Secretary's Advisory Committee on Human Research Protections

Meeting
March 29-30, 2004
Alexandria, VA

Summary Minutes

MONDAY, MARCH 29

Welcome and Opening Remarks

Ernest Prentice, Ph.D., Chairman, Secretary's Advisory Committee on Human Research Protections (SACHRP)

Dr. Prentice welcomed the official and *ex officio* members of SACHRP and thanked the public for attending. He reviewed SACHRP's mission, which is to advise the Secretary of the Department of Health and Human Services (DHHS) Tommy G. Thompson on all matters related to human subjects with a particular emphasis on special populations including children, neonates, decisionally impaired individuals, and prisoners. SACHRP also is mandated to address potential investigator conflicts of interest; international issues; research with individually identified samples, data, or information; and Office for Human Research Protections (OHRP) activities and plans.

Dr. Prentice highlighted one of SAHCRP's key goals, which is to restore public trust in clinical research. He underscored its importance with a quote from Secretary Thompson: "We must allow science and medical research to advance for the good of all Americans, but not at the expense of people who participate in clinical trials."

Report on the Issues

Bernard Schwetz, D.V.M., Ph.D., Acting Director, OHRP

Dr. Schwetz thanked all the participants and commended the Subcommittees for their work tackling SACHRP's substantial and critical tasks. The amount of work done by the Subcommittees between SACHRP meetings has enabled the Committee to make substantial progress.

Dr. Schwetz continues to meet with representatives of many organizations concerned about human research protections. The majority agree that SACHRP has identified and is addressing the key issues in the field. The representatives also have provided him with insights about issues the Office needs to tackle. Most notably, the Office should:

- Continue to encourage institutions to ask OHRP for input on their human research protection concerns.
- Help overcome the false impression that research is shut down for trivial reasons.
- Provide additional guidance documents concerning regulations.
- Share best practices, especially in the area of informed consent.

In response to this feedback and to its own internal discussions of goals and objectives, OHRP will:

- Enhance its focus on providing information as well as in enforcing regulations.
- Continue to increase its operational efficiency (Thus far, OHRP has reduced the backlog of compliance cases, and Anecdotal evidence indicates that institutions are receiving review results more rapidly.)
- Shift priorities to writing additional guidance documents and conducting more Quality Improvement (QI) visits
- Clarify what is meant by:
  - Research, especially regarding public surveillance and quality improvement programs.
  - HHS-funded research, particularly related to international studies.

The Office also will assess the impact of its education program and conduct a public outreach program to explain the benefits human research programs and to provide information about participating.

Dr. Schwetz asked SACHRP to continue advising and guiding the Office. During future meetings, SACHRP input would be especially appreciated about now germinating in the research community. These include: prioritizing and developing multiple guidance documents, resolving issues related to data and tissue banks, and identifying any changes needed in Subpart A of the Common Rule regulations governing human research.

Overview of Charges to the Subcommittees

Ernest Prentice, Ph.D.

Dr. Prentice explained that a maximum of three Subcommittees are active at any time, and each provides SACHRP with reports and recommendations for discussion. Every Subcommittee has between eight and twelve members, depending on the workload. The three current Subcommittees are the: Subcommittee on Research Involving Children, Subpart C Subcommittee, and Accreditation Subcommittee.

Subcommittee on Research Involving Children. The Subcommittee's initial charge is to provide recommendations for consideration by SACHRP on the 45 CFR 46.407 panel review process. This Subpart requires that an HHS review panel be convened when an Institutional Review Board (IRB) is unable to approve a research protocol under the other categories within Subpart D (i.e., 404, 405, or 406). The group's recommendations will help ensure that panel deliberations are transparent, clear, include public and expert input, and meet other goals identified by the Subcommittee. The final recommendations must be harmonized with those of the Food and Drug Administration (FDA), which has separate but equivalent regulations governing pediatric research. To assist the Subcommittee in its work, members have access to experts in the field and other resources including:

- Previous work by the National Human Research Protections Advisory Committee (NHRPAC)
- Current research by the Institute of Medicine (IOM)

The Subcommittee Co-Chairs are SACHRP members Celia Fisher, Ph.D., and Susan Kornetsky, M.P.H.

Subpart C Subcommittee. This group is addressing protections for prisoners. The initial charge was to provide recommendations for consideration by SACHRP on the (re)interpretation, and perhaps total revision, of Subpart C to ensure that regulations do not obstruct ethically and scientifically appropriate research. The current Subpart C regulations were issued in an earlier, distinctly different, era and need reassessment. The Subcommittee Co-Chairs are SACHRP member Mark Barnes, J.D., LL.M., and Nancy Neveloff Dubler, LL.B. Ms. Dubler serves as the Professor of Bioethics at Albert Einstein College of Medicine and directs the Division of Bioethics, Department of Epidemiology and Social Medicine at Montefiore Medical Center.

Accreditation Subcommittee. This Subcommittee will provide its recommendations on Human Research Protection Program (HRPP) accreditation for consideration by SACHRP. Human subject protection is a concern of the entire research establishment, and interest in accrediting HRPP programs continues to grow. The Subcommittee will provide answers to critical questions about accreditation, including:

- What is the currently perceived value of HRPP accreditation?
- What incentives exist, or should exist, to motivate institutions to seek HRPP accreditation?
- What methods should be used to assess the impact of accreditation?
- Should the Federal Government have any role in HRPP accreditation and, if so, what should it be?

The Co-Chairs are SACHRP members Thomas Adams, CAE, and Felix Khin-Maung-Gyi, Pharm. D.

Subpart D: Protections for Children Subcommittee

Celia Fisher and Susan Kornetsky thanked the Subcommittee members for their work and commended OHRP for their support. Their PowerPoint presentation described the group's concerns and activities since the December 2003 meeting

Recommendations for the 407 Process

Background. During the December 2003 SACHRP meeting, SACHRP endorsed the importance of the 407 process, which is "research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate problems affecting the welfare of children." The process is important because it:

- Provides protections for participants in pediatric research.
- Helps ensure that important research with children is conducted.

At the meeting, SACHRP also endorsed:

- The Subcommittee's overall 407 process goals: transparency, public and expert input, timeliness, clarity, consistency consensus, and harmonization.
- Seven steps recommended by the Subcommittee to streamline 407 procedures and increase transparency and public input:
    1. Provide increased guidance for IRB application procedures for the 407 process (The algorithm approved at the meeting should help with this.)
    2. Employ the application screening/feedback process endorsed by SACHRP.
    3. Incorporate public comments into the 407 review

4. Organize face-to-face meetings for the expert panels to facilitate their discussions.
5. Ensure that these meetings are open to the public.
6. Post experts' recommendations to the OHRP Website.
7. As appropriate, post the DHHS Secretary's decision and rationale to the Website.

Prior to the December meeting, SACHRP had requested that the Subcommittee recommend a model for the 407 panel, define the roles of the public members and experts on the panel, and review possibilities for OHRP/FDA harmonization. The Subcommittee also was asked to review options for 407 review of multi-site studies and suggest methods to enhance process monitoring. As part of its response, the Subcommittee provided four possible panel models at the December meeting. These were the:

1. Non-Federal Advisory Committee (FAC) closed model
2. Individual expert consultations (FAC does not apply)
3. SACHRP subcommittee (FAC applies)
4. Non-FAC open panel

SACHRP expressed its preferences for the non-FAC open panel model and asked the Subcommittee to provide a rationale for using this model that would ensure that the final recommendation was fully informed.

Rationale for the Recommended Model. As a starting point for developing a rationale, the Subcommittee compared three panel models:

- SACHRP Subcommittee
- Non-FAC Open Model
- Independent FAC (probably not feasible, included to ensure that the final recommendation was fully informed)

In addition to commonalities among the models, there also are significant differences in how well they meet the Subcommittee's criteria:

- ***Timeliness:*** The Open and Independent models would require only one meeting; the subcommittee would require at least two meetings.
- ***Transparency and Input:*** All of the models include face-to-face expert public meetings, public comment, and Web dissemination of opinions.
- ***Continuity:*** The Subcommittee and Independent models would have continuity of membership; the Open Model would have flexibility in expert input.
- ***Harmonization:*** The Open Model provides greater flexibility for joint OHRP/FDA reviews.
- ***Consensus:*** The Subcommittee and Independent models would produce consensus documents; the Open Model would produce individual expert opinions. (Consensus is a lower value criterion: OHRP values receiving the full range of independent opinions before making its decision. In addition, having independent opinions available might help promote harmonization with FDA and other agencies.

RECOMMENDATION:

SACHRP approve for adoption by OHRP the Non-FAC Open Panel Model for 407 review that includes the steps outlined and approved by SACHRP at its December, 2003 meeting.

Defining the 407 Panel Public Representative

The Subcommittee endorsed the inclusion of public representation on 407 panels and made the following key points:

- At least one public member must be able to represent prospective participant family views, and such views are best provided by a family member.
- While some scientific/ethics experts might also provide a family perspective, panel members should be selected to fill only one role.
- Although 407 protocols may include diverse family populations, at least one public representative on the panel should be a family member, with the understanding that other family views can be represented in public comments and at open meetings.
- When 407 protocols do not include a child population with a specific disorder or condition, a child advocate should be considered as the public member.

RECOMMENDATION:

Each 407 review panel should appoint at least one public member from a family that is part of the specific population to be involved in the research under consideration.

Dr. Fisher provided additional considerations to supplement the recommendation:

- When feasible and appropriate, more than one public member should be included on 407 panels.
- In some cases, a community representative in addition to a family member should be considered.
- When the protocol does not include a specific disorder or condition, at least one public member should be a child advocate.
- Individuals who have family as well as scientific or ethics expertise should be selected to serve in only one of these roles on a 407 panel.

OHRP/FDA Harmonization

Dr Fisher noted the similarities between OHRP 45 CFR 46.407 and FDA 21 CFR 50.54 and observed that joint OHRP/FDA reviews are expected. However, FDA is still developing its procedures for implementing 50.54. As a result, it is difficult to make specific recommendations.

RECOMMENDATIONS:

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 review process.

- As FDA continues to develop 50.54 review procedures, OHRP should have decisional flexibility to select procedures to best meet these goals.

- Joint adoption of these goals should be paramount even when the differing legal authorities lead to the creation of different review processes.
- Harmonization should be a priority where and whenever possible.

The Subcommittee also developed additional recommendations pertaining to situations when a joint review is conducted through an FDA FAC. These were that:

- The membership should be consistent with OHRP-adopted SACHRP recommendations regarding expertise, continuity, and public and expert input; additional members should be included as needed.
- An FDA FAC joint review model will produce a consensus document rather than individual expert opinions. Nonetheless, the meeting will be open to the public and meeting transcripts and the consensus document should be made available to the public in a timely fashion.
- As the FDA process is developing, OHRP should have decisional flexibility to select procedures to best meet the process goals.

407 Review of Multi-Site Protocols. Dr. Fisher noted that these were the most complex recommendations to develop. Unique challenges included: (1) independent IRB evaluations are held at each site, (2) IRBs can differ in determining when 407 reviews are needed, (3) study funding is tied to individual IRB site evaluations, and (4) sites can begin enrolling subjects on different dates. The Subcommittee deliberated on various aspects of 407 reviews of multi-site protocols, beginning with the screening process.

Screening Process. Three recommendations were made.

RECOMMENDATIONS:

- OHRP should initiate the screening process any time there is a request for a 407 review from an institutional member of a multi-site study.
- The funding agency and PI should be informed, but their decision to eliminate a site should not dictate the OHRP review process.
- The OHRP may seek information from other sites to determine whether a 407 designation is appropriate. However, if after feedback IRB requests 407 review, OHRP should proceed.

Enrollment during the Screening Process. The Subcommittee developed recommendations to assist OHRP in making decisions concerning enrollment during the screening process.

RECOMMENDATIONS:

- OHRP should exercise its discretion and authority to advise sites as to whether enrollment should be suspended or terminated during a 407 review.
- The final decision to suspend or terminate enrollment for the entire study should rest with OHRP, not with the funder or the PI.
- SACHRP should encourage the National Institutes of Health (NIH) and other funders to follow OHRP recommendations.

The Subcommittee discussed risk/benefit issues involved in determining when enrollment should continue during a 407 review. The group decided that it might be appropriate to postpone enrollment if the applicant IRB has raised concerns that: (1) a study judged by other IRBs to have no prospect for direct benefit poses more than a minor increment over minimal risk or (2) a study judged by other IRBs as 405 research does not offer the prospect of direct benefit.

RECOMMENDATIONS:

- OHRP should have the flexibility to determine whether suspension or termination of enrollment at other sites may be harmful to currently enrolled participants or to the gathering of information vital to the welfare of children.
- The final decision to suspend or terminate enrollment for the entire study should rest with OHRP, not with the funder or PI.

Communication to Families: During 407 Enrollment. As part of their discussion, the Subcommittee reviewed informing families about changes in enrollment.

RECOMMENDATIONS:

- When OHRP determines that enrollment should be suspended pending 407 review, each IRB should determine the most appropriate way to communicate the information to parents whose children are study participants.
- When OHRP determines that enrollment should NOT be suspended pending 407 review, families should be informed if it is reasonable to assume that knowledge that a review is being conducted would raise legitimate family concerns about withdrawing participation in light of a recalculation of risks and prospective benefits.

Communication to Families: The Subcommittee made recommendations about what should occur after the DHHS Secretary's makes stipulations about, or disapproves, a study.

RECOMMENDATIONS:

- If enrollment is permitted to continue but the risk-benefit calculus has significantly changed as the result of a 407 review, re-consent should be required for continued subject participation.
- If enrollment is stopped, but participants are permitted to continue in the study, guardians need to be informed that new enrollments have stopped.
- If a child has completed participation in as study, it may be unnecessary to notify families. This determination will be based on whether the 407 review has produced new information pertinent to the continued welfare of the child.

Extending 407 Review. The Subcommittee made the following two observations rather than any formal recommendation:

- At this time, the 407 review process is not the arena in which this issue should be first debated. OHRP may wish to enter into dialogue with the DHHS Secretary, as well as Congress, on whether current regulations are adequately protect children,

and others, participating in research not funded through HHS nor subject to FDA regulations.

- Despite the availability of any new streamlined 407 procedures, investigators and IRBs may still shy away from research that appears to meet 407 criteria because of lack of clarity in the definitions of 404, 405, and 406, or failure of these classifications to adequately encompass all forms of research that IRBs should be able to independently evaluate.

Monitoring the 407 Process. The Subcommittee developed recommendations congruent with, and building on, OHRP's plans to develop and regularize communications with SACHRP regarding 407 reviews.

RECOMMENDATIONS:

- OHRP should provide a yearly report to SCHRP on 407 activity related to the criteria developed by the Subcommittee (e.g., transparency).
- During the year, OHRP should keep SACHRP informed about the number of 407 applications received and reviews in progress.
- A SACHRP-designated subcommittee should work with OHRP to identify aspects of the process that are successful and those that can be improved.
- The designated subcommittee should issue an annual report and recommendations (if needed) to SACHRP on monitoring the 407 process.

Discussion of the Recommendations Made by the Subcommittee on Research Involving Children

407 Model

In response to questions, Dr. Fisher and Ms. Kornetsky explained that:

- Selecting either of the non-recommended models would not impact the Subcommittee's other recommendations.
- Panel membership would vary depending on the protocol being reviewed; however, a standing pool of potential members could be selected in advance.

Dr. Prentice recommended that a chairperson be appointed for a two- or three-year term. Dr. Schwetz suggested that a group of designated alternative chairpeople also be available to lead the panel if that became necessary. Dr. Fisher suggested that OHRP select a mechanism for chairing the committee and monitor the results.

Mr. Adams asked whether a process for selecting panelists had been developed. Ms. Kornetsky suggested using the OHRP system. Dr. Schwetz explained that the Office currently has a list of individuals who are qualified to assist with various projects. Dr. Fisher observed that, if the recommended 407 process is implemented, all of the information about possible participants would be publicly available on the OHRP Website.

MOTION:

Mr. Barnes made a motion to accept the Subcommittee's recommendation to adopt the Non-FAC Open Model for 407 panels. Mr. Adams seconded the motion.

ACTION:

The motion passed unanimously.

Public Membership on the Panel

SACHRP members made the following comments:

- Mr. Adams asked whether the Subcommittee had defined "child advocate"; the term as used in the recommendations could refer to individuals with a wide array of qualifications. Ms. Kornetsky explained that the term was not defined because the qualifications for an appropriate child advocate would vary across protocols.
- Dr. Fisher explained that when the protocol includes a disorder or condition, a family member should serve as the public representative; when a disorder or condition is NOT included in the protocol, a child advocate should be selected to represent the public.
- Mr. Barnes suggested that the public representative should be selected based on his or her: (1) ability to serve as an effective, competent voice for the population impacted by the research and (2) self-identification with the interests of that population.
- Dr. Weiner cautioned that Mr. Barnes' definition omits a critical factor: whether the representative has experience actually caring for a member of the targeted population and providing informed consent for that person to participate in a study.
- Dr. Prentice suggested that the definitional issue, and the concerns raised by Dr. Weiner and Mr. Barnes, might be resolved by modifying the language to eliminate inconsistencies between the "Recommendation" and the "Additional Considerations."

It was agreed that the "Recommendation" and third "Additional Consideration" would be rephrased.

REVISED RECOMMENDATION:

Each 407 review should appoint at least one public member who is identified as an effective advocate for the interest of children who would likely become subjects of the research and is himself identified with those interests. In the case of children with a specific, defined disorder condition, a family member or guardian of such child should be appointed as his public member.

REVISED ADDITIONAL CONSIDERATION:

The third bullet will read: If there is no such family member or guardian to voice the interest of children, one public member who is identified as an effective advocate for the interests of children should be appointed.

MOTION:

Dr. Polan recommended approving the revised recommendation including the additional considerations as modified. Mr. Barnes seconded the motion.

ACTION:

The revised recommendation including additional considerations as modified was passed unanimously.

OHRP/FDA Harmonization

Ms. Kornetsky observed that it was hard to develop these recommendations because FDA is still reviewing some of the issues. She and Dr. Fisher explained that the intent of the recommendations was to give OHRP the flexibility needed for harmonization, facilitate interagency communication, and help avoid the establishment of two separate review systems. Dr. Lepay noted that FDA will continue using interim procedures until the FAC pediatric committee establishes structures and mechanisms for 407 reviews. He added that the recommendations appear compatible with the FDA's perspective and goals. In addition, the pediatrics committee will create a communication pathway for OHRP and IRBs.

MOTION:

Mr. Adams moved that recommendations one and seven be adopted.

DISCUSSION:

Ms. Kornetsky noted that these two points really sum up the entire recommendation. Dr. Prentice added that the recommendation encouraging harmonization also should be accepted.

ACTION:

SACRHP unanimously accepted the following three recommendations regarding OHRP/FDA harmonization:

1. 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 review process.
2. Harmonization should be a priority where and whenever possible.
3. As the FDA process is developing, OHRP should have decisional flexibility to select procedures to best meet the process goals.

Screening Process

Ms. Kornetsky explained that the recommendations' primary intent was to provide guiding principles for multi-site trials. The Subcommittee consulted with OHRP to ensure that the provisions could be implemented as needed. Mr. Barnes asked:

- Does OHRP have the jurisdiction to conduct a review if the funding agency and PI are informed and the site is eliminated from the study?
- Do the results of such an OHRP study have any significant impact?

Michael Carome noted that situations do occur when one site/IRB believes that a study requires a 407 review but the other sites/IRBs do not. In these cases, the PI and sponsor

can either elect to: (1) stop the study and address the concerns related to the 407 review or (2) eliminate the site/IRB requesting the review and proceed with the research. In the latter instance, OHRP can restrict the assurances for the remaining sites; this would stop the research until the concerns are addressed. As a practical matter, OHRP prefers to negotiate with the PI and sponsor to address the 407-related concerns before site assurances are restricted.

Dr. Prentice raised a question about the third bulleted statement. As written, IRBs could demand that OHRP conduct 407 reviews. Dr. Carome observed that OHRP now has the authority to decide whether a 407 review is appropriate. Ms. Kornetsky suggested modifying the language to ensure that OHRP maintained this authority. Ms. Kornetsky explained that the first bulleted statement requires that OHRP conduct a screening process, not a full 407 review, in response to a site request for a 407 review. The third bullet ensures that OHRP retains the authority to decide whether the full review is needed.

REVISED RECOMMENDATION:

The final sentence will be modified to state: However, if after feedback IRB requests 407 review, OHRP should determine whether it is appropriate to proceed.

MOTION:

Mr. Barnes recommended that the recommendation be approved as revised. Mr. Adams seconded the motion.

ACTION:

SACHRP voted unanimously to approve the revised recommendation.

Enrollment during Screening Process

The recommendations are not meant to cover every specific situation; the intent is to provide guidelines for decision-making. Dr. Fisher suggested deleting the first three points and discussing the final two points. These two recommendations provides OHRP with flexibility in decision-making regarding stopping or postponing enrollment and key criteria based on risks and benefits to participants.

Dr. Carome observed that the recommendation should consider subjects in the study and those scheduled to enroll in the study. Dr. Fisher explained that the recommendation was the same in both cases: OHRP has the responsibility and the flexibility to make enrollment decisions.

Mr. Barnes suggested adding a statement covering the following:

- If OHRP has determined that enrollment at other sites should be suspended or terminated, the Office should first attempt to persuade the IRBs, the PIs, and the funding agencies to comply with the OHRP determination pending the completion of the 407 review.
- If OHRP is unable to persuade them, then the Office should use its authority to restricting assurances.

Drs. Prentice and Carome observed that this statement probably was not needed because it did not change OHRP's existing legal authority.

MOTION:

Mr. Barnes made a two part motion:

1. The two final bullets be adopted, with the first bulleted statement modified to read "OHRP should determine whether suspension or termination …"
2. A third bullet be added that incorporated his earlier points about how OHRP should proceed when the Office has determined that enrollment should be suspended or terminated.

Dr. Hauser seconded the motion.

DISCUSSION:

Dr. Prentice noted that the third bullet could be viewed as clarifying but not changing intent. He recommended that the actual changes in wording be crafted after action is taken on the entire motion.

ACTION: SACHRP approved the motion unanimously, with the understanding that the actual wording would be crafted shortly.

Communications to Families: During 407 Enrollment

Dr. Prentice raised a question about the second bulleted item: When OHRP determines that enrollment should not be terminated, which entity communicates with the families? Dr. Fisher and Ms. Kornetsky recommended that OHRP be responsible to ensure consistency of communications and uniformity of protections across sites; IRBs would be responsible for logistics. Drs. Prentice and Carome agreed that OHRP had the authority needed to support this recommendation. Dr. Carome added that communications would be developed in consultation with the IRBs, sponsors, and PI.

MOTION:

Mr. Barnes moved that the recommendation be adopted with a clarification made by Dr. Prentice:

> Regardless of whether enrollment is stopped, OHRP will make determinations regarding the provision of additional information. The IRBs will decide how that information should be conveyed to the families in question.

DISCUSSION:

Dr. Fisher explained that OHRP has the moral and ethical responsibility to ensure that parents are informed when the Office has determined that the study involves either no direct benefit to the subjects or greater harm than was originally anticipated. Dr. Prentice added that once informed about the OHRP determination, each IRB would develop plans for communications with the families and would decide whether the study should be terminated.

ACTION:

The modified recommendation was accepted unanimously by SACHRP.

Communications to Families: Following HHS Secretary's Decision

Dr. Prentice asked that this recommendation be modified, like the preceding one, to make it clear that OHRP is responsible for making determinations regarding additional communications with families. Dr. Polan asked that the third bulleted statement be modified to ensure that families are informed about new information regardless of whether their child has completed study participation. To do this, the third bullet should be modified: "unnecessary" should be changed to "it may be necessary."

Speakers generally agreed that OHRP has an ethical obligation to provide information after the child has completed study participation, but questioned whether the Office had the legal authority to do so when research is no longer proceeding. Laura Odwazny, J.D., Senior Attorney, Office of the General Counsel, explained that it would be difficult for OHRP to assert this authority after the research had been completed. However, OHRP could stress in their initial communications with participating institutions that these entities have an ethical responsibility to keep families informed after study participation has ended either for the child or the site.

In response to comments from Mr. Barnes, Ms. Odwazny explained that OHRP would have the authority to demand reconsent if changes in the research raised new significant risks to participants health. Mr. Barnes and Ms. Odwazny agreed that OHRP did have the authority to compel the provision of information to participants based on sufficient evidence of increased risk.

The following key comments were made regarding the second bulleted statement:

- Ms. Decot advised that the language be modified to indicate clearly that the study is being terminated and this is why enrollment has been stopped.
- Dr. Prentice recommended deleting "but participants are permitted to continue"; this would provide IRBs with flexibility regarding whether to let people continue in the study for safety reasons (e.g., the impact of being removed abruptly from treatment).
- Drs. Prentice and Fisher and Ms. Kornetsky agreed that the wording should indicate that the guardian needs to be informed when the study is stopped but continuation of current subjects is recommended. In addition, the rationale for the continuation should be provided.
- Mr. Barnes and Dr. Prentice asked whether reconsent is needed for continuation in this situation.
- Drs. Fisher and Prentice and Mr. Barnes and Ms. Kornetsky agreed that guardians need to be informed when a study is stopped. For participants for whom continuation is recommended, an additional consent procedure is needed.

MOTION:

Dr. Polan moved to accept both components of the "Communications to Families" recommendation ("During 407 Review" and "Following HHS Secretary's Decision") the as modified. Dr. Weiner seconded the motion.

ACTION:

SACHRP unanimously approved the motion.

Extending 407 Review
The Subcommittee decided to postpone making a recommendation because the issue extends beyond the group's purview. SACHRP took no action.

Monitoring the 407 Process
The Subcommittee developed a feedback system to be implemented once the 407 process is in place. Dr. Schwetz noted that OHRP already plans to analyze progress annually. A summary report could be posted to the Website and made available in hardcopy as requested.

MOTION:

Dr. Fisher moved that the recommendation be accepted by SACHRP. Dr. Jones seconded the motion.

ACTION:

The recommendation was unanimously accepted by SACHRP.

Transmittal of the Recommendations
Dr. Schwetz explained that OHRP would take the recommendations from the minutes and submit them to the HHS Secretary. He asked that the Subcommittee, with assistance from OHRP, craft single set of recommendations be crafted and included in the minutes.

Minimal Risk
Dr. Prentice reported that the Subcommittee is reviewing the requirements contained in Subpart D regarding defining various terms such as "minimal risk." He emphasized that minimal risk is the threshold level determining how requirements are applied progressing through Subpart D. In addition, he predicted that the number of 407/5054 reviews would increase if SACHRP and FDA agree to an absolute definition of minimal risk.

Subpart C Subcommittee *(Mark Barnes, J.D., LL.M.)*
On behalf of the Subpart C Subcommittee, Mark Barnes thanked Drs. Schwetz and Prentice and OHRP staff for supporting and guiding the group through the three in-person meetings and numerous conference calls held thus far. He then summarized the Subcommittee's deliberations to date and discussed their handout, *Draft Issues Summary, March 29, 2004*.

Early in their deliberations, Subcommittee members addressed how to balance the desire to loosen regulations so prisoners might access to biomedical advances with the need to ensure that regulations were tight enough to protect prisoners from possible research abuses. In striving to achieve this balance, members considered that many prisoners are predisposed to enter research studies as a way to get better care than that provided in the prison; they concluded that this is coercive. The Subcommittee decided that its goal was to protect prisoners without obstructing their access to research. In addition,

Subcommittee members will advocate for all prisoners to receive medical care that meets community standards, thus eliminating the element of coercion.

The Subcommittee also determined early in its deliberations that the current Subpart C regulations and guidance are inadequate and confusing. The standards embodied in Subpart C are inconsistent with standards elsewhere in the regulations and may not comply with the recommendations made in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* In addition, the four categories of approvable research described in the regulations are so complicated that it is impossible to understand their intent.

Based on these determinations, the Subcommittee probably will recommend that they rewrite the entire Subpart. In the near term, members are developing short- and intermediate-term solutions to some of the Subpart C issues. Mr. Barnes defined short-term solutions as those that would not create conflicts with existing OHRP guidance and that could be put in place quickly; intermediate-term solutions could entail guidance modification and would take longer to put in place.

Issues identified for possible short- or intermediate-term solutions include: (1) defining the term "prisoner," (2) responding to post-enrollment incarceration, (3) defining an appropriate prisoner representative to serve on the IRB, and (4) providing follow-up care after the study concludes. Considerations regarding each of these issues include the following:

1. ***The definition of a "prisoner."*** A functional definition should be developed using "whether the person can go, do, and act as he/she wishes" as the operational criterion. The definition would apply to public health confinement and some other statuses such as specific alternatives to confinement. Research subjects who were not in correctional custody when enrolled in a study would not be considered prisoners.
2. ***Post-enrollment incarceration.*** If it is reasonable to expect that the study population will be at risk for incarceration during the study, the PI and IRB should proceed in a manner consistent with Subpart C. When the risk is low but incarceration occurs, then the person in custody should not be considered a prisoner, but higher scrutiny should be given to his or her continuation in the study. Additional legal input is required concerning providing special protections in this instance. The presumption should be that the incarceration leads to withdrawal from the study, but exceptions can be made if the PI demonstrates that the subject can continue without being placed under duress or facing coercion. The IRB must approve the subject's continued participation. This Board approval requires input from individuals knowledgeable about the correctional system; however, it does not require a full IRB review.
3. ***The prisoner representative on the IRB.*** Representatives should be self-identified with the interests of the prison population. Each IRB in a multi-site study should have a prisoner representative. Conflict of interest (COI) rules laid out in Subpart A should be expanded in the following ways:

- No IRB member should be affiliated with the correctional system involved in the research.
- The prisoner representative should have some correctional expertise and serve, at a minimum, as a consultant to the IRB.
- The COI requirements for community representatives should be applied to prisoner representatives.

4. ***Follow-up care after the study concludes.*** This requirement is not clearly defined. The Subcommittee advocates that prisoners be allowed to participate in biomedical research only when they have access to care that meets the community standard both during the study and after it ends.

Mr. Barnes identified five issues that require long-term solutions, possibly to include being redrafted. These issues and their related considerations include the following:

1. ***Minimal risk:*** Definitions must be understood across the Subcommittees and reconciled across the Subparts.
2. ***Jurisdiction:*** At present, Subpart C only applies to studies funded by HHS, the Central Intelligence Agency (CIA) and the Social Security Administration (SSA). Much research, including that conducted by States and the Federal Bureau of Prisons, does not have to comply with Subpart C regulations. In some instances non-HHS research sponsors are reluctant to comply because they see underlying problems with the Subpart. Once Subpart C is clarified, it should be applied to a broader group of research sponsors.
3. ***Control group definitions and policies:*** These need to be teased out of the four categories of allowable research and clarified. Providing the community standard of care to prisoners not enrolled in research might eliminate the need to consider whether control groups should be allowed.
4. ***Secretarial review and consultation process:*** High-risk studies require a second level of review. The four categories of allowable research should be eliminated and a general risk/benefit analysis should be used to identify high-risk research.
5. ***Quality assurance /evaluation issues:*** Ongoing monitoring is needed and should be better tailored to the specifics of the protocol being implemented. Monitoring could be conducted by OHRP or the IRBs. The key issue is to ensure that studies are in compliance with the Belmont Report's essential principles.

SACHRP Discussion

In response to questions from Dr. Prentice, Mr. Barnes recommended that the Subcommittee develop ways to distinguish between high- and low-risk studies. He also explained that the level of benefit offered by the study would be an important factor in determining whether a subject incarcerated after enrollment should stay in the study.

Dr. Prentice asked whether it was realistic to require prisons to provide the standard of care found in the community setting, as this might lead to a decrease in research involving prisoners. Mr. Barnes replied that this was the only way the Subcommittee found to address the problem of coercion.

Susan Kornetsky and Robert Hauser questioned whether the presumption should be that incarceration leads to withdrawal from the study. Mr. Barnes explained that in actual prison settings, continued post-incarceration research participation is impossible unless the PI is determined to make this happen. He observed that the presumption could be scaled to reflect the subject's level of independence in making the decision to continue.

Accreditation Subcommittee Report *(Felix Khin-Maung-Gyi, Pharm.D., and Thomas Adams, CAE)*

Felix Khin-Maung-Gyi thanked the Subcommittee for their work and presented the final report supplemented by a PowerPoint presentation.

Observations and Findings

Based on their discussions with representatives from accrediting organizations and accredited institutions, the Subcommittee was encouraged that high-quality programs are being developed by two responsible, knowledgeable entities: the Association for the Accreditation of Human Research Protection, Inc., (AAHRP) and the Partnership for Human Research Protection, Inc. (PHRP). The Subcommittee also recognized that these entities were recently formed and will continue to evolve.

The Subcommittee was limited in making recommendations by the dearth of data in the field. For example, the Subcommittee could not:

- Conduct a valid review and make conclusions regarding the merits of HRPP accreditations at research institutions.
- Recommend that government agencies provide incentives to research agencies that seek accreditation.

To remedy the situation, the Subcommittee recommended that accreditation be systematically evaluated to determine its value as an assurance of research quality and human subject protections. This could be done by:

- Building on the grant from the Centers for Disease Control and Prevention (CDC) to AAHRPP.
- Mandating that regulatory agencies collecting information about IRBs and research institutions expand their purview to gather critical data about accreditation issues.

The Subcommittee predicted that the collected and analyzed data would validate the positive impact of accreditation. At that point, Federal agencies should identify incentives for research institutions to seek accreditation. These would complement natural market forces in encouraging research institutions to undertake accreditation.

The Subcommittee agreed that:

- The Government should have no role in endorsing accrediting bodies; however, there may be value in evaluating the processes and procedures used by these bodies.
- Any accrediting program should provide institutions with strong self-assessment processes.

- Participating in the accreditation process should remain voluntary. However, because accreditation is voluntary, those institutions most needing self-assessment and evaluation might be the least likely to undertake this process.
- The scope and cost of the accreditation process could present impediments for some institutions.

In addition, the Subcommittee suggested that HHS organize a summit meeting for all of the major accreditation stakeholders to examine the wide range of self-regulatory initiatives that have been developed and implemented by responsible parties during the last four years. (Among these initiatives, accreditation is closest to full implementation.) This meeting would enable participants to identify and investigate options and share best practices.

As a result of its deliberations, the Subcommittee recommended that the *Interim Report* be reaffirmed. This states that:

> "In the absence of additional experience and concrete information, the Subcommittee supports the concept of accreditation of … HRPPs for the protection of human subjects in research. 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."

SACHRP Discussion

Dr. Prentice asked how long it would take to accredit the majority of academic health centers. In response:

- AAHRRP Executive Director Marjorie Speers, Ph.D., indicated that this will take between three and five years.
- PHRP Assistant Vice President Jessica Briefer-French said that there were too many factors in play to make a firm estimate.
- *Ex officio* SACHRP member Kathryn Lynn Cates, representing the Department of Veterans Affairs, added that all 115 Veterans Administration sites should be accredited by 2006. Four site accreditations are completed each month, and 23 sites are currently accredited. She added that anecdotal evidence indicates that institutions provide their HRPPs with additional resources when the programs are preparing for accreditation.

Other comments included the following:

- Susan Weiner recommended that intermediate remedies be developed to address institution's accreditation problems; these would be applied before a study was required to shut down.
- Mr. Adams noted that, based on anecdotal evidence, pharmaceutical companies would be more likely to sponsor research conducted at accredited institutions.

***MOTION*:**

Mr. Adams made a motion to adopt the *SACHRP Final Accreditation Subcommittee Report, March 29, 2004.*

ACTION:

The motion passed unanimously.

Public Comment

John Mather, M.D.

Dr. Mather, Director of the Office of Compliance Review at the University of Michigan, said that accreditation:

- Is increasingly seen as a badge of approval by research sponsors.
- Provides institutions with invaluable opportunities for self-assessment.
- Will require varying amounts of time, depending on the institution's commitment to the process.

He also asked SACHRP to identify ways to incentivize weaker institutions to conduct self-assessments and obtain accreditation. Dr. Khin-Maung-Gyi responded that available data does not warrant moving from a voluntary participation environment.

Susan Vankowski

Ms. Vankowski, Research Regulations Specialist at the Johns Hopkins University Bloomberg School of Public Health, agreed that the self-assessment process is invaluable. She also noted that pre- and post-tests for accreditation measures are lacking and should be developed.

Marjorie Speers, Ph.D.

Dr. Speers, the Executive Director of AAHRRP, explained that her organization is developing performance indicators and measures as part of the CDC grant. These will be pilot tested in Year Two of the grant and made available in Year Three. Dr. Speers added that she would like to be in contact with OHRP and FDA to discuss outcome-related issues, especially developing longitudinal measures. She also noted two recent Federal actions that are increasing interest in accreditation among health care centers:

- The DHHS strategic plan includes support for voluntary accreditation of HRPPs.
- Legislators are preparing bills to require HRPP accreditation.

Mr. Adams observed that SACHRP is aware of these initiatives. Ms. Kornetsky suggested that accredited institutions should share best practices for self-assessment and accreditation.

Paul Goebel, CIP

Mr. Goebel, Vice President, Chesapeake Research Review, Inc., observed that powerful incentives exist for accreditation. Dr. Khin-Maung-Gyi agreed and added that IRBs are the portal for accreditation activities, but the accrediting entities look at the entire research enterprise. He also noted that the target audience for accreditation is large, expanding, and needs better definition.

SACHRP Membership *(Bernard Schwetz, D.V.M., Ph.D.)*

Dr. Schwetz asked for nominations for new SACHRP members to replace current members when their terms of office end. He added that the appointment of a public representative to SACHRP is being considered.

Summary of the Day's Activities *(Ernest Prentice, Ph.D.)*

OHRP Issues

OHRP is successfully becoming an agency with a national reputation for responsiveness and trustworthiness. Relations between the Office and research institutions are improving significantly and OHRP's compliance caseload is decreasing. Drafting guidelines is now a major OHRP priority. The Office also will be: (1) conducting more public outreach and QI activities and (2) continuing to identify key issues. SACHRP fully supports OHRP's efforts and is available to help develop guidelines, which is a critically important task. Dr. Schwetz added that it is likely that the OHRP charter will be renewed soon.

Subcommittee on Research Involving Children

The Subcommittee has recommended that a slightly modified non-FACA panel conduct 407 reviews. Both FDA and ORHP agree that reviews should be transparent, include public and expert input, and meet the other characteristics identified by the SACHRP Subcommittee. Some details of the harmonization process remain to be discussed after the FDA system is closer to implementation. The criteria for serving as a representative of the public on the 407 review panel have been identified. General guidelines were established for study suspension procedures. Reviews will be monitored and annual reports will be submitted SACHRP. Key information will be posted to the OHRP Website. Some of the recommendation language will be refined.

Subpart C Subcommittee

The Subcommittee remains undaunted by the enormity of its mission and is pursuing short- and intermediate-term solutions to the problems of Subpart C as well as planning for the rewrite of the regulations. Between three and five years will be required to complete the rewrite and approval processes. At the July SACHRP meeting, the Subcommittee will present its short- and intermediate-term recommendations as informed by their deliberations and today's discussion.

Accreditation Subcommittee

The *Final Accreditation Subcommittee Report, March 29, 2004* was unanimously approved by SACHRP. The *Report* emphasizes the importance of collecting additional data about accreditation.

Chairman's Prerogative: Comments on Accreditation

The *Final Accreditation Subcommittee Report* takes a neutral-to-positive approach to accreditation. However, based on his 20 years' experience with animal and human subject research protections, Dr. Prentice endorses accreditation more strongly. He made the following points:

- The work of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) has led to improved protections for laboratory animals and similar benefits will accrue to human subjects when HRPP accreditation is in place nationally.
- Accreditation forces institutions to provide additional resources, training, and personnel for HRPP programs.

- Institutions benefit greatly from conducting the self-studies needed prior to obtaining accreditation.
- Within the next ten years, the value of HRPP accreditation will be clearly demonstrated.

Concluding Remarks for the Day

Dr. Prentice thanked SACHRP and the Subcommittee members. He added that SACHRP, OHRP, and the FDA will continue working together with other agencies to develop practical, adoptable, recommendations. The efforts being put forth will be translated into a true difference in human research protections.

ACTION ITEMS: ***Monday***

1. A single set of recommendations is to be crafted by the Subcommittee on Research Involving Children and OHRP and incorporated in the meeting minutes.
2. Nominations for SACHRP position should be sent to Catherine Slatinshek, Executive Director, SACHRP.
3. The Subcommittee on Subpart C will:
   - Prepare recommended short and/or intermediate-term solutions for the July 2004 SACHRP meeting.
   - Obtain additional legal input about providing special protections to individuals not at high risk for incarceration who enroll in a study and then are incarcerated.