Secretary's Advisory Committee on Human Research Protections

November 1 and 2, 2005
Alexandria, VA

Minutes

TUESDAY, NOVEMBER 1

Welcome and Opening Remarks
Ernest Prentice, Ph.D.

The Chairman welcomed everyone to the meeting. He reminded attendees of SACHRP's Charter, issued on September 8 of 2004, which comprises protection of human research populations, especially vulnerable populations such as children and prisoners. He noted that there are two new members, Dr. James H. Powell and Dr. Neil R. Powe.

Dr. Prentice thanked *ex-officio* members of SACHRP, noting that Wednesday will largely be devoted to a discussion of issues presented by these members. He also expressed appreciation to all OHRP staff who work in partnership with SACHRP.

Report on Issues
Bernard Schwetz, D.V.M., Ph.D., Director, Office of Human Resource Protections (OHRP)

Dr. Schwetz updated SACHRP members on diverse developments since the committee's last meeting.

The Food and Drug Administration (FDA) now has an Acting Commissioner. OHRP will continue to work closely with the FDA in the regulatory arena.

The Alliance for Human Research Protection (AAHRP) has announced that it is no longer accrediting research protection programs. It is not clear what the effect of this decision will be, but OHRP continues to support and have confidence in accreditation as a process.

OHRP has suspended the assurance of Gothenberg University in Sweden. No Federally funded human research to which the assurance applied may continue at the University until the assurance is restored.

Many guidance documents have been issued. One is draft guidance on adverse event reporting, which has been posted on the OHRP Web site since October 11. Public input is being sought over a 90-day period that began August 11.

In response to a frequently asked question, OHRP has also posted information on IRB review of clinical trial Web sites. OHRP continues to post such questions and answers to its Web site as part of its education function. Recent additions include answers to a number of questions related to research involving children. OHRP has also posted documents on compliance oversight procedures and updates to the common finding document. The Web site now contains additional information on

international regulations as well. Dr. Schwetz encouraged members to check out and use this information.

The Director told SACHRP that the Environmental Protection Agency (EPA) has proposed a rule related to human subject protection and is receiving comments until December 12. It is a significant step forward for that agency.

OHRP has begun to offer two-day regional workshops for institutions with HHS-supported research. No more than 50 people will be in attendance, representing multiple institutions. The intent is to enable participants to improve their programs through hands-on, interactive education. Participants in a recent workshop in Baltimore reported they found the training useful.

Recognition of Departing Members/Swearing in of New Member
Ernest Prentice, Ph.D.; Bernard Schwetz, D.V.M., Ph.D

Dr. Prentice recognized departing members and swore in new members. Departing members included Mr. Thomas Adams, CEO of the Association of Clinical Research Professionals (ACRP). His contributions have included political astuteness and organizational skills. Dr. Schwetz added that Mr. Adams contributed a valuable perspective, a capacity to identify what is most important, and an ability to push things at the right time. The Secretary's letter to Mr. Adams was then read, which acknowledged the valuable service the departing member has provided.

Dr. Prentice also recognized the contribution of Mr. Mark Barnes, who was unable to be present. Mr. Barnes is an attorney specializing in health law with expertise in human subject protection. He co-chaired the Subpart C Subcommittee, which considered additional protections needed for prisoners who are research subjects. He "kept the group on its toes" and asked important questions.

The third departing member was Dr. Bob Hauser, a cardiologist, who contributed expert medical advice that helped SACHRP address the interface among science, medicine, and the protection of human subjects. Dr. Prentice expressed appreciation for Dr. Hauser's time and effort.

A swearing-in ceremony followed for a new member, Dr. James H. Powell, who has held many positions in the pharmaceutical industry, most recently as Senior Medical Director and head of the Clinical Pharmacology and Pharmacokinetics Department at Proctor and Gamble Pharmaceuticals. In August, 2002, the National Medical Association (NMA) acknowledged his efforts to improve the involvement of African Americans in biomedical and clinical research with a leadership award. The American Academy of Pharmaceutical Physicians designated him a certified physician investigator. Ms. Ada Sue Selwitz, who has been serving out the term of a departed SACHRP member, was sworn in at the same time.

Overview of Charges to Subcommittees; Approval of Minutes
Ernest Prentice, Ph.D.

The Chairman provided an overview of charges to existing SACHRP committees and complimented the committees on their work. One subcommittee deals with research involving children; Dr. Prentice said he was impressed with all the subcommittee has been able to accomplish. He also highlighted the new subcommittee on Subpart A, which will review and assess all provisions of Subpart A and consider how to reduce regulatory burdens that do not contribute to the safety of human subjects.

Minutes for the previous meeting (August 1-2, 2005) were approved unanimously.

Dr. Prentice then provided an overview of the meeting agenda.

Report of the Subcommittee on Research Involving Children
Celia B. Fisher, Ph.D., Co-Chair; Susan Kornetsky, M.P.H., Co-Chair

In its deliberations since the last meeting, Dr. Fisher reported that the subcommittee has paid careful attention to feedback received from SACHRP. She particularly acknowledged the assistance of *ex-officio* members, especially in addressing issues related to HHS/FDA harmonization. At this meeting, the subcommittee presented recommendations on terminology and procedures in Subparts A and D that may require clarification and sought consensus on recommendations related to parental permission and child assent. She explained that both Subparts are relevant to Institutional Review Board (IRB) decisions related to informed consent when children are to be research subjects.

Waiving Permission of Parent or Guardian Under §46.116(d)

Guidance provides that permission of parents or guardians can be waived under four conditions, some of which are stated in imprecise terms. One condition is when "the waiver or alteration will not adversely affect the rights and welfare of subjects." The subcommittee sought to clarify the meaning of "adversely affect" and define the conditions under which this guidance would apply.

Recommendation 1: "Adversely affect." *To determine that a parent/guardian waiver "will not adversely affect the rights and welfare of the subjects" under 116(d) the IRB should consider*

- *Federal, State, or local laws pertaining to parent/guardian permission,*
- *Local norms, and*
- *Appropriate mechanisms to protect the rights and welfare of child participants.*

Examples of applicable Federal laws include the Health Insurance Portability and Accountability Act (HIPAA), The Protection of Pupils' Rights Amendment (PPRA), and the Family Educational Rights and Privacy Act (FERPA).

Adequate consideration of local norms involves determining whether the investigator provided a reasonable argument that the waiver does not violate the norms of the community from which child subjects will be recruited. Examples of evidence this has occurred would be advice from a community advisory board or Parent and Teachers Association (PTA), or the presence of an unaffiliated IRB member who represents the participant population.

Appropriate alternative mechanisms to ensure protection would include the use of an independent participant advocate or a demonstration that the child is old enough to give informed and voluntary consent and that the child will not be coerced to do so.

Dr. Fisher illustrated the application of this guidance with an example of a survey on soft drink and fast food intake in which no laws require parental permission, the investigator has worked closely with the local PTA, and the children are old enough to assent and will not be coerced. However, if the study proposed to correlate eating patterns with middle student grade point averages, this would not be permissible under FERPA. If it also contains questions about foods that are prohibited in the orthodox religious community where the subject will be conducted, parents could object. If the study were to be conducted with a younger population, such as three-year-olds, the children would be too young to assent.

Recommendation 2: "Practicably." Three criteria were proposed for a demonstration that research could not be "practicably carried out" if parental or guardian had to be sought.

To determine whether parent permission can be waived under 46.116(d)(3) because the research cannot be "practicably carried out" the IRB should require investigators to provide:

- *A reasonable argument that scientific validity would be compromised if parental permission was required,*
- *A reasonable argument that alternative methods to obtain parent/guardian permission are not feasible, and*
- *A rationale for why the research could not be conducted with a population for whom parental/guardian permission could be practicably carried out.*

An example was presented in which a principle investigator (PI) proposes to waive parental permission for a national study of diet and after-school activities to predict U.S. Census track concentrations of respiratory disease in middle school children. This could be permitted because a large random sample is needed for statistical power, census tract neighborhoods vary with respect to the ability to contact parents through the telephone directory or other means, and it is important for all the census tracts to be included in order for results to be meaningful.

Recommendation 3: "Limitations on "Practicably"." The subcommittee wanted to ensure there were clearly understood limitations on the use of waivers granted because research would otherwise not be "practicable." It therefore proposed the following:

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

For example, IRBs may not waive parent/guardian permission because of funding limitations if those limitations result in procedures that do not provide the same degree of subject protections that better funded research would provide.

Recommendation 4: "Passive Consent." The subcommittee also felt it was important to revisit the "passive consent fallacy," which assumes that parental failure to respond to consent forms in the negative means that consent has been granted. Therefore, because this is poorly understood, the subcommittee asked SACHRP to reaffirm the following:

Passive consent (in which parents/guardians are sent forms describing the research and asked to respond only if they do not want their child to participate) is not an approvable mechanism for satisfying the parent/guardian permission requirement under §46.116 or §46.408.

When parent/guardian permission meets the requirement for waiver under §46.116 (d) and §46.408 (c), an IRB should consider whether parental notification and right of refusal is appropriate.

The recommendation is intended to underscore the fact that an IRB is waiving parental permission in such cases, and the investigator must demonstrate that a waiver is appropriate.

Waiving Guardian Permission Under §46.408(c)

This section provides that parental permission may be waived when "parent or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children)." The Co-Chair explained that a key difference between §46.116(d) and §46.408(c) is that the former applies only to minimal risk research, while the latter applies to minimal as well as greater than minimal research. However, she noted that minimal risk research that does not meet criteria for a waiver of permission from a parent or guardian under §116(d) may still meet waiver requirement under §408(c) because §408(c) addresses harm posed by parent/guardian permission itself. The subcommittee considered when grounds for a waiver might exist under this provision of the regulations, other than in instances of neglect or abuse.

Recommendation 5: "Reasonable requirement." *In considering parent/guardian waiver under §408(c), IRBs should consider justifications for "not a reasonable requirement" beyond the example of "neglected or abused children" given within the regulation and include instances in which parent/guardian permission would jeopardize subject welfare or fail to provide additional subject protections.*

Recommendation 6: "Reasonable Requirement to Protect the Subjects." Three criteria were proposed for waiving parent or guardian permission under §408(c), assuming that an appropriate mechanism for protecting the children has been provided:

- *The investigator has provided a reasonable argument that informing parents may result in harm to the child or*

- *The investigator has provided a reasonable argument that parent permission may not be in the child's best interest because of conflicts in parental role as it relates to the research or*

- *Research involves adolescents and (a) it is important to population health, (b) subjects have consent capacity, (c) participation is voluntary, and (d) procedures are commensurate with State law.*

Examples of instances in which getting permission from a parent or guardian might be found not reasonable included a study of patterns of psychological risk and resilience in high school students who identify themselves as gay or lesbian, for which the investigator has offered a credible argument that serious physical, social, or psychological harm might come to the subjects if the parent or guardian is informed. A second example is a study of coping behaviors in adolescents who have joined an Al-Anon group because of an alcoholic parent, for which the investigator has offered a credible argument that the parent or guardian might not make a decision about study participation in the child's best interest.

In regard to the requirement that procedures be commensurate with State law, Dr. Fisher explained that State law may provide for a "mature minor" to be treated as an adult for certain purposes, even though the individual has not reached the age of adulthood as defined by State law. Legal requirements will vary among States. An example in which this criterion might be applied might be a study of the attitude teenage girls 14 and older toward different forms of birth control. The research can be shown to be important to the subjects' health and well being, there is empirical evidence that adolescents by the age of 14 are capable of understanding informed consent at adult levels, and the PI has provided assurance that the study participants understand that services will not be affected by whether or not they participate in the study. State law permits the girls to receive birth control and gynecological services, and the types of questions that will be asked are commensurate with those that would be asked as part of those services.

Recommendation 7: "Emergency Waiver". The subcommittee proposed that OHRP guidance clarify that IRBs may apply the Emergency Waiver to research involving children *even when parents or guardians are present* under special circumstances. Obtaining permission might not be feasible because:

- *The intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and*

- *There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.*

An example would be an instance in which the proposed study will compare the efficacy of two treatments for a life-threatening pediatric seizure disorder, both of which must be administered at the time of hospital admission. Clinical equipoise exists between two emergency treatments, and there is no way to identify prospectively the children who will become eligible for the research. Obtaining permission would delay treatment, endangering the child's health.

DISCUSSION, RECOMMENDATIONS 1-7

Discussion of Recommendation 1: "Adversely affect." In regard to the requirement that the IRB must find and document compliance with the requirements of §46.116(d), Dr. Prentice asked the Co-Chairs to clarify what would constitute appropriate documentation. He asked whether the written record would have to show how each of the four conditions had been met, justifying the waiver. Ms. Kornetsky responded that there should be some "meaningful reflection" that these things had been taken into consideration, possibly within the minutes. Dr. Prentice suggested adding this should be documented, without prescribing how. The Co-Chairs agreed that this was important. Dr. Fisher added that the IRB was not responsible for researching the conditions, only for ensuring they were met.

Dr. Prentice asked whether the subcommittee had considered recommending the use of a consultant to ensure that community norms had been taken into account, since community representatives on IRBs may not represent all populations within a community. Ms. Kornetsky said the subcommittee had not meant to limit the IRB's options and would be willing to give additional examples of how this criterion could be met.

Dr. Gyi noted that a number of slides reference State and local regulations, and he wondered whether the subcommittee had considered cases in which State and local regulations are silent, particularly in regard to respect for local norms. Ms. Kornetsky said that there was considerable variation across the country regarding readiness to grant a waiver of parental permission, but that she had concluded this variation is consistent with the purpose of having a local and cultural review. Referring to the Kennedy-Krieger experience in a lead abatement study, Dr. Gyi recalled that the decision to go forward had been criticized. Dr. Fisher said that part of the problem in that instance had to do with parents' lack of understanding of what the study was about. She believed the proposed guidance would provide a hedge against such a lack of understanding. She said the regulations do not restrict the use of centralized IRBs, but do require that they must be competent to take local norms into account. Dr. Gyi still felt the requirement might be prohibitive for oversight in such a setting, especially in the absence of State and local laws, given that it applies to minimal risk research. He was concerned about the administrative burden placed on the IRB by the requirement.

Dr. Fisher said that there was, however, a difference between documentation and verification. She said the investigator should not receive a waiver without justification or documentation of why the

waiver was considered justified. Dr. Prentice agreed, noting that the investigator should be held responsible for presenting sufficient rationale and justification. He asked Dr. Gyi how often independent IRBs receive requests for waivers. Dr. Gyi did not believe the numbers are huge. Ms. Kornetsky observed that HHS and FDA regulations differ in regard to criteria for granting a waiver.

Ms. Selwitz commended the subcommittee for providing excellent, practical guidance. In regard to the issue of local norms, she doubted it was unusual to have subject populations that cross State lines. Dr. Fisher agreed, suggesting that the term "local" might be confusing. The point, she said, is that parents' perspectives must be considered. Ms. Selwitz suggested that alternative wording be considered.

Mr. Adams asked for further clarification about the age at which children were held to be old enough to give informed and voluntary assent. Dr. Fisher said the literature demonstrates that by age 14 or 15 children are generally able to understand their rights and elements of informed consent in the same way as adults. However, ensuring that their participation is voluntary is a separate issue. Ms. Kornetsky added that the subcommittee does not intend to be prescriptive about the age; much would depend on the nature of the research and what is being asked of the child.

Dr. Prentice stressed that a waiver of parental permission should not be done lightly or without considering norms and values. Dr. Jones was concerned, however, that the requirement would constitute a barrier to research. The Chair rejoined that while the recommendation means that investigators must consider the community's norms and values, it does not prescribe the kind of demonstration that is appropriate.

Ms. Selwitz raised the question of what documentation was expected of the IRB. Ms. Kornetsky said the guidance was intended to provide a reasonable way to think about the requirements. Dr. Prentice said the extent to which documentation was required would depend on the specific situation. The recommendation is not a new regulation, but guidance on how to meet the existing one.

Discussion of Recommendation 2: "Practicably." No further discussion.

Discussion of Recommendation 3: Limitations on "Practicably." Dr. Prentice called attention to the following clarifying phrase: "Guardian permission should never be waived under §46.116(d)(3) for convenience nor waived solely for reasons of cost or speed or other expedient measures *if doing so weakens protection of subjects' rights and welfare.*" He asked about the rationale for adding this qualifier. Dr. Fisher responded that the subcommittee had determined that if cost or speed were completely ruled out, it might lead to research that fully protected children being done less efficiently. Dr. Weiner added that the issue is not limited only to cost or speed, but any expedient measure.

In regard to the proposed limitation on practicability, Dr. Gyi raised the issue of how to ensure that grant applications are not being approved without sufficient funding to provide the protections being discussed. Dr. Fisher said IRBs should make it clear to funding agencies that they will not compromise their obligations to protect human subjects because of budget cuts. Dr. Barratt of the National Science Foundation (NSF) said her agency always looks at the issue of appropriate costs for conducting the research and sometimes gives grantees more than they requested for this reason.

Discussion of Recommendation 4: Passive Consent. No further discussion.

Discussion of Recommendation 5: Reasonable requirement. Dr. Jones noted that this recommendation used the term "subject welfare" while Recommendation 6 used the term "best interest." She asked whether the terms had the same meaning. Dr. Fisher said that "welfare" is

connected to harm, but the words that follow – "or fail to provide additional subject protections" – address the potential for conflicting aims.

Discussion of Recommendation 6: "Reasonable Requirement to Protect the Subjects." Dr. Jones questioned the second criterion – parent permission may not be in the child's best interest – on the grounds that this criterion goes beyond a presumption of harm. She felt care was needed in extending and broadening the phrase to this extent. Dr. Fisher said that the literature refers to what is or is not in the child's best interest, and this has not been a point of controversy. Dr. Jones pointed out that research is not always in the child's best interest. Dr. Fisher said, however, that the interest of the population of subjects would also have to be considered. The IRB must consider whether, given the topic of research, the parent might not be able to make a decision that is in the child's best interest. Also, one must bear in mind that the IRB has already made a determination about potential harm to the child. The issue at hand is how the individual participant would be affected by the research, and the parent might not be able to make this determination because of a conflict of aims, for example.

Dr. Fisher added, however, that paternalism, or scientific values overriding parental values, was not the subcommittee's intent; she was open to finding a more conservative terminology that could protect against this interpretation. Dr. Weiner suggested that it would help to clarify the circumstances in which the type of conflict envisioned might occur.

Dr. Patterson suggested changing the wording of the first criterion, "informing parents will harm the child," on the grounds that it is the behaviors or decisions that could result from this action that are the source of concern. Dr. Fisher agreed to consider new wording.

Discussion of Recommendation 7: Emergency Waiver. Dr. Prentice pointed out that the example given does not seem to meet the requirements of an emergency waiver, which is that "available treatments are unproven or unsatisfactory." Subcommittee Co-Chairs agreed to clarify the example. Also, Dr. Prentice noted that the waiver was intended to apply whether the parents are present or not, and Co-Chairs agreed to make this clear as well.

Dr. Patterson questioned whether, in the example given, it was really not feasible to get the parents' consent. She suggested resting with the language of the current regulation. Dr. Fisher felt the subcommittee was clarifying what was already contained in the regulation. Dr. Prentice expressed concern, however, that enrolling a child in a randomized critical trial when the parents are present opens a "Pandora's box" in terms of liability. He said that applying a waiver when there is no legally authorized representative is problematic in itself. Ms. Selwitz suggested narrowing the concept using a different example.

Other Discussion: Dr. Prentice asked when appropriate subjects would be provided with additional pertinent information after participation. Co-Chairs responded that they had not addressed this issue, but that they could ask the subcommittee whether this would be different for children than for adults. Dr. Fisher said the regulations seemed sufficiently clear on this point.

The Chair asked Co-Chairs whether the subcommittee had considered unique aspects of rights for parents of minor subjects, other than those specifically identified in the regulations. Dr. Fisher said the subcommittee had chosen not to define these rights outside of what might be in Federal, State, or local laws. They were concerned to avoid specifying rights in a way that might limit existing laws. Participants should call the IRB in order to get additional information on the subject.

MOTIONS AND ACTIONS, RECOMMENDATIONS 1-7

Recommendation 1: "Adversely Affect." ***Approved with one abstention. One change was made***: "The IRB should consider…local norms" was revised to a criterion that "the investigator has adequately considered the norms of the community from which subjects will be drawn."

Recommendation 2: "Practicably." ***Unanimously approved*** as written.

Recommendation 3: Limitations of "Practicably." ***Unanimously approved with two changes***. The word "weakens" was substituted for "dilutes." Also, "cost or speed" was revised to "cost, speed, or other expedient measures."

Recommendation 4: Passive Consent. ***Unanimously approved*** as written.

Recommendation 5: "**Reasonable Requirement."** ***Unanimously approved*** as written.

Recommendation 6: Criteria for "Reasonable Requirement to Protect the Subjects."
Unanimously approved with the following new wording for criteria 1 and 2:

1. The investigator has provided a reasonable argument that informing parents may result in harm to the child, or

2. The investigator has provided a reasonable argument that parent permission may not be in the child's best interest because of conflicts in the parental role as it relates to the research, or…

Recommendation 7: Emergency Waiver. The following revision was proposed: "….when parents/guardians are either present or not present." Recommendation 7 was ***tabled.***

Child Assent

Dr. Fisher reminded SACHRP that assent refers to a child's affirmative agreement to participate in research. She explained that the following recommendations apply to minimal risk research.

Recommendation 8a: "**Ensuring §402(b) Compliance**." *When an IRB determines that a child is capable of assent, it should ensure that the protocol describes how assent procedures will meet the requirements of §402 (b).* For example, Dr. Fisher cited a study in which a PI plans a blood draw and indicates that children will be told that the blood draw will help researchers better understand how children's bodies work. The IRB directs that children also be told that their participation is voluntary.

Recommendation 8b: "**Assent Waiver under §116(d).**" *In evaluating whether assent should be waived under §116(d) for research involving no greater than minimal risk, the IRB should determine that:*

1. *Research involves no greater than minimal risk.*
2. *Requirements for parent/guardian permission have been met,*
3. *Waiver of assent does not violate federal, state, or local law,*
4. *Scientific validity would be compromised without the waiver, and*
5. *The PI has presented evidence that alternative methods to obtain assent are not feasible.*

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

Recommendation 9: "Protecting Children's Dignity for All Research involving Children." *When the child's views may not ultimately be determinative, the investigator or parent/guardians should solicit the child's perspective without promising to follow his or her wishes. Investigators should only invite a child's decision about study participation when they intend to honor that decision. The practice of asking a child for a decision, then disregarding that decision if it conflicts with what the investigator or parent/guardians wish, is unacceptable.*

The subcommittee found the practice of asking a child for a decision and then disregarding it if it conflicts with the wish of the parents or guardians or the investigator to be unacceptable. A child's decision should not be requested unless it will be honored.

Recommendation 10: Documentation Discretion for Assent. When the IRB determines that assent is required, it should also determine whether and how it should be documented. Often, IRBs require children's signatures because they think they have to; however, in many instances these signatures are developmentally inappropriate and therefore meaningless.

- *IRBs should use the discretion permitted in federal regulations for different documentation procedures (e.g., child's signature or documentation in investigator notes that assent was granted verbally).*

- *To make such determinations, IRBs should draw upon knowledge of the child's developmental level and how different documentation procedures will best serve the goals of assent for particular research protocols and populations.*

DISCUSSION, RECOMMENDATIONS 8-10

Discussion of Recommendation 8a: Ensuring 402(b) Compliance. Dr. Gyi was concerned that the recommendation implied the protocol would have to be rewritten following IRB review. Dr. Prentice said this was not his understanding; rather, the recommendation simply means that the protocol should describe the assent procedures.

Discussion of Recommendation 8b: Assent Waiver under 116(d). Dr. Prentice confirmed that there would be instances in which the child's assent is waived, but the parents' permission is not waived.

Dr. Patterson asked whether item 4 is a new element or a refinement. Ms. Kornetsky said scientific validity is really one example of an instance in which assent is not practicable, and the language could be broadened to reflect this. It is intended to be an interpretation of the existing regulation that shows how an investigator might think about meeting the requirement.

Discussion of Recommendation 9: Protecting Children's Dignity for All Research involving Children. Dr. Prentice underlined the importance of this recommendation, which addresses a real problem.

Discussion of Recommendation 10: Documentation Discretion for Assent. Dr. Powell asked for verification that this recommendation, also, applies to all research involving children. Dr. Fisher said this was intended.

MOTIONS AND ACTIONS, RECOMMENDATIONS 8-10

Recommendation 8a: Ensuring 402(b) Compliance. ***Unanimously approved*** with new wording: "When an IRB determines that the subject population is capable of assent, it should ensure that the protocol describes how assent procedures will meet the requirements of 402(b)."

Recommendation 8b: Assent Waiver under 116(d). ***Unanimously approved*** with new wording that says that "the IRB may consider the following" rather than "should determine that." The fourth criterion now reads: "The study could not be practicably conducted (e.g., scientific validity would be compromised without the waiver)."

Recommendation 9: Protecting Children's Dignity for All Research involving Children. ***Unanimously approved*** with the clarification that the recommendation applies to research involving children.

Recommendation 10: Documentation Discretion for Assent. ***Unanimously approved with language added*** to clarify that the recommendation applies to all research involving children. Also, new language refers to "knowledge of the developmental level of the subject population." In response to public comment, appropriate language will be added by the subcommittee to reference State law.

Future Considerations

Dr. Fisher explained that FDA did not adopt the 408(c) waiver of parent/guardian permission in its Subpart D. Consequently, there is a lack of harmonization between OHRP and FDA regulations. FDA's initial decision to exclude this waiver was based on concern that the examples given for 408(c) were not the type of research regulated by the FDA, which was supported by a survey of FDA-regulated research identified only one study to which this would be applicable, and concern that it would be inconsistent with other Federal regulations regarding devices that require informed consent. Currently, FDA is consulting with other agencies on inclusion of a similar regulation in its own final regulation.

The subcommittee proposed that FDA address the following questions as it proceeds to consider harmonization:

a) To what extent might parent permission be waived for FDA-regulated research involving no more than minimal risk? Are there examples of such research?

b) Are there risks to child subjects unique to FDA-regulated research that are not adequately protected in Subpart D? Is there something unique about FDA's research that warrants a more stringent parental permission rule?

c) Does an absolute prohibition against parent permission waivers deprive some populations now or in the future of FDA regulated research that has the potential to significantly improve their health and welfare?

d) Does lack of harmonization jeopardize future joint FDA/ OHRP 407 reviews?

e) Has lack of harmonization created confusion and inconsistency in IRB review of research regulated either by OHRP or FDA?

f) If a 408(c) equivalent were added to FDA regulations, could language be included to require that protocols must meet the most protective standard (e.g., device regulations) or any other standards that would be consistent with such a waiver?

Dr. Lepay, an *ex officio* member who represents FDA, commented that this area has generated ongoing discussion for some years since the interim final rule was put into place at FDA. In addition to the concerns referenced by Dr. Fisher, FDA has been concerned about how the agency would establish and operate §50.54 panels equivalent to §407 panels; however, these issues have now been largely resolved. Remaining considerations include consistency with laws (not regulations) regulating devices, which FDA does not have authority to change, and regulations for drugs and biologics, where there is more flexibility. He noted that few FDA-regulated studies are minimal risk. While there are some risk devices in this category, the more "classic examples" are significant risk devices, drugs, and biologics. Consequently, the agency has some concern about what the justification would be to proceed with similar regulations in its particular environment. To date, he is unaware of relevant examples.

Dr. Fisher also highlighted some of the subjects the subcommittee expected to explore in future deliberations. She said members had identified one of the conditions under 408(c) in which assent can be waived that may not be clear. The regulation states "that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is only available only in the context of the research." It is not clear whether this would apply to available health coverage, non-responders to available treatments, or experimental treatments not yet available to the public.

The subcommittee also intends to continue its exploration of issues related to §404 including clinical equipoise, component analysis, and alternative treatments. Members also noted that the Institute of Medicine (IOM) recommended that SACHRP "develop guidelines for research with economically and educationally disadvantaged participants for use by OHRP in issuing guidance for researchers and IRBs." For the children's subcommittee, this might mean considering protection issues related to wards of the State.

PUBLIC COMMENT

The Chair invited members of the public to comment.

Ms. Cami Gearhart said she was with the Quorum Review IRB, an independent IRB in Seattle, Washington. She underlined the importance of considering community norms and said this was an issue IRBs struggle with frequently. She noted that a variety of mechanisms are available to assess community norms, and FDA has published guidance on possible strategies for assessment earlier this year. She felt that maintaining a diverse IRB membership sensitive to community norms was one of the strongest mechanisms for ensuring that local attitudes are understood.

In regard to Recommendation 10, which allows IRBs to use the discretion permitted by Federal regulations in documenting assent procedures, she noted that State law may be pertinent as well. For example, California requires that documentation must be provided for children six years old and above.

She informed SACHRP that her IRB, which focuses on FDA-regulated research, has not experienced problems in reconciling the requirements of FDA's Subpart D related to parental consent with those contained in HHS regulations.

Ms. Gearhart also commented, in reference to the issue of compliance with procedures for securing child assent under §46.402 (b), that a central IRB will need to consider not only the requirements of the protocol,, but also the procedures and processes used at each investigative site to secure children's assent. She expressed appreciation for the care that SACHRP is taking in the wording of its recommendations and she said her IRB is finding the committee's work extremely helpful.

Dr. Prentice thanked her and agreed that State law should be referenced in Recommendation 10 as suggested. *He asked Co-Chairs Dr. Fisher and Ms. Kornetsky to ensure the language is added*. He also said he understood her suggestions regarding protocol review, but said he interprets the word "protocol" as including site-specific extensions of the protocol.

OHRP's Draft Guidance on Adverse Events and Unanticipated Problems
Michael A. Carome, M.D., OHRP

Dr. Carome observed that there have been requests for harmonized guidance on adverse events (AEs) from a variety of interested parties for many years. When Dr. Schwetz was appointed acting director of OHRP, an HHS press release announcing the appointment noted that one of his priorities would be harmonizing the reporting of AEs. SACHRP has addressed the issue in December of 2003 with a panel on the topic and also passed a resolution in March 2004 recommending that OHRP and FDA promptly issue clear and consistent joint guidance on IRB review of both internal and external AE reports. In multi-center trials, he noted, external AEs may be particularly time consuming and problematic.

Shortly after this recommendation was made, the Federal Adverse Event Task Force was formed, with membership that includes the *ex officio* members of SACHRP. The task force has taken on a number of initiatives to harmonize guidance and address issues related to AEs. It reviewed several iterations of guidance on adverse events and provided comments. This draft guidance has now been posted on the OHRP Web site for a 90-day public comment period (October 13 through January 13). OHRP anticipates issuing a final guidance document in the spring of 2006.

The development of guidance is expected to be the first of several initiatives by agencies working cooperatively on the issue. The ultimate goal of these initiatives is to ensure that reporting and analysis of AEs are timely and meaningful.

The guidance is structured to address ten key questions. Questions and key elements of the proposed guidance were discussed.

What are AEs? No definition is proposed, since there are already many definitions and the concept does not seem to be problematic. Examples are used to illustrate this broad term. The words "unexpected" and "unanticipated" are seen as equivalent.

What are external and internal AEs? Internal AEs are those that occur at the site for which the IRB has responsibility. External AEs are those occurring in the context of multicenter research in which a subject experiences an AE at a site other than the site for which the IRB is responsible..

What are Unanticipated Problems (UPs) and how do they relate to AEs? Unanticipated problems are events that are not expected or anticipated given the nature of the research procedures and the subject population and that suggest that research places subjects or others at greater risk of harm or discomfort than was previously known or recognized. Three categories of AEs that are considered UPs:

- AEs that are serious, unexpected, and related or possibly related to participation in the research;
- Serious AEs that are expected in some subjects but are determined to be occurring at a significantly higher frequency or severity than expected; and
- Other unexpected AEs, regardless of severity, that may alter the IRB's analysis of the ratio of risk to potential benefit and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

How do you determine which AEs are UPs that need to be reported under 45 CFR part 46? Guidance on this question was not discussed in the presentation.

What should the IRB consider at the time of initial review with respect to AEs? The IRB should ensure that, if appropriate, there is an adequate plan to monitor data, including AEs and UPs, and that the full spectrum of AEs has been considered. The IRB itself is not the appropriate entity to monitor research. OHRP would recommend, but not require, monitoring plans to include the following elements:

- Type of data or events to be captured,
- Who will be responsible for monitoring the data collected and their respective roles,
- Time frames for reporting AEs and UPs,
- Frequency of data assessments,
- Definition of specific triggers or stopping rules that will dictate when some action is required, and
- As appropriate, procedures for communicating the outcome of the reviews by the monitoring entity to the IRBs, the study sponsor, and other appropriate entities.

How should reports of external AEs, internal AEs, and UPs be handled? It is neither useful nor necessary under the regulations for reports of AEs to be distributed routinely to investigators or IRBs at all institutions conducting the research. Ideally, AEs should be submitted for review and analysis by a central monitoring entity that would determine whether a report of the event should be distributed to all sites. The reports distributed by the central entity or sponsor should explain why that AE or series of AEs represented a UP and propose a response. One proposed approach to handling AEs – which is not the only or prescribed approach – is comprised of the following chain of events:

- If PI or IRB at a particular site propose changes in the research, consultation with the study sponsor or coordinating site should occur.
- Only the institution at which a particular AE has been determined to be a UP needs to report to the agency head and OHRP. Generating a hundred reports is not necessary or helpful.
- For internal AEs, OHRP recommends identical procedures, except that the PI should report to the central monitoring entity, if required, and the institution should report to the agency head and OHRP.

What is the appropriate time frame for reporting UPs? The HHS regulations require *prompt* reporting, but do not define what this means (although FDA has done so in its own regulations). The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm. In general, OHRP interprets *prompt* to mean that the report is given within a couple of weeks from the time when a determination is made that an event represents an UP. However, the appropriate time frame varies depending on the specific circumstances. In some cases, the requirement to report promptly may be fulfilled by submitting a preliminary report.

What should the IRB consider at the time of continuing review with respect to AEs/UPs? This question was not discussed further during the presentation.

What interactions should occur between IRBs and DSMB/DMC with regard to AEs and UPs? When a DSMB/DMC determines that an AE or series of AEs represent a UP, the DSMB/DMC should follow procedures for ensuring that this event is reported promptly to the PI/IRBs at each participating site. OHRP recommends that if the DSMB/DMC determines during monitoring that AEs are occurring at the expected frequency and severity level – that is, there are no unanticipated AEs – the DSMB/DMC or study sponsor submit a periodic report to that effect to the PI and IRB at each study site.

What should written IRB procedures include with respect to reporting UPs? This question was not discussed further during the presentation.

DISCUSSION

Harmonization. Dr. Prentice asked to what extent FDA was "on board" with this draft guidance. Dr. Carome noted that FDA was included on the task force and had the opportunity to review and comment on several iterations of the draft guidance. Many substantial revisions were made in response to their comments, as well as those of other task force members. The Chair asked whether guidance would be issued if FDA did not agree to issue it as joint guidance, and Dr. Carome responded that it would be issued as OHRP guidance. Dr. Patterson added, on behalf of the Federal Advisory Task Force, that the agencies are hopeful that FDA will issue guidance consonant with OHRP's guidance and hopeful that the two documents will support each other.

Dr. Lepay confirmed that FDA is "on board" and intends to develop guidance in the area. The agency is interested both in OHRP's guidance and in the related public comments, which will direct FDA to key "pieces" that must be taken into account. Currently, he said, sponsors report to FDA but not to the IRBs, and it is not possible to require changes in what is being required of sponsors without rulemaking. When Dr. Fisher asked Dr. Lepay to identify any significant barriers to implementing the proposed guidance from FDA's perspective, Dr. Lepay reiterated that FDA had worked in harmony with OHRP during development, though it will be providing written comments on some areas about which the agency has concerns.

Dr. Gyi underlined the critical importance of FDA issuing guidance as soon as possible. He was particularly concerned that the agency takes action to reduce the burden on IRBs. Dr. Lepay assured SACHRP that the issue was high on the agency's agenda and said he expected FDA guidance to be issued soon, though the clearance process was not in his direct control. He said FDA agrees that individual unanalyzed reports to the IRB are not helpful to the IRB and do not add protection to human subjects.

Ms. Kornetsky stressed the importance of harmonized guidance by OHRP and FDA, noting that differences will cause a real problem and undermine the work that has been done. She added that education will be needed regarding reporting obligations. The examples given in the guidance were seen as extremely helpful.

Time frame. Dr. Prentice also asked about the proposed time frame for releasing guidance and inquired about the number of comments received to date. Dr. Carome responded that the target release date is spring, 2006. So far, OHRP has received comments from 7 or 8 from individuals, generally positive. It is too early to have a feel for public reaction.

Suspension of research. Dr. Prentice asked whether OHRP guidance states that the IRB only has the authority to suspend or terminate approval of research if there is unexpected serious harm. Dr. Carome explained that OHRP believes that IRBs have broad authority to suspend research for any reason.

Reportable event. The Chair then asked for further clarification of what constitutes a reportable event. Dr. Carome said that if the IRB determines that a particular event is an unanticipated problem involving risk to subjects or others that makes it a reportable event. Dr. Prentice asked how an AE that is not held to be an unanticipated problem would be handled. Dr. Carome said that if guidance is followed, an external AE would not be reported unless it is found to be an unanticipated problem. If there is no such finding, one approach would be for the investigator to review the report and make the initial judgement, conferring with the sponsor if necessary. In the event that the external site did not call the event a UP but the IRB receiving the report concludes that it should be considered a UP, it should be reported to OHRP (although the guidance does not address this directly). One way to handle this would be for the investigator to confer with the sponsor or coordinating site, explaining reasons for this determination; it is hoped this would result in a report from the coordinating site or from the site at which the event occurred. If there was resistance from these sites, the site that believed a UP occurred should then report it to OHRP.

Dr. Prentice asked whether, after receiving such a report, OHRP would be obligated to report it to other participating sites. Dr. Carome said that if OHRP agreed that there was a serious event that could expose subjects to avoidable harms, it would have to consider taking action to be sure sites are informed and could take action to avoid that harms. This would probably require conferring with the sponsor. Dr. Carome then underlined the expectation that a clear monitoring plan would address reporting responsibilities prospectively.

Unanticipated problem. The Chair observed that the section of the regulations dealing with unanticipated problems has not been changed since the Common Rule was promulgated. He asked Dr. Carome to verify that nothing has changed since this time. Dr. Carome agreed.

Ms. Selwitz asked who makes the determination of what time frame is appropriate. Dr. Carome said OHRP had not specified an answer, and he was uncertain whether the responsibility should belong to the IRB or the investigator. He invited comments on the topic. Ms. Selwitz noted that her IRB attempted a reporting system quite similar to the one recommended, but it has not been working because of difficulties with the FDA "side of the house" and with industry sponsors. She therefore underlined the importance of harmonization in determining whether or not the system proposed can be implemented effectively.

Ms. Selwitz observed that the proposed definition of "unanticipated problem" appeared to be broader than the one approved by the Institutional Biosafety Committee (IBC); she asked whether IBC had plans to broaden its definition. Dr. Patterson said she did not perceive significant differences and asked for illustrations. Ms. Selwitz agreed to send her some illustrative examples.

Reporting process. Because of a concern to avoid duplicative reporting, Ms. Selwitz asked for clarification on whether AE reports were expected from both the sponsor and the PI. Dr. Carome said the intended flow was from sponsors, to PIs, to IRBs. Dr. Gyi suggested, however, that while this flow would work well when there is a one-on-one relationship, if there is a many-to-one relationship the sponsor should submit one report to the IRB on behalf of multiple investigators.

The Chair suggested that SACHRP determine the appropriate time for reports from OHRP and FDA at future meetings.

Subpart A Subcommittee Report
Felix Gyi, Pharm.D., M.B.A., CIP, Co-Chair; Daniel Nelson, M.S., CIP, Co-Chair; Gary Chadwick, Pharm.D., MPH, CIP

Mr. Nelson reviewed the charges of the subcommittee, which included to review and assess all provisions of Subpart A of 45 CFR 46 and relevant OHRP guidance documents, then, based on this review and assessment, to develop recommendations for consideration by SACHRP. Specific goals of the subcommittee are to

- Enhance protection of human subjects,
- Reduce regulatory burdens that do not contribute to the protection of human subjects, and
- Promote scientifically and ethically valid research.

Subcommittee meetings to date have included a January 18, 2005 teleconference; a meeting February 14, 2005 in Alexandria, VA; a May 20, 2005 teleconference; a meeting July 20-21 in Alexandria, VA; and a teleconference on October 4, 2005.

Working groups have been established for continuing review and for expedited review. At its second on-site meeting, the subcommittee reviewed draft reports from each subcommittee, considered issues related to minimal risk, and heard input from federal agency representatives.

Continuing Review

Dr. Chadwick continued with the subcommittee's presentation. He stressed that the topic of continuing review (CR) is intertwined with subjects addressed in other reports, such as expedited review, adverse events, investigator responsibilities, and criteria for review and approval. Consequently, recommendations may need to be rethought as related work is presented and other decisions are made.

The speaker reminded SACHRP that the regulations grew out of the infamous syphilis study that came to light in the 1970s. A major concern about that study was that it continued so long without review or oversight. To prevent this happening again, regulators wanted a mechanism that would ensure research is reviewed on an annual basis, providing a "snapshot" of how things are going. The goal was to prevent continuing research activities in the face of unacceptable harm, futility, or technological or ethical obsolescence.

The subcommittee assumed that CR plays a central role in the IRB process and is an important tool. At the same time, it assumed any practices that do not demonstrably enhance the safe and ethical conduct of research diminish human subject protection.

Duration of Continuing Review: Only §109(e) addresses the Continuing Review process. Dr. Chadwick observed that the regulations give wide latitude to IRBs as to what they will consider in continuing review, and the area has engendered many requests for clarifying guidance. The subcommittee considered 14 questions. The first was: *When can continuing review stop?* HHS regulations do not address this question, and existing guidance is not sufficiently specific. In current practice, for example, cooperative oncology studies often remain open for many years simply to track the deaths that occur in the cohort of participants.

> **Recommendation 1.1: Duration of Continuing Review**. *OHRP should revise/clarify existing guidance on the required duration of IRB continuing review. For this guidance, the Subcommittee*

recommends clarifying that a study ends when all interventions are over and/or data collection is complete, as described in the approved study plan/protocol, at the research site for which the IRB has oversight.

The subcommittee believes that a revision of existing guidance could address this point. Guidance should state that a study ends when all interventions are over and/or the data collection is complete at the research site for which the IRB has oversight.

Members pointed to examples that illustrate the complexity of the topic. Dr. Weiner noted that in phase one studies, there may be a handful of children who are surviving as a result of a novel therapy although the data collection is complete. The cooperative group has agreed to keep the trial open in such cases, while the operating center continues to ensure sites are conforming to whatever procedures are relevant. After this, the treating physician may file a compassion use protocol. Dr. Chadwick rejoined that this instance still involves an ongoing intervention for which continuing review could reasonably continue. The subcommittee's concern extends to instances in which the drug or therapy is no longer being administered. Dr. Prentice added that a physician could be informed of new information by the cooperative group regardless of whether an open protocol existed.

The subcommittee was concerned about instances in which the principal investigator completes all work with human subjects, but takes years to complete the analysis. This could occur, Ms. Selwitz observed, in a single as well as multi-site study. Mr. Nelson said the practice in the field appears to be that as long as there as there is data in someone's hands, the study must remain open and CR is required. Dr. Prentice introduced another example in which children are off the therapy but are being followed for decades – an instance in which he sees no value to keeping the protocol open, since human subject protection is no longer an issue.

Dr. Chadwick said that FDA and OHRP expectations in such instances are different. For FDA, Dr. Lepay confirmed, IRB oversight can stop once a study has completed data collection, even though analysis is incomplete. Ms. Borror from OHRP confirmed that a determination from OHRP indicates that CR must continue as long as analysis of private identifiable data is ongoing. Ms. Kornetsky added that in a multicenter FDA trial, one site may remain open while another has completed its work and closed.

Members focused on the issue of whether the collection of survival data should require continuing review. Dr. Prentice clarified that in a cooperative study, survival data goes to the cooperative group (in coded form) rather than to the individual site. In such an instance, he said, there is no value to keeping the study open at multiple individual sites. Ms. Selwitz added that if there were a breach of confidentiality, that information could still be brought to the IRB's attention, regardless of whether there was a currently active protocol.

Members observed that "intervention" and "interaction with subjects" are regulatory language that would be clearer than original wording. Following discussion, original proposed language was clarified as follows:

For this guidance, the Subcommittee recommends clarifying that a study ends when all <u>research</u> interventions <u>or interactions with subjects</u> are over and/or data collection <u>for research purposes</u> is complete, as described in the approved study plan/protocol at the research site for which the IRB has oversight.

However, though they were in general agreement following discussion, members did not feel the recommendation was sufficiently clear. Dr. Prentice asked the subcommittee to consider the recommendation in light of cancer cooperative studies and make sure it did not open up any problems for such study.

Frequency of Continuing Review: The subcommittee explored the following question: Are there circumstances where continuing review can appropriately be conducted less often than once a year? Many believe that, for minimal risk research, the requirement for yearly review is not necessarily appropriate to the degree of risk. However, only an change in the regulatory wording would permit IRBs to set a longer review interval. The subcommittee therefore suggested that OHRP seek broad-based input on whether the regulation should be changed. Recommendation 2.1 was proposed:

> **Recommendation 2.1: Setting Review Dates Beyond One Year for MR studies.** *OHRP should issue an Advanced Notice of Proposed Rulemaking (ANPRM) to seek comments regarding changing section §46.109(e) to allow IRBs latitude in setting review dates beyond one year for minimal risk studies, but potentially for other studies as well.*

Dr. Chadwick observed that while there is no regulatory basis for the current content of the continuing review process itself, both HHS and FDA have pointed IRBs to the 8 criteria for study approval cited in §46.111 as the measure for continuing as well as initial study review. This seems to exceed the original intent of the regulations for a "simple process." In fact, he pointed out, the Preamble published with the regulations in 1981, states: "The precise procedure adopted by the IRB for continuing review [without unnecessarily hindering research] should be left to the discretion of the IRB."

The subcommittee felt that three major criteria should apply to continuing review: that the risk/benefit balance remains acceptable, that subject selection is equitable and appropriate, and that the safeguards employed in the original research remain effective.

> **Recommendation 2.2: Establishing Simplified Criteria and Expectations for CR.** *In the Advanced Notice of Proposed Rulemaking, OHRP should also seek comments on the regulatory application of §46.111 to continuing review, and/or adding a new section, that would define simplified criteria and the expectations for the content of continuing review being based upon current risk level.*

The subcommittee also proposed that, in the interim, OHRP revise existing guidance and issue new guidance on the subject.

> **Recommendation 2.3: Revising Guidance for Application of §46.111 to Continuing Review.** *In the interim, OHRP should revise its interpretation and develop new guidance to permit IRBs to develop, within their written procedures, policies and procedures for the selective application of section §46.111 to continuing review.*

Expedited Review: The subcommittee considered whether categories 8 and 9 from the expedited review list (November 1998), which are specific to continuing review, should be expanded or clarified. Members proposed that there are certain types of reviews where a full review is not needed. The current interpretation is that if anyone has been enrolled, a full board process is needed on a continuing basis, even if there has been no activity. The subcommittee disagreed with this interpretation and presented the following recommendation, which applies to multicenter trials:

Recommendation 3.1: Expedited Review Categories 8 and 9. *OHRP should modify its interpretation of expedited review category 8b so that expedited review is permitted if no additional risks have been identified at any sites and no interventions or other study activities have occurred at the IRB's research site since the preceding review. Guidance should be revised to reflect this interpretation.*

After Dr. Chadwick and Dr. Prentice illustrated the recommendation with examples, Recommendation 3.1 was unanimously approved.

The subcommittee felt that category 9 promotes flexibility as written. However, many IRBs are not currently using this category as widely as it might be and may need to be informed about it. Additional examples and expanded guidance might help IRBs to place studies in this category when appropriate.

Recommendation 3.2: Use of Category 9. *OHRP should revise its current guidance to give more examples of when continuing review is not necessary and when category 9 may be used.*

The recommendation was approved without further discussion.

Literature Searches: The subcommittee explored the question, "what is the role of the IRB in literature searches at continuing review?" The regulations do not require such a review, and this scientific activity should, members felt, be the responsibility of the investigator.

Recommendation 4.1: Responsibility for Literature Search. *OHRP should revise its guidance to clarify an expectation that the investigator is responsible for the review and interpretation of "recent and relevant" literature.*

Ms. Selwitz asked for a clarification of what section of the regulations made the IRB responsible for a literature review, and Dr. Prentice explained that the determination letter directed to Johns Hopkins is the source of the impression that IRBs will be held accountable for deficiencies in the literature search. Dr. Gyi explained that IRBs have now added staff trained to perform such searches, though he believes they should be the responsibility of the sponsor or investigator. Dr. Fisher agreed, but held that the IRB does have a responsibility to perform a meaningful evaluation of this information. The recommendation was clarified as follows:

OHRP should revise its guidance to clarify an expectation that the investigator is responsible for the review and interpretation of "recent and relevant" literature for IRB evaluation. Guidance should clarify that it is not an IRB responsibility to perform a review of the scientific literature or to verify the completeness of the investigator's search.

With this revision, Recommendation 4.1 was accepted unanimously.

Continuing Review for Exempt Research: The subcommittee also considered the application of CR to exempt research. The subcommittee considered that since there was no requirement for initial IRB review, there is also no justification for requiring continuing review. They noted, however, that OHRP has cautioned IRBs and institutions against allowing investigators to self-certify their studies as exempt. Consequently, IRBs are now making the determination that an exemption is appropriate. Many of them, unnecessarily, use an expedited review or even full board process to review potentially exempt studies. The subcommittee held that such unnecessary work harms the credibility of the process, and therefore made the following recommendation:

Recommendation 5.1: Continuing Review for Exempt Research. *OHRP should revise its guidance to emphasize that once a research protocol is determined to be exempt, and all subsequent research activities continue to meet exemption criteria, that there is no regulatory requirement for ongoing review.*

The Chair agreed that this made sense. Dr. Fisher, however, asked how it was possible to determine that subsequent activities meet exemption criteria without review. Dr. Prentice said some IRBs had clear policies that require the investigator to notify the IRB if the study no longer qualifies for exemption, while others require changes to come to the IRB. However, this would be considered a change in protocol, rather than a CR process. Ms. Selwitz then clarified that the recommendation does not prevent any IRB from doing a CR that wishes to do so. With these clarifications, Recommendation 5.1 carried.

Consolidating and Integrating Existing Guidance. Members observed that in order to get guidance on a particular topic, IRBs now need to consult a variety of online resources, including determination letters. The field needs simplified, unified, practical guidance. The subcommittee therefore made the following recommendation, adding that OHRP may wish to consider consulting with people in the field if it proceeds to implement these recommendations.

Recommendation 6.1: Regulations on CR vs. Interpretation. *OHRP should revise its continuing review guidance and clearly delineate those CR actions required by the regulations and those that are derived from the regulations by interpretation.*

Recommendation 6.2: Simplified, Unified, and Practical Guidance on CR. *OHRP should prepare simplified, unified, and practical guidance for CR that focuses on the substance of review.*

Recommendation 6.2 was unanimously approved without further discussion.

Review for UP and AE Reports. Section 103 requires "written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others." While the subcommittee felt it was reasonable and useful to review such cases, it noted that current HHS guidance states that IRBs should even review "adverse events." The subcommittee held that this would not be helpful or effective in protecting human subjects. However, because adverse event reporting and review is such a major problem for IRBs, and because other groups including OHRP, FDA, and NIH are actively addressing this topic, further discussion and the development of recommendations were deferred pending review of the recently released draft OHRP guidance and progress on a solution by other groups.

Interface between data monitoring committees (DMCs) and the IRB during CR. Only section 111(a)(6), addresses monitoring. Because this issue affects more than just continuing review, the subcommittee believes further discussion and development of recommendations on DMCs should be a topic for the full SACHRP group. Efforts to integrate or harmonize the HHS guidance, FDA guidance, and the many NIH policies on DMCs would provide a valuable opportunity to enhance substantive review – both initial and continuing. Defining an appropriate role for DMCs and clarifying the interface between IRBs and DMCs would reduce both investigator and IRB burden and improve the safety of human subjects. The presenter noted that this is a particularly important area to clarify, with repercussions that extend beyond CR.

"Resubmit-as-new Reviews." Some IRBs have established as institutional policy a "resubmit-as-new review." The subcommittee considered whether this should be considered a best practices model.

While members generally agreed that this is a helpful activity, it considered it only as an option for those institutions that would derive a value from the process. The subcommittee was concerned that recommending the practice in official guidance might make it a fixed requirement. Consequently, it recommended that this and other best practices models should be communicated by venues other than OHRP.

Setting the date of CR: Guidance states that "in order to determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs." However, the speaker said this approach ignores the actual process employed by most IRBs to ensure complete review and ensure that modifications necessary to approve research are properly accomplished. The speaker observed that the IRB almost always requests changes after the initial review of a protocol – a process that may take days, weeks, or months. This means that the first approval period is artificially shortened if it is pegged to the initial review meeting; protocol approval may actually come as long as six months later. In light of this, the subcommittee recommended a policy that allowed the chair to make a determination that conditions had been met after stipulations from the full board meeting that the approval was in essence equivalent or similar to the process that takes place under expedited review, in which the approval date is the date on which the "sign-off" by the Chair or experienced reviewer occurs.

The subcommittee believes that allowing IRBs to set the date to the day when the research receives its final approval is a more appropriate approach and prevents both premature research activities and artificially shortened approval periods. Such a policy is fully supported by the wording of the regulations, conforms to the intent stated in the 1981 preamble, and is consistent with the regulatory authority given to the IRB to extend to the Chair or experienced reviewers the full approval powers of the assembled board – i.e., the expedited approval process.

> **Recommendation 10.1:** *OHRP should revise guidance to reflect that the final IRB approval of a study "sets the clock" for continuing review. For multi-site reviews, this may differ by site.*

Dr. Prentice reminded SACHRP that regulations require IRBs to conduct CR at intervals appropriate to the degree of risk but no less than once per year. OHRP has interpreted this to mean that the research must be reapproved within the specified approval period. The subcommittee is proposing that the date when the final IRB approval letter goes out – which could theoretically be several months from the date of the IRB meeting – is the date that "sets the clock" for continuing review.

Ms. Kornetsky was concerned that investigators may "sit on things" for as long as nine months or even longer. This could mean that AEs are occurring at other centers involved in a multi-site study and the IRB is not receiving that information. Dr. Fisher agreed that updates would be required in this situation. Dr. Prentice noted that some IRBs have stated limitations on the time within which investigators must resubmit their protocols with required changes. Dr. Chadwick suggested that such issues should be address in IRB guidelines and policies.

Ms. Selwitz supported the recommendation because she felt it would be helpful to eliminate any confusion about the actual approval period in IRB records.

Recommendation 10.1 was unanimously approved.

The 30-Day Rule: Guidance states that "OHRP recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project. When continuing review occurs annually and the IRB performs continuing review *within 30 days* before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing

review must occur." Given the iterative process for approvals, the subcommittee felt, this guidance places an unnecessary regulatory burden on the review process and does nothing to enhance human subject protection. It causes artificially shortened review periods and sometimes causes "floating" expiration dates that are hard for IRBs and investigators to track. The "30-day rule" sets an artificially short window for granting approval that has no basis in the regulation. The need for review to be meaningful and substantive requires time for the IRB to ask questions, for the investigators to respond, and for the IRB to seek further clarification. These two requirements work against each other and therefore against human subject protection.

Dr. Chadwick observed that most IRBs send out notices of CR 90 or 60 days in advance, to which some investigators respond right away. If the IRB waits to process the data for as long as 60 days in order to ensure the reapproval is "closely yoked" to the expiration date as required, it is looking at out-of-date information.

> **Recommendation 10.2:** *OHRP should withdraw its "30-day rule" and allow IRBs to set more flexible review schedules.*

Members pointed to potential confusion in interpreting the recommendation. The primary area of concern was the potential length of the continuing review period, which could be considerably longer than 12 months in practice. Recommendation 10.2 was returned to the subcommittee for further work.

Temporary lapses: Guidance states, "if an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval."

Dr. Chadwick said that in instances in which the investigator has failed to submit a timely report, the research should stop. However, when the investigator has filed a report and the IRB is in the process of reviewing it, subcommittee members felt the research should not be automatically suspended. A caveat was included, however, to the effect that strategies should be in place to prevent routine delays and open-ended reviews, along with specified conditions and activities that would be permitted in such circumstances. Dr. Chadwick suggested that if the 30-day window "went away," there would be fewer automatic suspensions forcing lapses.

The recommendation was tabled pending further clarification by the subcommittee.

> **Recommendation 10.3:** *OHRP should modify guidance so that, when continuing review is underway, automatic study suspension is not required.*

Ms. Kornetsky asked what was meant by "underway"; would that mean the study is submitted to the IRB office or actually is in the process of being reviewed. Dr. Prentice expressed the opinion that having the materials "in the box" would be insufficient. Mr. Nelson wondered what it would mean to say someone is "looking at" the materials. Dr. Prentice suggested that when materials go to a specific reviewer, the CR might be considered underway. Mr. Kornetsky suggested, however, that IRB members initiate the CR when they begin reviewing the submission to be sure it is complete. Dr. Chadwick said the subcommittee's original intention had been that the CR is underway as soon as it is received. Members agreed that the subcommittee's intention was unclear and sent Recommendation 10.3 back for additional work.

Individual Subjects. The subcommittee also found varying interpretations of the meaning of "best interest of individual subjects" in the guidance just cited above. Despite clarifications from OHRP that this is not OHRP's intent, the subcommittee noted that some IRBs have interpreted "individual subjects" to mean that the IRB must process a request for each person remaining on the study. This change would be less necessary, however, if the "30-day rule" were no longer in effect. Accordingly, the subcommittee proposed the following:

> **Recommendation 10.4:** *Wording in current guidance that refers to "individual requests" should be revised to clarify that approval of a general request for all research subjects to continue in the research during the review process is acceptable.*

After Dr. Chadwick observed that OHRP has already clarified that this was its intent, SACHRP approved Recommendation 10.4 without discussion.

Verification from Sources Other than the Investigator: IRBs are required to verify "from sources other than the investigators that no material changes have occurred since previous IRB review." The work group found no significant concerns in this area and does not propose further review.

Accreditation Standards and Oversight: The work group considered the following questions: In light of accreditation standards, what types of oversight are appropriate and reasonable in CR? What data and information improves human subject protection? The work group and subcommittee discussed these questions and sought to identify areas of inappropriate burden. Members expressed the hope that both federal regulators and voluntary accrediting organizations would recognize and support the fact that different mechanisms can be used to achieve safe and ethical research. The subcommittee did not propose this observation as a formal recommendation.

Multi-site Reviews: The work group considered the following questions: For research sites with more than one IRB, does the CR need to be kept on the same board that made the initial approval? How do "specialty" IRBs that only conduct CR impact the process? The work group did identify a concern about the impact of multiple reviews being sent to a single continuing review board, which might become overloaded. However, the work group saw this as an instance in which it would be up to the institution to provide adequate resources to fulfill this obligation.

Documentation for CR: The work group considered the following question: what documents does the IRB need to be given to conduct a continuing review? Current HHS guidance states that "all IRB members should receive and review a protocol summary and a status report on the progress of the research" and "at least one member of the IRB should receive a copy of the complete protocol including any modifications previously approved by the IRB." The latter requirement is the source of the "five-year rule," which was intended to force investigators with multiple amendments and revisions into applying at least once every five years as if they were proposing a new study.

Subcommittee members felt that a "protocol summary" might or might not be a separate document; it should not be necessary to create a new document by cutting and pasting from other sources available to the IRB. Also, the subcommittee observed that if a primary reviewer system is used, there is no added benefit of requiring that all IRB members receive an extensive summary, however, the entire protocol should be available to all members on demand. The following recommendation was presented:

> **Recommendation 14.1:** *Guidance should be revised to State that a "protocol summary" may or may not be a separate document; that combination of information sources, such as consent forms and the CR application, appropriately constitute a "summary" for the members.*

Dr. Prentice asked Dr. Chadwick to clarify whether the recommendation still maintains that a member must have a copy of the complete protocol. Dr. Chadwick clarified that one person acting on behalf of the IRB must review the complete protocol.

Use of qualified IRB staff in CR: Dr. Chadwick pointed out that IRB professionals have now emerged, creating a new professional category that should be legitimized and recognized for their expertise.

> **Recommendation 14.2:** OHRP should clarify its guidance to state that qualified IRB staff may act as a consultant to the IRB and accomplish the review of the full study protocol.

Both Recommendations 14.1 and 14.2 were unanimously approved with minimal discussion.

MOTIONS AND ACTIONS: Subpart A Subcommittee, Continuing Review

Recommendation 1.1: Some changes were made to the recommendation (see above) but it was ***tabled.*** The subcommittee was asked to develop clear examples and consider its recommendation in light of issues that arise in cooperative studies.

Recommendations 2.1, 2.2, and 2.3: ***Tabled.***

Recommendation 3.1: ***Unanimously approved.***

Recommendation 3.2: ***Unanimously approved.***

Recommendation 4.1: ***Unanimously approved with revised wording.*** OHRP should revise its guidance to clarify an expectation that the investigator is responsible for the review and interpretation of "recent and relevant" literature for IRB evaluation. Guidance should clarify that it is not an IRB responsibility to perform a review of the scientific literature.

Recommendation 5.1: ***Unanimously approved.***

Recommendation 6.1: ***Tabled.***

Recommendation 6.2: ***Unanimously approved.***

Recommendation 10.1: ***Unanimously approved.***

Recommendations 10.2 and 10.3: ***Tabled.***

Recommendation 10.4: ***Unanimously approved.***

Recommendations 14.1 and 14.2: ***Unanimously approved.***

WEDNESDAY, NOVEMBER 2

Welcome and Opening Remarks
Ernest D. Prentice, Ph.D.

The Chairman provided an overview of events for the day. He also reminded attendees of upcoming meeting dates for SACHRP, which are:

- March 13-14, 2006
- July 31-August 1, 2006
- November 2-3, 2006

IOM Update: Report on Research Involving Prisoners
Larry Palmer, LL.B.

The Chairman reminded attendees that consideration of Subpart C resulted in establishment of an Institute of Medicine (IOM) committee to consider and articulate the ethical foundations of protection of prisoners involved in research. Mr. Palmer is a member of that committee.

Mr. Palmer explained that the committee will determine, after examining the modern context, whether the conclusions reached by the 1976 National Commission are appropriate today or should be updated. Specifically, committee will

- consider whether the ethical bases for research with prisoners differs from those for research with non-prisoners,

- develop an ethical framework for the conduct of research with prisoners, based on the ethical framework developed,

- identify considerations or safeguards necessary to ensure that research with prisoners is conducted ethically, and

- identify issues and needs for future consideration and study.

The whole purpose of the committee's work, he said, is to give SACHRP a framework that can be used to revise the recommendations. It hopes to have its report either ready for release by SACHRP's March, 2006 meeting, following deliberations, preparation, and extensive internal peer review.

Mr. Palmer said the committee includes bioethicists and people who have done research in prisons, with Nancy Dubler, Co-Chair of the SACHRP Subcommittee that addressed this topic, as an expert adviser. The committee also includes Steve Cambra, a former correctional official who worked in the California system. A prisoner liaison group was formed as well, with some very articulate members whose prison experience is recent. To further supplement its understanding of the prison environment, the subcommittee has done interviews with representatives of the Department of Corrections, supplemented by surveys. Others have aided the group through presentations. The committee has commissioned papers from experts to provide a basis for the report. Research assistants and consultants have also been used to assist in the literature review.

With Mr. Cambra's assistance, the committee also benefited from site visits to California prisons. One prison members visited was San Quentin, which is the reception center for all people going into the California prison system from northern California, a medium security prison, and a place where

more than 600 men on "death row" are housed. No weapons are allowed in prison in order to prevent their being taken from the guards. The yard is ethnically and racially segregated to reduce the threat of violence. Prisoners are controlled with nightsticks, and systems exist to protect prisoners who are being moved from violence by other prisoners.

Members also visited Vacaville, the medical facility for California, where Dr. Jack Beck – a member of SACHRP's subcommittee on prisoners as research subjects – gave a presentation. Mr. Palmer learned that there is a large aging population in prisons, and most prisoners die of diseases such as kidney failure, cancer, and diabetes. Vacaville has a hospice at which volunteers keep a 24-hour vigil with dying prisoners. While cells may be as hot as 95 degrees, the medical facilities are air conditioned.

DISCUSSION

SACHRP members posed a series of questions, which were addressed as follows:

Do you think we're not doing enough clinical research in prisons in general because of Subpart C restrictions? The committee's data gathering process is aimed at answering this question and will inform the committee's report; however, the speaker was not prepared to answer at present.

Do you think prison authorities are supportive of research in prisons? There is a great deal of interest in gathering data that may not fit the definition of research – for example, the effectiveness of techniques to control gangs, the health status of specific populations, or quality improvement data.

Considering differences in security measures, are there circumstances where it is simply not possible to do research in prison? Will there be disparities based on type of prison? In terms of clinical or behavioral research, California has a statute that bars biomedical research, and other States have restrictions as well. Some prison officials see the issue as one of access to treatment and are therefore supportive. The committee is seeking data from a broad array of states.

You have limited your comments to prisoners who are behind bars. Are you also addressing others who have had some of their civil rights removed but are not literally behind bars, perhaps including those in juvenile detention homes? Yes, the committee has receiving data on this topic and will address it.

Is the committee addressing private prisons? The committee has discussed them. The practice of contracting out the prison management function has been subject to litigation in some areas. Whether the prison is public or private, prisoners do have a legal right to healthcare (in fact, they are the only people in this country who do). That obligation cannot be removed by means of a contract. However, it is not yet clear whether or not more research might be occurring in private prisons. The committee will seek this information.

Will the committee be giving recommendations on some of the thorny concerns related to what constitutes incarceration in individual states so that it is clear how the issue should be approached on a State-by-State basis? The committee is trying to think about such problems systemically and provide a framework that will help SACHRP write regulations. It is getting a good idea of what is happening in States of different sizes and in those that have more privately run prisoners than others.

It would be helpful to SACHRP if the committee has addressed situations in which a study participant suddenly becomes a prisoner – including examining the different relevant subparts of A, B, C, and D – to identify any gaps in protection or bars to research.

You raised an interesting question about quality assurance, which is problematic across the board, not just in prisons. A concern of the committee is to ensure that research is not conducted under the guise of quality assurance. The subcommittee is aware of this concern. Mr. Palmer noted that a researcher could feel forced to cast a study as evaluation that the researcher would rather call research because of the need to publish results. The subcommittee also recognizes that people today share data in a variety of ways other than publication.

Do former prisoners see participation in research as a justice issue, i.e., they want opportunities to participate in research that would benefit prisoners? Or do they primarily fear exploitation? The committee has heard both perspectives. Some prisoners, particularly at Vacaville, feel competent to make the decision whether or not to participate in proposed research. The subcommittee is also aware that this issue is part of a larger tension highlighted in the Hastings Center report. Mr. Palmer noted that a recent presentation by the American Psychiatric Association (APA) claimed that prisons constitute the largest mental health treatment system in the country. The mental health issues in prison, and the cycles of people going in and out of the prisons, add another layer of issues to be taken into account.

Update of FDA/OHRP Joint HHS 45 CFR 46.407 ("407") Review Process
Sara Goldkind, M.D., Ph.D., FDA; Kevin Prohaska, D.O., CDR-PHSC, OHRP

Remarks by Kevin Prohaska

Dr. Prohaska updated SACHRP on recent changes to the §407 review process following SACHRP's recommendations in the spring of 2004. He reminded SACHRP that the §407 process addresses research involving children as subjects which the IRB cannot approve under sections 404, 405, or 406, but which the IRB feels presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Review of the proposed research is accomplished by a panel of experts who make recommendations to the HHS Secretary. Between 1991 and the November of 2002, 12 such panels were convened, all of which were closed.

SACHRP made several recommendations that were forwarded to the HHS Secretary on July 8, 2004, who responded affirmatively on Dec ember 29, 2004. The recommendations were intended to improve the effectiveness and efficiency of these reviews. They included the following:

- OHRP should screen all requests and provide guidance to the institution. This provides an opportunity to detect and return any deficient application to the IRB for further consideration under §404, §405, and §406.

- The review process should be open, with more opportunities for public participation (including via review of materials posted on the Web).

- The expert panel should include at least one member of the public (i.e., an advocate in the subject area).

- OHRP and FDA approaches should be harmonized.

- The §407 process should be monitored.

- The Subcommittee on Research Involving Children (SRIC) and SACHRP should receive regular updates.

OHRP issued related guidance in May of 2005 which is available on the Web site under the children's page. The guidance outlines necessary IRB findings to justify a request for a §407 review and the steps necessary in submitting a package; explains possible OHRP responses to such a request; and gives details about the review itself and its possible outcomes. OHRP now updates SRIC at monthly meetings and provides annual updates to SACHRP (this being the first).

When a request is received, OHRP now does an initial assessment, as recommended by SACHRP. It then forwards materials to FDA so it can determine whether its regulations apply. If they do, OHRP has delegated authority to the FDA to convene the review panel. However, if this is the case, OHRP remains engaged and consults with FDA frequently to facilitate the process. Mr. Prohaska detailed the steps in an OHRP/FDA review as follows:

- OHRP notifies the funding agency.
- A panel of experts is identified that includes at least *two* public members (more than recommended by SACHRP).
- OHRP requests written permission from the IRB and the PI to post all relevant material.
- The FDA publishes Federal Register Notices for meetings and solicits public comments. Concurrently, relevant study material is posted on both OHRP and FDA Web sites for public references.
- The Pediatric Ethics Subcommittee (PES) creates a consensus report, ideally with the PI's participation, and presents to the Pediatric Advisory Committee (PAC).
- PAC makes recommendations to FDA Commissioner which are ultimately transmitted to OHRP through Office of Pediatric Therapeutics. Both PES and PAC transcripts are posted when available and forwarded to OHRP.
- The Commissioner's Memo and OHRP's recommendations are forwarded to Assistant Secretary of Health for final determination.
- Throughout the process, stakeholders are informed of the status of the process.
- If the Secretary's determination is that the protocol should proceed after modifications, the investigator must modify the research proposal, parental permission/assent forms, and other documents as appropriate, and submit the revisions to the IRB for review and approval.
- The IRB or other appropriate institutional official must then submit the approved revised documents to OHRP for final concurrence before the research can proceed with funding.
- OHRP closes out the review once acceptable final materials are received from the IRB. Final findings are posted.

Dr. Prohaska informed SACHRP that two open panels have been completed since the process was redefined, both of which were joint OHRP/FDA panels (which are expected to be the most common approach in the future). Another one is pending.

Remarks by Sara Goldkind

Dr. Goldkind explained that FDA has a more limited experience with the Subpart D process, since it did not adopt the Subpart D regulation until 2001 and has had only four referrals that went through the process in that time. Most of its experience has occurred since the formation of the PAC in 2003.

The FDA has embraced many of SACHRP's recommendations, and she believes a "truly open process" now exists. Any public comments received during the public comment period that follows the Federal Register notice – a minimum of 30 days is allowed – are replicated in total for panel members when feasible. Both PES and PAC have open public hearings, allowing significant

opportunities for comment. Furthermore, the relevant protocol and all pertinent IRB documents are posted on both the FDA and OHRP Web sites.

Dr. Goldkind said that face-to-face meetings were held with all pertinent expert consultants. Briefing materials sent in advance to expert consultants and to the PAC members, each of whom has the opportunity to express opinions, review all materials, and listen to public comments before rendering recommendations. She believes a "close working relationship and harmonization" now exists between OHRP and FDA. The process has been streamlined and is now much more timely and efficient. PES meetings have been scheduled to occur within a very short period before Advisory Committee meetings, for example, and efforts are underway to facilitate information exchange between PES and PAC. At least two members of PAC are required to also be part of PES, and the Chair of PAC participates in the PES as well. Any materials presented to the PES are transmitted to the PAC as well.

Both FDA and OHRP review the applications at the outset to be sure they meet basic requirements, and a joint telephone conference occurs with the IRB investigator or representative, as well as the principle investigator, to make sure the reasons underlying the referral are well understood and that they, in turn, understand the process. Their participation is encouraged, including attendance at meetings of the PES and the PAC where the protocol will be discussed.

Dr. Goldkind believes the current process "greatly contributes" to pediatric research, to IRBs, to investigators, and to sponsors and ethicists.

DISCUSSION

Dr. Prohaska and Dr. Goldkind responded to several questions from SACHRP members.

Why were there were no panels between 1983, when the children's regulations were issued, and 1991? Dr. Prohaska said there was not a "great appreciation for the process," even during the 1990s. Dr. Goldkind added that the process is now better known. Also, the passage of FDAMA in 1997 may have contributed to greater use of the process; it included stipulations regarding pediatric exclusivity that catalyzed pediatric research. Also, Dr. Prohaska believes that there is a greater awareness today of the need for research with children.

There are probably hundreds of IRBs that still do not have a grasp of how to interpret and apply Subpart D. Are there projects that should be referred for a §54 review that are not? Also, when FDA reviews an Investigational New Drug application (IND), is there a check system during which FDA could recognize a need for a §54 process? Dr. Goldkind agrees that that many IRBs do not understand Subpart D. FDA is working internally to make reviewers more cognizant of specific issues they need to consider when reviewing pediatric trials. Also, many Centers are forming special pediatric working groups to increase awareness of these issues.

Has OHRP received any submissions that it concluded were not 407s? Yes, we received one for which there was inadequate consideration of certain provisions of Subpart A and inadequate materials. It was sent back.

How can we publicize to IRBs that the guidance exists? OHRP sent a message to IRBs on its ListServe informing them that the guidance was available. It also has various outreach programs and meetings that provide opportunities for education.

The next important part of this work is the development of guidance with clear definitions of key terms such as minimal risk.

After the 407 process occurs and the project is approved, what is next step? From the FDA's perspective, the protocol goes back to the local IRB to make sure the appropriate changes have been made. Dr. Prohaska further explained that once the determination is made, the information goes back to the IRB and the PI. The PI makes the required changes and submits them to the IRB, which forwards them to OHRP for concurrence after their own approval process. Once concurrence is affirmed, the funding agency, PI, and IRB are all notified.

How does oversight occur? Does the IRB communicate with you to be sure issues are appropriately addressed? Yes, the IRB can contact OHRP at any time with questions. Stipulations must be met before the funding agency releases funds.

Are the recommendations that come back from the Secretary of HHS made public? Yes, they are posted on OHRP's Web site.

What happens if the Commissioner of FDA and the Secretary of HHS Secretary disagree? It is hoped differences would be ironed out, Dr. Prohaska said, but in general the Secretary's opinion would overrule the Commissioner's. Dr. Goldkind added that by the time the recommendations reach the Secretary, so much thoughtful and varied input has occurred that such a disagreement is unlikely. Dr. Prohaska agreed, assuring SACHRP that everything possible would be done "behind the scenes" to avoid such a disagreement.

Ms. Selwitz congratulated the speakers and their agencies on a more thorough, timely, and transparent process.

Dr. Schwetz stressed the importance of public input and asked speakers to comment on the sources of public comments received to date. He also invited SACHRP members to comment on how to fully engage a broad spectrum of public opinion, including the opinions of researchers working in related areas. Dr. Prohaska said that a full spectrum of opinions were being received, including comments from people in university settings, association members, interest groups, and members of the general public. The number of questions received for the various "407s" varies according to the topic. Patient and subject advocates included in the process itself are another source of input from the public.

Dr. Weiner suggested that the best route to getting feedback is through organized, disease-specific parent organizations. While outreach to such organizations may be a labor intensive effort, she said, these organizations include the most interested, motivated, and educated parents. Dr. Goldkind added that subject advocates often come from such organizations. She also said the agency was continuing to monitor the process very carefully. Each panel meeting is followed by a post-meeting wrap-up and review of timelines.

Identification of Future SACHRP Priorities: International Research, Multi-Center Studies, Evidence-Based Practice, and Exemptions
SACHRP Ex-Officios

The Chairman introduced presentations by *ex officio* members of SACHRP on four issues and priorities that have "risen to the top" of the list of possible future priorities. These include international research, multi-center studies, evidence-based practice, and exemptions.

International Research

Remarks by Dr. Marguerite (Peg) Barratt, National Science Foundation

Dr. Barrett pointed out that international research is growing rapidly, suggesting a need for sound policies and procedures to ensure subject protection. As a researcher plans to conduct ethical research in another country, he or she must consider a number of questions about the local IRB:

- Does the local IRB have the expertise to figure out whether the proposed research is appropriate? Should the research be reviewed by in-country IRB?
- Does that IRB have a Federal-wide assurance (FWA)? If so, does it really follow the Common Rule in a way equivalent to the way it is followed within the U.S.?
- Are there other in-country clearances that might be required?
- Is that IRB really going to provide the kind of oversight that would be expected from an IRB in this country?

A variety of recruitment and other issues will arise:

- Is there is the possibility of coercion? A financial incentive that is appropriate here might be coercive in an impoverished country, or access to health care might in itself be coercive.
- How can informed consent be handled in a culturally and linguistically appropriate way?
- How will AEs be handled?
- How will follow-up health care be provided after the project is complete?
- How will accusations and complaints be addressed?

The Human Subjects Research Subcommittee now has an International Working Group that is working to ensure that there are adequate protections for subjects in international research. Members include all agencies that subscribe to Common Rule. The group has invited presentations by 13 different agencies and is engaged in completing a table to capture answers to such questions as the organization's purpose, involvement in human subjects research, oversight, and priority issues. It is also creating a country-specific document describing protections in each country.

After reviewing the issues outlined in the Working Group's report to SACHRP in March of 2004, Dr. Barratt found significant progress in two of three key areas: :

1. *The need for infrastructure*. This includes training of PIs and overseas IRBs. Progress can be seen in the increased number of FWAs around the world.
2. *The need to systematically review what is happening.* The Working Group is reviewing the current situation by agency and country.
3. *The question of regulatory equivalence*. This issue has not received comparatively little attention to date.

Remarks by Ms. Joan Porter, Department of Veterans Affairs

Ms. Porter said the issues that remain unaddressed to the satisfaction of the original committee include the need for equivalent education for PIs conducting research abroad and for Federal harmonization of international standards. The Working Group has identified key concerns to explore in the following categories:

- *Regulatory issues.* What are appropriate procedures, policies, and guidance? What is desirable in terms of consistency? Is more harmonization needed? How can policies and

procedures make any real difference to ethical conduct of research abroad? What constitutes "equivalent protections"? Who determines this and how? What clearances are needed and appropriate? What in-country clearances might be necessary? (HHS and the Department of Defense use the FWA international assurance, but it is not well used by other agencies). How does the Health Insurance Portability and Accountability Act (HIPAA) apply in other countries?

- *Ethical issues.* How can policies and procedures really affect the principles of autonomy, beneficence, and justice? What is owed to individuals in other countries by the U.S. Federal sector when it undertakes research collaborations? How do policies and deliberations support justice in international settings? Should there be minimum requirements for compensation to subjects if they're injured in international research that is conducted by entities within the United States? In countries that have few resources, is there the possibility of coercion and undue inducement? What kinds of community involvement are expected in the international settings? And how should this be incorporated into the international research protocols?

- *Communications issues.* Good communication underlies the success of everything, and there are some significant gaps. How should U.S. Federal entities communicate with international bodies to ensure protections? How do U.S. and local international IRBs communicate about a project? What are the roles of PIs, the IRBs, the institutions, and the Federal sector in promoting these communications? Where the gaps and what are are their consequences? How can U.S. Federal authorities and IRBs make sure that research is done with knowledge of the local context? How and where can training regarding human subjects protections abroad best be handled? Is harmonization of polices and procedures among Federal departments and agencies warranted? Is an enhanced harmonization effort involving international participants required?

Currently, Ms. Porter said, the U.S. Department of State is not informing embassies about research, and it is not clear whether this is needed.

The Working Group would like to see SACHRP debate some of these issues and ensure they are closely examined with full body deliberations and high visibility.

Alternatives for Reviewing Multi-site Studies
K. Lynn Cates, M.D., Department of Veterans Affairs

Dr. Cates reported that *ex officios* would like SACHRP to consider alternatives for reviewing multi-site studies as one of its priorities. The purpose would be to see how best to promote the highest quality review while enhancing efficiency. Alternatives for multi-site review include the following:

- *Multiple local IRBs review the same study.* This is a costly and time consuming way to proceed, but it is the most common approach. By the time all sites' have completed their review, the science may be outdated and funding cycles may be off.

- *Independent IRB review.* All sites agree to accept one site's conclusions. Examples are Chesapeake, Quorum, and Western.

- *Facilitated central IRB review*. A good example is the pediatric central IRB at the National Institutes of Health (NIH).

- *IRB reciprocity among multiple sites.* An example is MACRO, in which five academic institutions agreed that one of them would serve as the primary IRB for collaborative studies.

Discussion has largely centered on the use of central IRBs. Advantages of the use of central IRBs include consistent expert ethical and scientific review, with a larger pool of experts than may be available at relatively small institutions; more training and experience in certain kinds of protocol reviews; centralized accountability; earlier identification of trends in AEs and other problems; absence of local conflicts of interest (an important consideration, since grant funding may be placed at risk by such conflicts), reduced local administrative burden, a more efficient review process (weeks as opposed to months, or even years), and improved access to multi-center trials for both investigators and subjects (a key advantage for institutions with limited resources).

There are also many challenges in the use of this model. One of the most important is local accountability, including determining who is actually responsible for human research at the local level. Ensuring sensitivity to community attitudes is also a challenge, as are liability and conflicts of interest. Some local IRBs may go out of business if this model is used more widely. A major challenge will be the sense of "ownership" by local IRBs and chairs, which will need to build trust in a process they do not control.

An IRB invitational workshop has been planned to develop concrete models of approaches to study review. The workshop will be held November 17-18, 2005, in Washington, D. C. The steering committee includes representatives of the Association of American Medical Colleges (AAMC), the American Society for Clinical Oncology (ASCO), the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), and the Department of Veterans Affairs (VA). The small size of the workshop is intended to facilitate the work of model development. Attendees will bring diverse backgrounds. Together, they will consider a range of topics including institutional responsibilities and concerns (including liability), ways to reduce burdens (especially for multi-site trials), and barriers to adopting alternative models. Follow-on activities will include the development of a report for SACHRP on alternative models and strategies to overcome barriers to their use. A public meeting will follow in which all interested stakeholders may participate in refining the models.

Levels of Evidence
Dr. Sally Flanzer, Agency for Healthcare Research and Quality

Dr. Flanzer proposed that SACHRP address the need to develop an evidence base for effective human protection as a future topic. At present, she said, there is an expert-based system that is short of organized evidence. She pointed to the need for practice-based research that can be translated into practice guidelines – for example, systematic reviews, randomized controlled trials, cohort studies, ecological studies, and case-control studies, as well as expert opinion. Human protection program operations would benefit from an evidence-based approach that asks such questions as the following:

- What has been the impact of accreditation on participant protection and on AEs?
- Will clinical trial registries affect the public's perceptions and feelings about honesty and science?

Dr. Flanzer felt that SACHRP could contribute to the effort in four ways:

- Make preliminary suggestions about the shape of a coordinated research activity,
- Prioritize the content of a research program,
- Make suggestions about how to fund the activity, and
- Make a recommendation about a Federal home for this research activity.

In order to determine the best ways to shape the program, she suggested a systematic review and analysis of the literature and existing data is required. Even if the analysis were restricted to federally funded research, it would be a valuable first step. Also, data on AEs, Office of Research Integrity (ORI) infractions, and OHRP investigations are all available and provide a place to start.

Within the organized frame provided by such an analysis, SACHRP could identify knowledge goals and prioritize most the pressing questions. A research program to address these questions might address the need for knowledge in any of the following areas: process, risk, risk assessment, outcomes research, and identification of best practices. Studies to establish performance or quality indicators, business impact, or the usefulness of comprehension assessments before obtaining informed consent would all help improve IRB operations and enhance protection.

Dr. Flanzer asserted that many disciplines are interested in such subjects, but need a funding stream to support their research into these areas. More than 100 studies of IRB operations have been published since 1999, and ORI receives a respectable interdisciplinary response to its request for applications.

Three vehicles might be used to start a Federal research program on human protections. One option would be for OHRP to commission a specific National Research Council (NRC) report to examine the existing evidence base and define a research agenda. Diverse audiences engaged in research could each make small contributions to support such research. A second option would be for OHRP to issue contracts, perhaps through interagency agreements, to gather existing data and issue periodic reports. The speaker pointed out that a window of opportunity exists at present, as HHS switches to the use of the electronic 424 submission form instead of the PHS398. The data collection could be justified in part by an acknowledged lack of evidence, as well as by past disasters and the failure of one of the two accrediting agencies. Finally, SACHRP could recommend an extramural competitive grant program. The committee could offer a mandate and make suggestions for seed money. The program would help build a cadre of young researchers helping to improve the field. Planning and consensus conferences would be held through any of these vehicles, helping to develop a direction and alert the field to the government's intentions.

Dr. Flanzer also encouraged the committee to recommend an appropriate "Federal home" for this effort that will allow access to funding, commitment, and researchers.

Regulatory Burden in Public Health Practice
Deborah Holtzman, Ph.D., Centers for Disease Control and Prevention

Dr. Holtzman's remarks referenced §101(b) of the Common Rule, which defines exempt categories. Her specific focus was category 5, which includes research and demonstration projects that are designed to study, evaluate, or otherwise examine public benefit or service programs. Undated OHRP guidance states that such programs include any of the following:

- Those that deliver a public benefit or service,
- A project conducted pursuant to specific federal statutory authority,
- Those for which there is no statutory requirement for IRB review, and
- Those that include no significant physical invasions or intrusions upon privacy.

Dr. Holtzman argued that this guidance is not specific enough. For example, it is not clear what is meant by "public benefit or service" or what invasions or intrusions on privacy would be considered "significant."

She proposed that SACHRP examine Category 5 and recommend an expanded interpretation that includes a broader range of public health activities. Examples of such exempt activities would include such activities as collection of biological specimens for authorized surveillance purposes and data collection for government accountability in service programs. She also proposed allowing State, local, tribal, and foreign governments to use the waiver of informed consent at §116(c) in the same way as the Federal government does.

She suggested that public health stakeholders such as the Council of State and Territorial Epidemiologists, the Association of State and Territorial Health Officers, and the American Public Health Association be included in the decision-making process.

As rationale, the speaker cited a recent article by James Hodge that asserted: "Misclassification of public health practice activities as research can result in these activities being delayed or conducted less efficiently or at higher costs due to the need to adhere to the regulations"(*Journal of Law, Medicine, and Ethics* 33:1: 125-141, 2005).

Additional issues raised by Dr. Holtzman included the following:

- Should child exemption to category 2 be less restrictive, e.g., when the child is a third-party subject? Allowing the collection of identifiable, private information on children from parents seems consistent with the intent, but is currently not exempt.
- Should prisoner research be exempt under category 4?
- Can research with prisoners who are third-party subjects be exempt under category 2?

DISCUSSION WITH PANELISTS

The Chairman allotted time for discussion of each of these areas between SACHRP members and panelists.

International Research

Questions and responses were as follows.

How far are other countries behind us in terms of human subject protections, or do we know? Dr. Barratt commented that in general, we do not know. Canada has the largest amount of overseas research, and there is little need for worry since their work in the area has followed a similar trajectory. Ms. Porter added that other countries may simply be different rather than "behind." Currently, she said, we do not have a good standard for what is acceptable or for adopting or recognizing international codes.

Do we know whether other countries are following these international codes and standards? No, we do not have data.

How can we blend equivalent protections and enforce them in a way that ensures compliance is really feasible? It is important to acknowledge that the U.S. is not the only country that has thought about or cares about these issues. The FWA brings in under the terms of the assurance other aspects of the Common Rule that may not be addressed in the international codes cited by other institutions.

It is unclear how Federal regulations actually operate internationally and how much of it comes under the rubric of HHS vs. FDA. It is hard to get a handle on that. There are clearly millions of dollars being spent on research conducted overseas.

Many of the drivers for the use of lower cost countries for human research are associated with private sponsors. Do you expect that there will be different standards based on where data will be used – in the U.S. or the specific locale where research occurs? Dr. Barratt said a source of concern is when data is collected through private sector investments and Federal agencies what to use it in a public regulatory context. Also, there is no checkpoint that would make the State Department aware of privately funded research in a particular country, which would be a potential problem if mistakes and accusations arose. Ms. Porter highlighted the issue of justice implicit in the question; if the research conducted does not benefit the human subjects, how can the principle of justice be addressed?

Learning from existing education programs: Ms. Kornetsky observed that a recent round of grants was just announced for education and training in international research. She asked whether information is available on what has been successful in these programs. Dr. Barratt responded that she was not sure we know the answer to that question. She noted, however, that there is an ongoing need for training because of the growth of the enterprise. Ms. Porter added that the Centers for Disease Control and Prevention (CDC) have a program to train investigators who are doing international studies. Many other agencies have such programs, but they are not all shared or consistent. Ms. Kornetsky stressed that since some Federal money has been spent in addressing issues related to international research; it is important to learn from what has been done and avoid "reinventing the wheel." There could already be some good ideas about consistency and standards.

Alternatives for Reviewing Multi-site Studies

Questions and responses were as follows.

Currently, there are only two Federally-funded central IRBs, the NCI adult and pediatric IRBs. Are there any plans to have more central IRBs in other institutes? Ms. Cates reported that the VA will definitely have a central IRB, now in the planning stages. Dr. Patterson said there has been no formal discussion of expanding the NCI model in other institutes, but there are other institutes considering the model. Ms. Decot said the Department of Defense has a central IRB for cancer research and is considering additional topical IRBs.

Has there been a formal evaluation of the effectiveness of NCI's central IRBs? Dr. Patterson explained that there is an evaluation underway. She felt sure that Dr. Jacki Goldberg, the program's administrator, could present findings to SACHRP on request. However, Dr. Patterson was uncertain of the timeline for completing the study.

How are you dealing with the issue of purview for the VA's central IRB, since some of the research that occurs in the VA is funded through the VA and some is not? Are there any other aspects of program setup you could share with us? We are starting with low-risk studies because they involve dozens of sites, if not all, and VA does a lot of this type of study. We plan to go on to riskier things after making sure the setup is solid. VA does not have to face the challenge of liability, but otherwise the challenges are the same as for everyone. Our major concerns are ensuring local accountability (making sure that there is someone on the ground looking into what is going on) and ensuring that community attitudes have been considered. VA will be working with affiliates to be sure there is a smooth transition at affiliated sites.

Liability issues: Dr. Gyi noted that the independent IRB model, in which one IRB assumes responsibility and liability, is one way of clarifying these issues. He also noted that insurance

products have become available through Lloyd's of London this year. Ms. Cates observed that some highly qualified attorneys will be attending the IRB invitational workshop to ensure this concern is taken into account.

SACHRP timeframe: SACHRP members and speakers sought to clarify the timeframe appropriate to addressing the issues raised in this area. Ms. Cates explained that an invitational workshop on central IRBs is planned for November of 2005, with a public meeting following in 2006; a report from the workshop will come to SACHRP. Dr. Schwetz said review of the report will provide SACHRP with an opportunity to respond with endorsements or other comments that would be taken into account as the public meeting is planned. Dr. Prentice added that following the public meeting, SACHRP can determine next steps.

Ms. Selwitz added that it is important to develop a series of practical alternative models, not just one or two. She said that models must clearly address local concerns if they are to be considered viable options.

Evidence-Based Practice

Questions and responses were as follows.

Private sector involvement will be essential in the project described. What has the Federal government done to use its own resources to answer these questions? Public Responsibility in Medicine and Research (PRIM&R) and the Applied Research Ethics National Association (ARENA) are among stakeholders who should be involved. Others include professional associations. There is no coordinated overview at the Federal level that would lead to the creation of a data base.

NIH has an internal working group on bioethics. Is that a small place to begin? That is an excellent to begin the discussion of partnerships, but it does not address social and behavioral research.

Where do you feel something like this should be held? Dr. Flanzer said her personal opinion is that the National Science Foundation would be the appropriate "home" because it is in the business of looking at questions about science policy.

A key question relates to identifying appropriate outcome measures that relate to problems that affect the public's trust in IRBs or use of IRBs. Most of your presentation focused on process evaluation. A related issue is the need for an evaluation of the accreditation process to see if it contributes to quality assurance. Also, please explain how your proposal is different from the RFPs going out from ORI and others for research. In response, Dr. Weiner commented that two outcome measures that are important to the public are the public representatives on IRBs and the length of time required to review projects. Dr. Flanzer responded, however, that identifying outcome measures was not part of her goal for her presentation, though it is an appropriate activity for SACHRP. She observed that the question of public interest is a compelling one, and without it, the expenditure of Federal dollars may not be justified. Unfortunately, public interest often follows disasters, and the purpose of this endeavor is prevention.

Regulatory Burden in Public Health Practice

Ms. Selwitz observed that the questions raised are the kinds of issues the Subpart A subcommittee will be addressing. Dr. Prentice agreed, and said he fully expected the subcommittee to pursue these issues.

Dr. Fisher asked Dr. Holtzman to explain the ethical rationale for expanding the exempt category in public health research. The speaker responded that the purpose would be to reduce regulatory burden without harming human subjects. Dr. Fisher said she would like to see a supplement to the report that would document whether individuals who participate in each type of "research" proposed for exemption are participants and whether or not their rights are protected.

Ms. Selwitz asked what kinds of ethical standards and framework exist for these activities. Dr. Holtzman said there is nothing explicit. She questioned whether a program was needed that would covers all activities, regardless of whether or not they are really research.

PUBLIC COMMENT

The Chair invited members of the public to comment.

Mr. Peter Kim, regulatory counsel for the Quorum independent IRB, informed SACHRP that FDA issued guidance in March of this year on the use of centralized IRBs for multi-center research. He said the guidance included workable models for addressing the challenges in conducting multi-center research through a centralized review process, including local accountability, community attitudes, and participant population concerns.

Dr. John Mather, Vice President of Chesapeake Research Review, also an independent IRB, commented on the status of issues related to the use of central IRBs. He noted that as alternative ways of protecting human subjects such as independent IRBs emerge, the issues of "who is accountable for what in this structure" comes into focus. He noticed an increasing tendency by medical centers to identify specialized IRBs to handle certain work and list it under their FWA. A variety of regional consortia exist, including one centered on Michigan State University.

Dr. Mather observed that ethical issues exist even in exempt research, and he raised the question of whether an institution that has decided it is exempt from the Common Rule has a clear responsibility to track activities classified as operations research, including public health practice and monitoring for the purpose of quality control and assurance. He suggested that quality improvement activities could in fact become research as the "next step" is taken and comparisons are made for research purposes.

Dr. Prentice agreed that responsibilities are not well delineated in emerging models for human research protection, and he hoped the upcoming workshop on IRB models would provide input on how to make these models effective. He added that issues related to the distinction between research and program evaluation or quality assurance programs would be addressed by the Subpart A subcommittee. OHRP also has a current initiative to address this issue.

Dr. John Mills of the Mayo Clinic commented on the proposed guidelines for AE reporting. He stressed that unless FDA comes on board with guidance that can be harmonized with OHRP guidance, the work of OHRP will probably be for naught. Like Ms. Selwitz's institution, the Mayo Clinic tried to design a more limited AE reporting guideline, but found it had no effect.

Dr. Mills also said that Mayo Clinic sees the discussion of issues related to central IRBs and multi-site trials as a positive step. He urged SACHRP and participants in the upcoming workshop to consider not only what mechanisms such as central IRBs can do to comply with regulations and ethical guidelines, but also how to break down barriers in academic medical centers to the use of such alternatives. He would like to see a central process that was still capable of recognizing institutional differences, such as unique policies.

The Chair invited SACHRP members to respond to public comments. Dr. Gyi said that institutions must retain a certain amount of responsibility for research oversight. He believes there are workable models for central IRBs working with institutions that should be brought forward as quickly as possible.

Dr. Weiner stressed the importance of defining the circumstances in which alternative models would be appropriately used and developing guidelines to reassure institutions as they think through whatever challenges they face. Dr. Prentice said that he once opposed the use of independent IRBs by academic institutions, but has since learned more about how central or independent IRBs can work effectively with academic institutions.

Identification of Future SACHRP Priorities
SACHRP Members

The Chair allotted the remainder of the meeting to consideration of future SACHRP priorities, which were not limited to the four topics presented by ex officio members. He said addressing alternative IRB models at this time would not be useful until the report from the upcoming workshop becomes available. He also noted that the issue of exemptions will be addressed by the Subpart A subcommittee and also required little discussion at this time. This leaves the issues of international research, on which SACHRP has already had one panel, and evidence-based practices.

Dr. Weiner raised the question of whether taking on major new projects made sense, given that the charter is set to expire in October, 2006. Dr. Prentice said he was optimistic that the charter would be renewed. Dr. Schwetz said OHRP had received no indication that there is a possibility or likelihood that SACHRP would not be rechartered. He therefore encouraged SACHRP to proceed with future plans.

Protection for Decisionally Impaired: Dr. Weiner observed that SACHRP had not addressed the needs of the decisionally impaired, a population named in SACHRP's charter. Dr Prentice said that OHRP is currently drafting an advance notice for proposed rulemaking that will allow the public to comment on whether additional rules are needed in this area. Dr. Stith-Coleman, an OHRP staff member, added that this is a joint notice that will come from FDA as well. The Chair felt it might be premature for SACHRP to begin discussion of this issue before public comments are received.

Dr. Weiner suggested that an expert panel on issues related to protections for decisionally impaired subjects might be helpful. Dr. Fisher agreed that the issue was an important one, and suggested that creation of a Subpart E might not be the only way to address it. She also noted that, like prisoners, this is not a static population; consequently, defining them will be difficult. Dr. Fisher felt that existing guidance, including guidance developed by NIH, is not sufficiently specific. Dr. Prentice agreed. *The Chair said he would explore the possibility of a panel on the topic with OHRP.*

Wards of the State: Ms. Kornetsky highlighted the issue of guidance for wards of the State under the children's regulations. She suggested that the subcommittee on children's regulations might address this topic. *Dr. Prentice encouraged subcommittee members to determine the directions they felt were needed.*

Accreditation: Dr. Gyi, who co-chaired a subcommittee on accreditation nearly two years ago, reminded members that the subcommittee had recommended waiting to pursue its recommendations on the topic to allow market forces to operate. The subcommittee felt strongly, however, that

accreditation has true value in the protection of human subjects. He asked SACHRP whether it is now time for the committee to take further action.

Dr. Prentice acknowledged receipt of a letter addressed to Dr. Schwetz and to him, in which Dr. Gyi reviewed the three recommendations the subcommittee brought forward earlier. The first was a call for a systematic evaluation of accreditation as an assurance of quality research and subject protections. Dr. Prentice asked for an update on the CDC grant received by Association for the Accreditation of Human Research Protection Programs (AAHRPP) to identify measures that could be used to evaluate accreditation programs. Dr. Holtzman said a final report is expected late next year. The Chair suggested it might be premature to pursue the issue until the report is complete, but Dr. Gyi said the grant would not provide the data the subcommittee envisioned.

The subcommittee's second recommendation was to develop a list of incentives to encourage IRBs to seek accreditation. Dr. Gyi suggested motivating IRBs to become accredited by reducing regulatory burden. However, Dr. Prentice rejoined that carrying out and documenting deliberations more thoroughly accompanies accreditation, actually increasing the work load. Dr. Gyi then suggested examining how to use accreditation as a cornerstone of daily practice. One possibility would be to have a conference with stakeholders. (The subcommittee's third recommendation had been that HHS organize a conference to examine a wide range of self-regulatory initiatives undertaken over the last five years.) At present, Dr. Gyi said, there is no means of showing that accreditation is a positive step. While it is possible to wait for data before holding the conference, he said, something should be done to increase the value placed on accreditation. Ms. Kornetsky agreed and emphasized the need for data.

Dr. Weiner felt that moving on the subcommittee's recommendations would be premature, but noted that one potential outcome of accreditation may be enhanced public trust. However, this outcome may be difficult to measure. Another would be heightened public awareness of what human research protection programs are about. This might be reflected in increased enrollment rates for clinical trials.

Dr. Prentice proposed to consult with AAHRPP and ask for advice on when to pursue the issue of a systematic evaluation. He also felt the CDC study would yield some useful information that should be considered. Dr. Gyi agreed.

Investigator Perspectives: Dr. Jones suggested inviting investigators to comment on how to improve human research protections, identify barriers, describe resources and education requirements, and suggest creative strategies to make regulations as functional as possible. Dr. Gyi agreed, and said a panel could be helpful to the Subpart A subcommittee, which has been charged with looking at whether new regulations for investigators would be helpful. Ms. Kornetsky added that she has met very active clinical investigators who are educated and have creative ideas about possible improvements. Ms. Selwitz suggested going to associations such as FASAB (???) to locate suitable spokespersons. She also suggested that OHRP regulations should include rules for investigators similar to those already developed by FDA.

Dr. Prentice was skeptical that a panel of investigators would be useful; he said he believed he understood the barriers as seen from their perspective, and he held that many of those barriers could readily be removed if IRBs were not overloaded and under-resourced. He also pointed to the difficulty of finding a representative sample among thousands of investigators. Dr. Fisher also doubted that a panel would be productive; she pointed out that SACHRP had had a panel of social science researchers already and had not acted on their input, but Dr. Prentice responded that their advice was under consideration by the Subpart A subcommittee. Ms. Kornetsky added that the previous panel had placed additional issues on the table. She stressed the importance of choosing

well-seasoned, educated investigators in order to ensure the session was useful. Both Dr. Prentice and Dr. Fisher observed that investigators are basically required to behave in an ethical way.

No specific follow-up action was determined.

Collection and Documentation of Race and Ethnicity: Dr. Powell highlighted the need to address diversity in the clinical research process. He noted that NIH requires researchers to present a strategy for appropriate inclusion of ethnic and racial minorities in clinical trials. He said that while FDA had issued a guideline this September on the need to collect and document data on ethnicity and race, it has no requirement that ethnic and racial minorities be included in trials. He pointed to the problem of new medicines being issued without data on their safety and effectiveness in different segments of the population.

Dr. Fisher said the issue was a critically important one. She maintained that analyzing data after the fact is not good clinical science practice; it is necessary to identify population characteristics required for appropriate representation in advance. Dr. Powell added that it is especially critical that the ethnic and minority population for biomedical research projects be proportionately similar to the population that has the disease.

Dr. Lepay agreed that this was an important area and needed to be addressed. He confirmed that FDA did not have specific criteria for inclusion of minorities, though he said these issues may be discussed between sponsors and the FDA as protocols are designed. He also noted that the FDA and NIH have differences in funding and legislative authority that must be taken into account in any discussion of harmonization.

No specific follow-up action was determined.

International Research: Ms. Porter said she and Dr. Barratt had given further consideration to priorities in this area and concluded that the issues identified by the first invited panel on this topic provided a good starting point. Priority issues included:

- Understanding and agreeing on equivalent protections;
- Assessing how the FWA mechanism is constructed, whether it works, how useful it has proved, and whether other Federal departments and agencies should use a similar mechanism;
- Identifying training requirements for U.S. IRBs and for U.S. researchers;
- Discussing how to achieve understanding of the local context, including offsetting coercion, addressing vulnerabilities, and involving the community;
- Ensuring appropriate oversight; and
- Evaluating the need for systematic clearances for the Department of State.

She said these issues could be addressed through a subcommittee structure or sent to individual groups for consideration. Some of them could also be addressed by the Subpart A subcommittee, since §101(h) under the Common Rule addresses the issue of equivalent protection.

Dr. Prentice asked Ms. Porter to clarify what work a subcommittee could perform in regard to equivalent protections and training. She responded that the subcommittee could review the regulations and glean the "minimal things we would accept and expect an international institution to follow, and those we would expect to be followed by U.S. researchers and U.S. IRBs when that kind of research is carried out." In regard to training, she called for a systematic review of what is currently being done.

Dr. Carr, representing NIH, asked for feedback on OHRP's request for public comment on a proposal to establish a working group to develop criteria for equivalent protections. Dr. Schwetz said comments were received and are being analyzed, but there is little pressure from other agencies to expedite the process. Ms. Porter said the issue was a high priority for VA and asked if a SACHRP subcommittee could be helpful. Dr. Schwetz said it was OHRP's responsibility to analyze the comments, but SACHRP could appropriately draw conclusions and make recommendations as a next step. He said the guidance document would help in evaluating whether protections were equivalent, but OHRP is not envisioning a detailed, step-by-step document. Ms. Porter expressed concern that multiple Federal agencies might define equivalency in different ways. Dr. Gyi agreed and called for substantive and meaningful guidance. Dr. Schwetz clarified that any international regulations that do not cover the provisions of the Common Rule would not be considered equivalent.

In regard to the use of FWAs, Dr. Prentice said there was no guarantee that any institution would follow the provisions named simply because the document was signed. Consequently, it is not clear how to answer the question of whether or not the mechanism "works."

Ms. Selwitz asked whether agencies knew what percent of their resources were used to support international research involving human subjects. Dr. Carr said NIH staff members had examined the issue and has a handle on it, though she did not have the data handy to present. She reported that NIH's extramural research program is examining issues in international research and staff might be able to present some of their work to SACHRP. They consulted with other agencies and attempted to identify best practices. Ms. Porter said other agencies probably have less oversight and understanding of their international research.

Dr. Prentice asked whether the Pharmaceutical Research and Manufacturers of America (PhRMA) had any data on clinical trials placed overseas by country. Dr. Powell said it was unlikely such data would be available in a central place. The Chair asked whether any of the major pharmaceutical firms might be receptive to discussing their overseas clinical trials with SACHRP. Dr. Powell thought this was likely and would be an "interesting exercise."

The Chair summarized that there is an apparent consensus that although there is a "tremendous migration" of clinical research overseas, few data are available. He suggested sponsoring a panel where data that do exist would be shared. Ms. Porter felt this would be helpful. She said the International Working Group Subcommittee has asked each member agency to present key information on its international research and policies. It is pulling together a report, due in January. Conclusions could be presented to SACHRP and inform future actions.

The Chair suggested a panel of presenters sharing data on international research, perhaps including representatives of the pharmaceutical industry, at one of the three SACHRP meetings in the coming year. Members were supportive of this approach.

Evidence-Based Practices: Dr. Prentice agreed that the issues Dr. Flanzer raised were important; he observed that the IRB enhancement grants NIH offered no longer exist, and he asked whether such issues were on the "radar screen" of any Federal agencies at present. Dr. Flanzer doubted that the type of effort she envisioned was likely to occur as a result of agencies acting on their own.

Dr. Carr commented that the NIH grant program was coordinated at the central level by NIH's extramural research program; however, Dr. Carr was unaware of any plans to renew the effort. Ms. Selwitz suggested that SACHRP ask for a report on what was learned through the enhancement awards. She also suggested that SACHRP consider recommending that a similar program be offered again.

Dr. Jones asked how Federal agencies could be encouraged to examine their own process data. Dr. Flanzer said resources to perform such analyses are normally requested as part of each agency's budget justification. She emphasized that her recommendations did not pertain to the level of individual agencies, but suggested a systemic look across all of government.

Dr. Weiner stressed the importance of addressing the issues Dr. Flanzer raised, but said she was uncertain that SACHRP was the right place to pursue them. Dr. Prentice said both SACHRP and OHRP would consider how best to address this priority. No specific follow-up action was determined at the meeting.

PUBLIC COMMENT

The Chair invited members of the public to comment.

Mr. John Mather, Vice President of the Chesapeake Research Review, reflected on the discussion of the effectiveness of accreditation. He asserted that "we are not even at first base…in terms of descriptive data." He noted that an IOM report had made recommendations on the need to collect data on accreditation which had not been pursued. He said the issue crosses agency lines and a subcommittee may be needed to address it.

Mr. Mather also expressed an interest in increasing the understanding of the interaction between the investigator and the participant and how to make it effective. He noted that some institutions have established codes of ethics for investigators, while others have bills of rights for participants.

Dr. Prentice agreed that there is little data available on this topic, and there is no adequate basis to say what works. He observed that it is much easier to know when the system is breaking down.

Mr. Jeff Rodamar from the Department of Education, speaking in a personal capacity, said a "mega study" is not needed. He pointed to 180 empirical studies of IRB operations and impacts that already exist. Much could be done, he suggested, in the context of existing studies. A review of what we know and don't know would be in order.

Dr. Gyi agreed that a synthesis of available information would be an excellent step, but wondered who might perform such a meta-analysis. Dr. Flanzer said a Federal agency could issue a contract to have a literature review performed, but someone would need to identify funding and act as contract officer.

Wrap-up and Adjourn
Ernest D. Prentice, Ph.D.

Dr. Prentice said that next steps will be discussing identified priorities with OHRP and staff to agree on next steps that are feasible given staff support. Many of these issues involve multiple agencies, so they are not straightforward. SACHRP members as agendas for future members are developed.

Dr. Stith-Coleman informed SACHRP that the Centralized Institutional Review Board (CIRB) evaluation will begin in several weeks. The hope is that it will be completed in six months.

Dr. Jones said that the topics on the table are all important, but said she did not feel that the timing was right for a new subcommittee. However, she said it was important to show that the committee

does want to see them move forward. Dr. Prentice agreed. He said that progress was clearly being made in addressing AEs. In the area of international research, he said he would like to see data that would suggest a productive direction. He was also open to the possibility of creative input from investigators. However, the committee's time is limited.

The Chair said he was struck by the quality of the conversation and the commitment of SACHRP members, as well as the involvement and commitment of OHRP staff, *ex officio* members, and others.

Secretary's Advisory Committee on Human Research Protections
Meeting
November 1-2, 2005
Alexandria, VA

Certification of the Summary of Minutes

I hereby certify that, to the best of my knowledge, the foregoing summary of minutes is accurate and complete.

ORIGINAL SIGNED BY MARCH 13, 2006

Ernest D. Prentice, Ph.D., Chair Date