July 28, 2005 SACHRP Chair Letter to HHS Secretary Regarding Recommendations

July 28, 2005
The Honorable Michael O. Leavitt
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Recommendation Letter
Dear Secretary Leavitt:

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, approved by SACHRP at their April 18, 2005 meeting. These recommendations represent the third in a series of recommendations from SACHRP; two previous letters containing SACHRP recommendations were presented to Secretary Tommy G. Thompson. Additional correspondence 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 will outline the committee's interpretation and conclusions on issues associated with the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR part 46, with appendices that provide appropriate rationale for these conclusions. This report also contains a brief description of on-going SACHRP work projects and those in the immediate planning stage.

Research Involving Prisoners

In 2003, the Subpart C Subcommittee was charged by SACHRP with reviewing the text, interpretations and practical implementation of problems associated with compliance with subpart C of 45 CFR part 46 (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). The Subcommittee formulated a number of recommendations which were shared in detail with SACHRP. The following recommendations were approved by SACHRP on April 18, 2005, and are detailed in the Subcommittee's final report (see Appendix A).

Amendment of Subpart C

Subpart C should be rewritten to reflect changes that have occurred in the criminal justice system and research community since the regulations were originally promulgated in 1978. These revisions should also consider the increasing number of mentally ill persons in prisons and jails, the disproportionate number of persons of color, and the increased request by prisoners that they be included in, and not excluded from, participation in research.

SACHRP's recommendations have been sent to the newly formed Institute of Medicine (IOM) Committee on the Ethical Considerations for Revisions to HHS Regulations on Protection of Prisoners Involved in Research, at the request of the Office for Human Research Protections (OHRP). SACHRP suggests that the IOM committee further examine the possibility and wisdom of establishing a wider jurisdiction for the protection of prisoners in research, as well as the role standard of care plays in the ethical review of prisoner research. A summary of recommendations follow.

Summary of 45 CFR 46 Subpart C Recommendations:

1. **The Definition of a Prisoner under Subpart C:**
   The interpretation of the term prisoner, as defined by HHS regulations at 45 CFR 46.303(c), should be kept as it is, narrowly defined by the words of the regulations. At the same time, OHRP should consider some additional circumstances in which liberty is so restricted that informed consent cannot be said to be voluntary (e.g., community correctional settings and halfway houses, probation and parole), and in which those in restricted custody would not be considered "prisoners," but do deserve heightened protections. SACHRP recommends that for all subjects for whom there is a "nexus" between their conditions of restricted liberty and the decisions of the civil or criminal justice system, research involving those subjects should be reviewed consistent with the protections under 45, CFR part 46, subpart A (Basic HHS Policy for the

Protection of Human Research Subjects), particularly including protections under 45 CFR 46.111(b) for subjects "vulnerable to coercion or undue influence."

2. **Research Protections for the "Subsequently Incarcerated":**
   OHRP guidance on the issue of the "subsequently incarcerated" should be changed, so that when any research subject is subsequently incarcerated, and the study has not been reviewed under subpart C, subpart A protections under section 46.111(b) should be deemed to apply, and there must be a focused inquiry by the researcher(s) and the institutional review board (IRB) regarding the risks and benefits to that particular subject of continuing in the protocol as a "prisoner."

3. **Identification of the Prisoner Representative:**
   OHRP guidance should be provided to assist IRBs searching for a prisoner representative and to suggest the qualifications of persons who may meet the requirements. The primary goals in selecting a prisoner representative should be:

   1. Adequate representation of the rights and interests of prisoners;
   2. Particular knowledge of correctional settings, including awareness of local conditions in which the study will be conducted; and
   3. Ability to express views independent from the prison administration.

4. **Prisoner Representative on IRBs in Multi-Site Studies:**
   OHRP guidance should state that though formally under subpart C, one IRB with one prisoner representative is sufficient for multi-site study review, the IRB of appropriate jurisdiction should be responsible for determining the specific conditions in the local prison or jail that are pertinent to subject protection before approving the protocol for the local site.

5. **Definition of "Minimal Risk" under Subpart C:**
   The existence of greater situational risk for prisoners does not justify a greater tolerance for research risk in the deliberations and judgments of the IRB. Therefore, risk standards for prisoners should be referenced to healthy persons in safe environments, and should not reference healthy persons in a prison or correctional environment.

6. **Expedited Review:**
   SACHRP recommends that in cases in which expedited review is used for protocols involving prisoners as subjects, it would be preferred that a prisoner representative would be one of the reviewers.

7. **Control Group vs. Placebo:**
   OHRP guidance should be changed to be more in accord with standard views of the research community, under which standard of care would be considered to be an arm of a trial providing benefit. In addition, guidance should specify that a protocol with a placebo arm in a study for which there is standard treatment for the condition, would be considered an arm not "benefitting from the research," thus requiring an expert panel consultation.

8. **Interpretation of Follow-Up Requirements:**
   Follow-up examination and care should be interpreted to include examination or care that is necessary after the end of a study or after a subject can no longer participate in a study due to release.

Research Involving Children

HHS regulations at 45 CFR part 46 include subpart DCAdditional 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 is 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 on April 18, 2005.

Recommendations related to 45 CFR 46.404:

1. The definition of "minimal risk" at 45 CFR 46.102(i) when applied to subpart D should be interpreted as those risks encountered during daily life by normal, average, healthy children living in safe environments or during the performance of routine physical or psychological examinations or tests.
2. The evaluation of minimal risk under subpart D should be indexed to risks in daily life and routine medical or psychological examinations experienced by children the same age and developmental status as the subject population.
3. The uniform, age-indexed definition of minimal risk should represent the upper not lower limits of risk to which children can be exposed under 46.404.
4. Research procedures involving children can be approved as "minimal risk" only if the probability and magnitude of harm are equivalent to or less than the risks of daily life or routine examinations with respect to (1) duration, (2) cumulative characteristics, and (3) reversibility of harm.
5. A "routine physical or medical examination" has no precise, universally accepted definition but what is sometimes called a well-child visit offers one reasonable basis for comparisons to both, routine medical and routine psychological, examinations or tests.
6. Index routine psychological tests to standardized screening or assessment measures such as the following: child and adolescent intelligence tests, infant mental and motor scales, educational tests, reading and math ability tests, neurological or motor disorder screening, social development assessment, family and peer relationship assessments, emotional regulation scales, and scales to detect feelings of sadness or hopelessness.
7. Research which is conducted under subpart D outside of the United States should utilize the same uniform standard of minimal risk which is applied in the United States.

Recommendations related to 45 CFR 46.405:

1. When research presents the prospect of direct benefit for the subject the ceiling on risk is determined by whether it is proportional to the probability and magnitude of benefit.
2. As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be independently approved by an IRB if the anticipated benefits are not at least as favorable to the subjects as available alternative approaches.
3. The evidentiary basis for the risk-benefit decision should be scientifically sound to justify undertaking whatever risk is involved.
4. Any benefit of monitoring listed in a research protocol approved under HHS regulations at 45 CFR 46.405 must be an objective of the study, and for approval under 46 CFR 46.405, the monitoring procedure must have the intended, not incidental, potential benefit of influencing the individual child's management of the disease. Each research procedure in a treatment study must be evaluated independently in terms of potential benefits and risk to the subject (i.e. component analysis). Different procedures in a single trial may be approved or disapproved under different subpart D standards.
5. The responsibility to demonstrate to the IRB which procedures do or do not have the prospect for direct benefit is the responsibility of the investigator. If procedures without the prospect of direct benefit are included in a treatment trial, investigators and IRBs should consider an opt-out provision for those procedures. However, if the research cannot be reasonably conducted without procedures with no clinical relevance for the child's treatment, and the procedures represent no more than a minor increase over minimal risk, the informed consent must clearly explain the nature and rationale for such procedures. To avoid family exploitation, IRBs should require strong evidence that the study cannot be conducted without each of the non-beneficial procedures.

Recommendations related to 45 CFR 46.406:

1. Criteria for "minor increase over minimal risk" should include the following (a) the procedure does not meet minimal risk criteria, and (b) the investigator has presented sufficient evidence about the procedures, population, and the qualifications of research personnel to assure the IRB that:
    i. The increase in the probability and magnitude of harm is only slightly more than minimal risk.

ii. Any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm (restricted to time of procedure or short post-experimental period).
iii. There is no or an extremely small probability that participants will experience as severe the potential pain, discomfort, stress, or harm associated with the procedure.

2. The term condition should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health and well being or to increase their risk of developing a health problem in the future.
3. For interventions or procedures to be considered of "vital importance" there must be clear and significant scientific evidence that their use is likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of a condition or disorder.
4. In applying the commensurate criteria IRBs should determine that research interventions or procedures are reasonably similar to those procedures and interventions that children with the condition or disorder as a class have or are expected to experience. Commensurate should not be introduced to gauge the acceptable level of risk. Under 45 CFR 46.406 the level of acceptable risk is determined by the definition of "minor increase over minimal risk." The commensurate criterion mean that some children may not be permitted under 45 CFR 46.406 to experience even a minor increase over minimal risk, either because of their or their parents/guardians= unfamiliarity with the procedure, or the research imposes an unfair burden on the subject.

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

1. SACHRP has begun 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. SACHRP recently formed a Subpart A Subcommittee to consider these issues.
2. As a result of discussions with invited panelists on IRB issues during the October 4 and 5, 2004 SACHRP meeting, it was decided that OHRP staff should consider planning an exploratory workshop to address the use of alternative institutional review board (IRB) review mechanisms for human subjects research.
3. SACHRP has been and will continue to be briefed on the progress of the Federal Adverse Event Task Force (FAET).
4. SACHRP has discussed issues including social and behavioral research, subpart B of 45 CFR part 46 (Additional Protections for Pregnant Women, Fetuses and Neonates Involved in Research), investigator training, international capacity building and compliance oversight.
5. SACHRP plans to host a panel to address patient advocacy concerns at its upcoming August 1-2, 2005 meeting in Alexandria, VA.

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 which will enhance human subject protections and advance science for the benefit of all Americans.

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

Enclosures

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

Related Recommendations

Appendix B: Recommendations regarding risk in research involving children
Appendix A: Who is a "prisoner" under Subpart C, Research Protections for the "Subsequently Incarcerated," identification of prisoner representative, prisoner representative on IRBs in multi-site studies