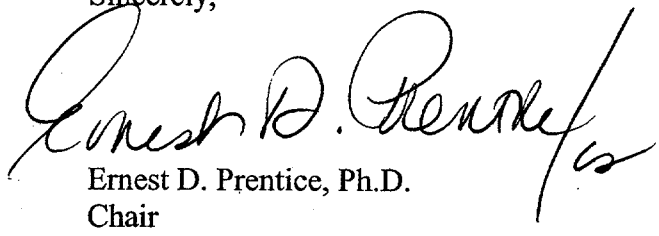
4. SACHRP will begin shortly its review of 45 CFR part 46, subpart B.

5. SACHRP has discussed international research and deferred further action.

6. SACHRP has discussed litigation and its impact on research and IRBs. Further action was deferred. A brief report will be sent to the Institute of Medicine.

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 worked closely with Dr. Bernard Schwetz and has benefitted greatly from his leadership and the expertise of OHRP staff. We look forward to continuing our work and providing you with recommendations which will enhance human subject protection and advance science for the benefit of all Americans.

Sincerely,



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

Enclosures

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