Secretary's Advisory Committee on Human Research Protections

July 26-27, 2004 Meeting
Washington, D.C.

Summary Minutes

MONDAY, JULY 26

Welcome and Opening Remarks

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

Dr. Prentice welcomed members of SACHRP, ad hoc members, and members of the public. He acknowledged the hard work of the staff of the Office for Human Research Protections (OHRP) who support the work of SACHRP with expert advice and briefing books for the meeting.

The Chairman reminded those present of the SACHRP charter and quoted Secretary Thomson: "We must make sure we allow science and medical research to advance for the good of all Americans, but not at the expense of the people who participate in clinical trials." He noted that SACHRP committee members were all present, with the exception of Dr. Hauser. He then introduced Dr. Schwetz, Executive Secretary of SACHRP, and Cathy Slatinshek, Executive Director of SACHRP.

Report on the Issues

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

Dr. Schwetz thanked members of SACHRP and its subcommittees and assured them that their discussions were a daily part of the thinking of OHRP staff. He also said that information from the committee's deliberations was now being relayed to the Office of the Secretary through letters and briefings.

He informed the committee that its ex officio members meet regularly on related issues and highlighted two of their activities that are related to the work of SACHRP. The first is the adverse event reporting process. SACHRP recommended that OHRP work with the Food and Drug Administration (FDA) to provide guidance for institutional review boards (IRBs) on reporting procedures. This work is progressing. Ex officios are working to reconcile terminology related to adverse events in two common dictionaries and to define the content and format of adverse event reports. Secondly, ex officios are discussing the distinction between research and public health surveillance (a nonresearch activity), which is pertinent to many Federal and state agencies. Dr. Schwetz also highlighted OHRP's concern to establish an understanding of the ethical issues related to Subpart C to provide a firm foundation for rewriting it. It is currently considering the possibility of doing this through an Institute of Medicine (IOM) study.

OHRP is planning a November 16 event to celebrate the Belmont report and is making a video record of Commission members' recollections. Other relevant activities highlighted briefly include the following:

- OHRP is working with FDA to develop a database for mandatory registration of IRBs. A proposal is now out for public comment.
- OHRP and expert consultants are drafting guidance for the regulations and would welcome input from SACHRP and others on recommended priorities.

Finally, the Director asked SACHRP's input on how to anticipate and avoid human tragedies, as well as how to "change the culture of our work" to better take advantage of near-misses.

Overview of Charges to Subcommittees

Ernest Prentice, Ph.D.

The Chairman reviewed the charges of the SACHRP Subcommittees:

- The Subcommittee on research involving children (Subpart D) has completed its initial charge (to make recommendations with regard to the 407 panel closest to the Secretary) and is now developing recommendations for interpreting the requirements of Subpart D and of §46.404, §46.405, and §46.406 under Subpart D. He thanked Co-Chairs Celia Fisher and Kornetsky and subcommittee members for their hard work.

- The Subcommittee on research involving prisoners (Subpart C) is providing recommendations on the interpretation, reinterpretation, and ultimately revision of Subpart C in order to ensure that regulations do not obstruct ethically and scientifically appropriate research. The subcommittee is supportive of the proposal for IOM to examine the ethical underpinnings for revising Subpart C. He thanked Co-Chairs Mark Barnes and Nancy Dubler and subcommittee members.

The Chairman then reviewed the agenda for the day and invited public comment. Hearing none, the committee moved on to remaining business.

Subpart D. Subcommittee on Research Involving Children

Celia B. Fisher, Ph.D.

Dr. Fisher reported on the third meeting of the subcommittee and presented preliminary proposals to clarify key Subpart D terminology (§404 and §406). The Co-Chair explained that she wanted feedback from the full committee to determine whether the subcommittee was headed in the right direction.

The definition of "minimal risk," she stressed, is especially important. Section 404 says that "DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is represented only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408." This applies to research in which there is no direct benefit for children. Since it provides the foundation for other research classifications, the subcommittee suggests approaching it from a conservative stance. The key decision is whether these risks are a *uniform standard* (the comparison is to an average, healthy child) or a *relative standard* (the type of risks to which particular children involved in experiments like this are typically exposed).

Historically, she noted, the understanding of the standard has evolved from a uniform to a relative standard. In 1977, the National Commission recommended the use of the uniform standard. This understanding of minimal risk was incorporated in Subpart C and proposed for Subpart D. However, after analyzing comments on the proposed rulemaking, the definition of minimal risk was removed from Subpart D, making the definition in Subpart A operative. The preamble to the final rule for Subpart A states that HHS intends minimal risk to be defined by a relative standard – "the daily life of the subjects of the research." However, the final rule itself does not explicitly refer either to a uniform or to a relative standard, resulting in inconsistencies in the application of the standard.

Dr. Fisher reviewed the ethical issues involved in decision making on the issue. The justice argument for the uniform standard would be that children should not be subjected to even greater risk because their daily lives are already filled with greater risk than those of healthy children in safe environments. Those who argue for the relative standard would state, however, that such children should not be deprived of the knowledge benefits of research. The subcommittee concluded that the justification for the relative argument is false, since having the concept of minimal risk indexed to the healthy child in §404 would not deprive a less healthy one from participating in research under §405, §406, or §407. The subcommittee therefore proposed the adoption of a uniform standard. Proposals presented in the first part of the presentation were as follows:

- **Proposal 1: Adopt a Uniform Standard.** The subcommittee proposed that SACHRP adopt a uniform standard for the definition of minimal risk for research involving children under Subpart D. The subcommittee argued that approval of procedures as minimal risk should apply to all children, pointing out that the protections offered in §404 are a critical baseline for additional protections and that children constitute a vulnerable population that requires greater protections.

- **Proposal 2: Use Proposed Language for Definition.** Specific proposed language would define the frame of reference as "normal, average, healthy children living in safe environments" and the routine psychological and medical examinations they would be expected to encounter. Subcommittee members believe that children whose lives already involve elevated risks, such as those who live in violence-prone neighborhoods or take toxic drugs to treat cancer, should not be subjected to greater risks than other children.

- **Proposal 3: Minimal Risk should be Age Indexed.** Assessment of minimal risk should take into account the fact that children face differing risks at different ages.

- **Proposal 4: Uniform Standard Defines Upper Limits of Risk.** The uniform standard should be taken as a ceiling. In determining minimal risk, the IRB should take into account special and unique characteristics that might make a population more vulnerable than average children, such as hemophilia.

- **Proposal 5: Equivalent Procedures are Consistent with Minimal Risk.** In applying the standard, the IRB is not confined to approving the same exact procedure common in daily life, but could approve a procedure that is essential equivalent (as defined in proposal 6).

- **Proposal 6: Use Recommended Factors to Determine Equivalence**. In deciding whether a

procedure is "equivalent" to another encountered in daily life, the IRB should consider the magnitude, probability, duration, and cumulative characteristics of the specific event.

- **Proposal 7. Recognize Contextual Constraints for "Daily Life Experience."** The subcommittee noted that not all socially approvable risks are minimal risks; their context must be considered. For example, broken bones might be an acceptable risk for a healthy child participating in football, but it would not be acceptable to expose a child to similar risks in nonbeneficial lab research. However, it would be permissible to monitor the heart rate of a child playing football, because the procedure at issue is simply the act of monitoring the activity.

- **Proposal 8. Index Routine Medical Procedures to a Well-Child Visit.** Procedures that would be used on a well-child visit provide a good standard for acceptable magnitude and probability of risk.

- **Proposal 9. Index Routine Psychological Examinations or Tests to a Well-Child Visit.** Questions that would be typical in a well-child visit for a child of a given age would be considered within the parameters of minimal risk. For example, pediatricians normally ask adolescents about health-compromising behavior such as illicit drug use and smoking, so probing this type of high-risk behavior does not exceed minimal risk.

- **Proposal 10. Index Routine Psychological Procedures to Standardized Measures**. Investigators should provide information showing that a proposed question is similar to a question that would be posed in a standard test for a child of a given age.

- **Proposal 11. There are Exceptions to Routine Psychological Assessment Equivalence Proposals.** The subcommittee proposed a possible exception to the above based on the duration of the testing, which should be age appropriate. Members also observed that questions about physical or sexual abuse or any childhood traumas, questions specifically about suicidal ideation, and questions about criminal activities that the investigator is legally mandated to report may be greater than minimal risk, since there could be persistent post-experimental reactions. These would be of particular concern if no follow-up is intended. Therefore, they also proposed an exception if an established body of scientific evidence or clinical knowledge suggests that certain questions may cause post-experimental reactions.

DISCUSSION

Prior Work/Precedents

Dr. Kornetsky commented that the subcommittee's approach is consistent with the previous work of the National Human Research Protections Advisory Committee (NHRPAC) and IOM. The series of committees that have addressed these issues have built on each other's work.

Dr. Prentice asked what precedent might exist for clarifying the definition of minimal risk in Subpart D as proposed, given the existence of the preamble stating that minimal risk should be tied to the daily life of the research subject. Dr. Fisher said that one approach would be to change the regulations to insert the definition of minimal risk (as has been done in Subpart C). An alternate approach would be to develop a history of the use of the term and release guidance on that basis without changing the actual regulation. However, the subcommittee considers the choice of strategy a matter for OHRP to determine.

Delays in Participation
Dr. Harris pointed out that children who are ill are the subject of the greatest number of research questions and raised the concern that adoption of a uniform standard would delay the opportunity for them to participate in research and possibly impede research that might ultimately benefit them. Dr. Kornetsky responded that while participation might be delayed under certain circumstances, much of the research that is greater than minimal risk has the potential for direct benefit. Even if there is no potential for direct benefit, she said, IRBs can use another category that requires additional justification from the investigator. This could, however, result in an increase in proposals that go to OHRP for review. Dr. Fisher added that keeping the relative definition blurs a distinction between §406 and §404, since it is not possible to reach a relative conclusion for §404 without using the factors identified in §406 (e.g., does the child have a disorder or condition?).

Expedited Reviews
Dr. Gyi asked whether the subcommittee had any guidance for IRBs on what reviews could be expedited. Dr. Fisher noted that regulations permit expedited research under whichever definition of minimal risk is accepted. The subcommittee has not discussed the issue; she suggested, however, that if OHRP encourages IRBs to select the option of expedited review, this would be an argument for a conservative approach that would allow the expedited review to occur at the most protective level possible for children. Dr. Kornetsky suggested that in fact IRBs would be more likely to expedite risk if the definition is clarified. Dr. Fisher added that guidance should include examples that would help IRBs make this decision more comfortably.

Current Standard Use
Dr. Prentice asked the Co-Chairs whether IRBs, especially those at pediatric hospitals, use a uniform or absolute definition of minimal risk. Dr. Kornetsky said she believed there has been a movement toward the uniform standard and that those taking this position are now probably in the majority.

Minimal Risk Procedures/Equivalence
Dr. Prentice asked whether the Subcommittee intended to go beyond the work of NHRPAC and IOM by drafting a list of procedures that qualify as minimal risk. Dr. Fish said this was not the Subcommittee's intent; however, it does intend to look at cases and review the list developed by IOM. It also intends to provide more examples, especially in the area of psychological assessments, which should make IRBs more comfortable making a determination.

Dr. Weiner commented that the assessment of equivalence relates to procedures, not to the research study as a whole. Individual assessments of each procedure are required.

Mr. Gyi highlighted the need for education related to definition thresholds for investigators, IRBs, and the public. He also asked if he had understood correctly that individual procedures within the protocol should be considered on the basis of relative risk. Dr. Weiner explained that separate procedural components needed to be evaluated independently. Dr. Prentice added that this is called a "component analysis of risk." If a research protocol has five interventions and only one is above minimal risk, the protocol is no longer under §404. If it also offers no benefit, it can now be considered only under §406. Mr. Gyi emphasized the need to provide sufficient guidance to IRBs to help them make this type of determination.

Mr. Barnes gave the example of a study proposed for adolescents under 18 who come to STD clinics related to sexual behavior and HIV risk factors. He asked whether such a study could be considered minimal risk under the circumstances and whether, if mandatory reporting requirements might be generated by responses, it would no longer be considered eligible for minimal risk analysis. Dr. Fisher said, in regard to the first question, that such questions would be minimal risk for that population and age group. The extent to which confidentiality-related issues constitute a risk goes beyond Subpart D. She suggested that when reporting could lead to consequences such as loss of health insurance of a criminal sanction, some Federal history suggests that this situation may be construed as greater than minimal risk. The participant must be aware of any statutory reporting requirements (as in the instance of reported child abuse) and the possible consequences. Dr. Kornetsky emphasized that the context of what is asked and what is done with the responses is very important.

Dr. Jones highlighted the importance of guidance and standardization to help in decision making, since both investigators and IRBs are increasingly burdened by the need to make decisions based on complex ethical issues. Dr. Kornetsky concurred with this concern, which IOM and NHRPAC have both tried to address.

Dr. Harris returned to the issue of well child equivalence, noting that restraint and even coercion may be required for reluctant children to engage in specific procedures, such as drawing blood. Dr. Kornetsky noted that each individual subject and each individual situation have distinctive elements that must be considered. Dr. Fisher commented, however, that determining whether a procedure is acceptable that the IRB finds to be minimal risk, such as a blood draw, is up to the parent, who knows how the individual child may react. The fact that a child does not like a pinprick does not elevate it to a level above minimal risk.

Mr. Adams asked whether the subcommittee envisioned developing guidelines for establishing the level of risk at different ages. Dr. Kornetsky did not expect to develop an exhaustive list, but did see giving examples for educational purposes. Dr. Fisher also said case examples would be useful, but it would be more important to explain the way of thinking used to address different situations.

Parental Consent

Dr. Polan raised the concern that parents signing informed consents on behalf of their children also need to fully understand pertinent facts about the research. Dr. Fisher noted that the IOM report has a section that specifically addresses this issue, but the subcommittee has not yet specifically dealt with it. Adequate parental permission and child assent procedures are essential layers in the "Russian doll" that constitutes the assessment of risk process.

Dr. Polan asked who is considered responsible for informing the parents. Dr. Fisher responded that the principle investigator (PI) is required to submit the informed consent form to the IRB, but the research team administers the form. Dr. Weiner added that, in addition to the parents, the public members of the IRB bear an important role in making this proxy judgment.

Implications of Standard for Review Process

Dr. Prentice observed that as IRBs currently using a relative standard begin to use a uniform one, many more research protocols may require consideration under §406, and that many of them may not be able to meet the §406 requirements. This could result in more protocols processed under §407. Dr. Fisher did not

believe, however, that issues related to minimal risk alone would have this result. It might push some IRB decisions into §406, but clear guidance would also facilitate some expedited review.

Dr. Jones asked how the minimal standard would apply when a benefit exists: would the same definition be used? Dr. Fisher said that procedures with direct benefit would fall under §405. Again, component analysis would be necessary. However, §405 does not introduce the term "minimal risk."

Minimal Risk Standard for Adults

Dr. Prentice asked whether the standard of minimal risk for adults, which is currently interpreted as either relative or uniform by IRBs, should also be a uniform standard. Dr. Fisher said she had fewer problems with the use of a relative definition for adults, since a good informed consent process gives them greater protection. Dr. Kornetsky noted that inconsistent definitions could be problematic, but agreed with Dr. Fisher that children have more need of the greater protection conferred by a uniform standard.

Interrelationship of Subparts

Mr. Barnes noted that Subpart C also uses the uniform standard, which is written in; this could lead to the conclusion that the intended standard in Subpart A is a relative one. Dr. Prentice asked how the standard in Subpart B would be interpreted. Mr. Barnes agreed to consider this topic as "homework."

Dr. Prentice stressed that not only does the ethical and regulatory integrity of Subpart D depend on this definition, but it also has implications for Subparts A, B, and C.

Dr. Fisher, Dr. Kornetsky, and Dr. Prentice asked committee members if they were ready to endorse the uniform standard of minimal risk as a proposal (as opposed to a recommendation). Mr. Barnes said he wanted to hear how §406 fit in before reaching this determination. Dr. Fisher agreed that it would be clearer to members what their endorsement actually meant after §406 has been discussed.

CONTINUED PRESENTATION, SUBPART D

Dr. Fisher continued the discussion by addressing the additional problems and challenges associated with §406, which establishes criteria for funding research that presents more than minimal risk to children without a prospect of direct benefit. One criterion is that the risk must represent a minor increase over minimal risk; an associated question that has puzzled IRBs is the meaning of "minor increase." A second criterion is that it presents experiences to subjects reasonably commensurate with their actual or expected experiences; here the terms to struggle with are "reasonably commensurate" and "actual or expected." The third is that the intervention or procedure is "likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition." Here, the terms "disorder or condition" and "vital importance" have proved problematic. Finally, adequate provisions must be made for assent and parental permission. Dr. Fisher noted after this overview that the use of a relative definition of minimal risk for §404 would result in an evaluation similar to what is required in §406 (e.g., does this child have a disorder or condition, and is the experience reasonably commensurate with their actual experiences).

Why should children be exposed to research that is greater than minimal risk that has no prospect of direct benefit? The suggested rationale has been that it might have a foreseeable benefit to an identifiable class of children (National Commission, 1977). However, the National Commission (1977), NHRPAC (2002),

and the IOM (2004) have all emphasized that it is not fair to expose children to a higher degree of risk with no direct benefit simply because they have a disorder or condition. The problem is that too lax a definition of "minor increment" would make children vulnerable to exploitation and an unacceptable degree of risk, while an overly stringent one would deprive them of the benefits of research that might ultimately improve their health and welfare. An overly lax definition might result in a false §405, while an overly strict definition could push all research into §407.

This challenge has been dealt with in various ways. The preamble to the final rule left the determination to the IRBs for unknown reasons. Committees have reworded the term as "just a little bit," "a little more than minimal," or "a slight increase," none of which seemed helpful to the subcommittee. The subcommittee sought to determine whether "minor" should be interpreted in a uniform sense (the same for all children) or a relative sense (specific to an individual child's situation). The subcommittee did not find a way to quantify the concept of "minor," so instead it proposed five criteria for determining whether an increment is minor (delineated in proposal 12).

- **Proposal 12: Accept five Criteria for "Minor Increase."** These include *magnitude, probability, duration, cumulative effect,* and *irreversibility of risk*. The first four criteria are similar to those used to determine "minimal risk," but the fifth was added. The committee felt it was important to consider whether or not the risk incurred might have irreversible consequences for the child. Essentially, if IRBs apply these five criteria uniformly, then the decision making process can achieve uniformity without the necessity of defining "minor" in a quantifiable way.

While the term "disorder" can be identified fairly readily, the term "condition" has proven more difficult for IRBs. For example, is simply being a child a condition? Is living in a poor environment a condition that justifies exposure to higher risk levels? It is important not to have an over inclusive definition that might result in unfair exposure to risk. The subcommittee proposes an approach that is consistent with that taken by the IOM.

- **Proposal 13: Interpret the Term "Condition" as Stated.** The term "condition" should be interpreted as referring to a specific (or set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an *established body of scientific evidence or clinical knowledge* has shown to negatively affect children's health and wellbeing or to increase their risk of developing a health problem in the future. The subcommittee believes such a definition would protect vulnerable groups within children from being "samples of convenience," but would not deprive them of research that could help them. The onus of proving the condition does have a negative effect in stated terms would be on the investigator and then on the IRB. The subcommittee is still unsure whether or not to include the term "clinical knowledge," which might "water down" the requirement.

- **Proposal 14: Accept three Criteria for "Vital Importance."** To determine whether the data would be of vital importance to children with a given condition or disorder, the subcommittee proposed that the procedure should not be something that could be achieved by less risky procedures, that it be essential for the scientific understanding or evaluation of procedures to alleviate the disorder or condition, and that it be perceived as essential to the understanding or amelioration of the child's disorder by practitioners and family stakeholders.

- **Proposal 15: Accept Equivalence in Defining Commensurate Risk.** The subcommittee observed that the term "commensurate" could be seen as a way of determining whether parents and children understood what they were agreeing to; therefore, the concept is important in achieving informed parental permission and child assent. It debated whether the term was meant to imply that the upper limit of what constitutes a "minor increment" could vary depending on the child's previous or expected experience. Does it mean, for example, that a hurtful procedure might be acceptable if the child had already experienced hurtful procedures? The subcommittee was not sure of this latter point, but did feel clear that the intent was to ensure that the proposed procedure was sufficiently similar to procedures the family had experienced for them to determine whether the child should incur the risk.

The full text of the §46.406 criterion in which the term "commensurate" is used is as follows: "The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." The subcommittee agreed that the term "actual or expected…situations" could refer either to situations experienced by the child who is the potential research subject or by the child's parents. Some members felt it might also refer to a sibling who had observed rather than experienced a procedure.

Dr. Fisher noted that there is controversy around whether the use of a hypoglycemic clamp in research for a child who has diabetes and has experienced it before constitutes a "minor increment" over minimal risk. If this is a minor increment for that child, would it also be a minor increment for the sibling who watched? A concern is that the healthy child could be subject to coercion to undergo the procedure. She therefore wondered whether such cases should be reviewed under §407.

- **Proposal 16. Identify Four Sequential Steps in the 46.606 Decision-Making Algorithm.** Dr. Fisher then reviewed a tentative decision making tree prepared by the subcommittee to guide IRBs. Four questions are considered to determine how a procedure should be classified:

    1. Is the research risk a minor increment over minimal risk? If not, refer to §404 or §407.
    2. Does the proposed child research population have a disorder or condition? If not, refer to §407.
    3. Is the research likely to yield generalizable knowledge of vital importance to the understanding or amelioration of the subjects' disorder or condition? If not, refer to §407.
    4. Are the research procedures reasonably commensurate with those inherent in the subjects' actual or expected medical, dental, psychological, social, or educational situations? If not, refer to §407. If yes, refer to §406.

- **Proposal 17. Affirm Application of §46.111.2 to Subpart D.** This states that IRBs should consider "only those risks and benefits that may result from the research," not those of the therapies the child might receive anyway. For example, if a research procedure is an "add on" to a procedure the child would ordinarily undergo, such as additional blood or fluid drawn for testing, only the add-on is to be reviewed.

Dr. Fisher stressed that the subcommittee needs the benefit of feedback from the committee. Next steps, if the proposed approach to "minimal risk" are acceptable, would be to review case examples and determine the impact of these proposals on decision making.

SECOND DISCUSSION, SUBPART D

Relative or Absolute Standard for "Minor" Increase

Dr. Prentice asked Co-Chairs to confirm whether the subcommittee was rejecting a relative standard in regard to whether or not a procedure is a "minor" increase or whether the subcommittee was "waffling" on the issue. Dr. Fisher said there was a notion that the standard should be absolute in order to protect children from higher degrees of risk, but she did not see how the standard could be absolute when the concepts of "condition" and "commensurate" are taken into account. Ms. Kornetsky said the subcommittee probably was waffling.

Criteria for "Minor" Increase

Dr. Prentice asked the Co-Chairs' opinion of the advisability of adding the concepts of "commensurability" and possibly "condition" to the five criteria identified for determining whether an increase is "minor" (Proposal 12). He gave the illustration of a bone marrow aspirate performed for research purposes: a child with leukemia who had had the procedure would understand the adverse effects, but for a healthy child it could not be considered a "minor increase" over minimal risk. Ms. Kornetsky commented that this implies a relative standard. Dr. Polan observed that for a cohort of children in a family, any kind of sibling research might constitute a benefit for the family, especially given a condition with possible patterns of genetic expression. Mr. Adams emphasized the importance of finding a way to ensure that IRBs and the public can have a common understanding of what is meant by "minor."

Dr. Jones raised the case of a researcher who asked for another 10 ccs. of bone marrow aspirant from a draw that was going to occur for a required diagnostic. He wondered whether this would be a minor increase over minimal risk. Ms. Kornetsky suggested that it is probably minimal risk.

Dr. Fisher said the subcommittee had been striving for something like the ceiling it established for minimal risk and had not been able to identify it, given the number of different possible procedures. Mr. Barnes commented that the calculus of risk necessarily depends on the condition of the child of that group of children; otherwise, everything would be thrown into §407. Dr. Fisher agreed.

Dr. Weiner observed, however, that something that is "commensurate" is not necessarily minor for the child. She added that the parent of a child with a disorder or condition seeks to normalize that child's life as much as possible, and to subject that child to kinds of assessment that normal children would not experience runs counter to that aim. Dr. Fisher commented that a parent whose only goal is normalization should not permit the child to participate. However, the consequence of nonparticipation might mean there is no progress in treating the child's condition.

Mr. Barnes asked if the intent of the fifth criterion, irreversibility of risk, actually means "irreversibility of harm if the harm occurs." Dr. Fisher concurred that that was the intent. Dr. Prentice suggested the language, *"reversibility of harm."* Dr. Fisher accepted this revision.

Mr. Barnes raised the question of how to assess diagnostic interventions that are done when it is unknown

whether the child actually has the condition. Dr. Fisher said that screening and diagnostic tools might be considered minimal risk. It is not clear whether the routine testing needed to further diagnose a problem would be considered a "minor" increment.

Dr. Fisher pointed out that the more narrowly "minor" is defined, the more decisions require a §407 process that takes away the IRB's ability to make an independent judgment about the ethics of proposed research. She wondered whether the §407 process was the right vehicle or whether it would be possible to craft an approach to §406 that could allow IRBs to make a decision for themselves. Dr. Prentice noted that the situation at present is that an IRB could determine that a research design is ethical and yet not be in compliance with the regulations.

Commensurate Experience

Mr. Barnes asked the source of the link between "commensurate…experience" and either parents' or siblings' experience, noting that he was aware of no support for this view in the text or the history. Ms. Kornetsky said this reference was in the National Commission proceedings.

Dr. Weiner added that the experience of a sibling watching would be different depending on the sibling's age.

"Condition"

Dr. Weiner was concerned that the way "condition" is formulated in Proposal 13, any child could be considered to have a genetic predisposition and therefore a "condition." Dr. Polan observed that it is extremely important to understand the new science and how it may inform the concept of who would benefit from research. Dr. Fisher suggested a standard for acceptable scientific evidence might be required to determine whether a population might benefit from a study.

In terms of the word "condition," Dr. Harris suggested that a condition might not necessarily be something negative, but something different from the average such as unusual muscular development. Dr. Fisher agreed but wondered whether there could be positive characteristics that would make it ethically acceptable to accept greater than minimal risk in a study.

Algorithm

In regard to the proposed four-step algorithm, Dr. Gyi asked whether the IRB would have to "kick" the research under review to a §407 or if it could simply disapprove it. Dr. Fisher and Ms. Kornetsky responded that disapproval is an option. Dr. Prentice asked what would happen if the IRB disapproved the proposal and the investigator asked for a §407 review. Dr. Fisher believed that only an IRB is entitled to apply for a §407 review.

MOTION:

> Mr. Barnes moved that SACHRP accept the idea of a uniform standard for minimal risk analysis on a preliminary basis, but with the caveat that continued acceptance is contingent on successful resolution of issues related to research that involves more than minimal risk and no prospect of direct benefit. Various members seconded the motion.

ACTION:

The motion was approved unanimously.

The Chairman suggested that there was no need to act on the subcommittee's other proposals at this time. The Co-Chairs said the discussion of these proposals had been helpful.

Subpart C. Subcommittee on Research Involving Prisoners

Mark Barnes, J.D., L.L.M; Nancy Dubler, L.L.M.

Mr. Barnes, Co-Chair of the Subpart C Subcommittee, introduced Co-Chair Ms. Dubler, who was previously the Co-Chair of NHRPAC, which also reviewed Subpart C issues. Ms. Dubler framed the report with a reminder that the U.S. incarcerates more of its population than any other Western nation. Inmates are disproportionately poor and people of color. Many have sexually transmitted diseases that are inadequately treated during their incarceration, posing public health dangers. Incarceration may be used not simply to prevent people from escaping, but as society's way of putting a set of troubling health and social issues out of sight behind stone walls. She quoted Sister Antonia, a prison chaplain who recently commented, "I think prisoners are viewed in the United States the way slaves were viewed in the 1800s. Good people can still look at them as less than equal to other humans."

She said that much of the language of Subpart C is opaque, and the ambiguity poses barriers to useful and important research. The subcommittee believes that, in the short term, changes to OHRP guidance could address many of the issues IRBs have struggled with. It has been working closely with the Office of Counsel at DHHS to see which issues fall into this category and which can be addressed only through a more long-term process of changing the regulation itself, a process that requires publication in the Federal Register. The Co-Chairs' presentation focuses on problems that it believes could be addressed through changes in guidance.

Research with Incarcerated Populations

There is no registry of prison research. Only the Central Intelligence Agency (CIA) and the Social Security Administration have signed on to Subpart C, leaving other studies outside OHRP's jurisdiction. The Bureau of Prisons has its own version of Subpart C that governs research in Federal prisons, providing many parallel protections. Based on the reports of subcommittee members, policies related to research vary widely among state prison systems, as well as among city and county jails nationwide.

Intern Courtney Storm reviewed published studies from peer-reviewed journals to determine what type of research is being conducted. Many studies relate to mental illness, substance abuse, HIV/AIDS, TB, and Hepatitis A, B, and C. Most are social and behavioral studies as opposed to biomedical interventions. It is possible that much of the research being done is carried out by graduate students and is not published in a readily accessible location.

Who is a Prisoner?
While regulatory language defines a prisoner as "any individual involuntarily confined or detained in a penal institution," the subcommittee suggests that the term should not be restricted to those in penal institutions and believes the concept can be broadened through guidance as opposed to a formal change of the regulation itself. The subcommittee believes that the definition should encompass any individual involuntarily confined or detained in either of the following circumstances:

1. In a penal institution, medical or mental health facility, work release facility, halfway house, or prerelease facility, as a result of a criminal proceeding, or
2. In a penal institution due to commitment pursuant to a civil statute, including those confined for civil or criminal contempt or as material witnesses.

Persons in mental institutions would be considered prisoners if they are there are a result of:

1. Commitment pursuant to a criminal proceeding for evaluation of mental competency or for treatment due to a finding that the individual is not fit to stand trial;
2. A finding of not guilty by reason of insanity/mental disease or defect, or guilty but mentally ill;
3. A finding in a criminal proceeding that the charges were dismissed or suspended and that such commitment is implemented as an alternative to criminal prosecution or incarceration in a penal institution; or
4. Commitment pursuant to a civil statute confining an individual who was convicted of a sex offense and is completing his/her sentence whose subsequent placement in a mental institution does not involve a finding of mental illness.

This guidance is based on the notion that people may have their liberty constrained so that they are unable to leave a particular place or secure their own health care as the result of actions taken by various courts, by count orders, or by statutes. Subpart C is triggered when there is a "nexus," or clear connection, between the terms and conditions of confinement and the loss of liberty. If the connection is one that does not trigger Subpart C, it might still fall under Subpart A. The underlying logic is based on the understanding that, in prison, it is impossible to distinguish between a refusal of care and a denial of care, as the reason for missed appointments is often unclear. Also, because the space is owned by corrections, everything that goes on occurs under the supervision of this authority.

Status of a Subject Who is Incarcerated After Enrolling
In 2003, OHRP issued guidance stating that when a protocol has been approved under Subpart A with no prospect that a participant would be incarcerated and a participant is subsequently incarcerated, the investigator is required to resubmit the protocol to the IRB for approval under Subpart C. This results either in much work for IRBs and investigators or in inmates being discontinued. The subcommittee believes, based on consulting with HHS General Counsel, that the stance taken in the 2003 guidance has not solidified and could be altered through new guidance, if desired.

Subcommittee members observe that the individual's original consent was not coerced in the context of a correctional setting. While additional inquiry is needed in view of the subject's new circumstances, the subcommittee envisions a focused inquiry by the investigator into risks and benefits caused by this adverse and unexpected event. The researcher's review would encompass the risk of the research, the enhanced risk resulting from the individual's incarceration, and the importance of the research to the

inmate's health and wellbeing. This would result in a report for deliberation by the IRB that reviewed the original proposal. The IRB would need to examine whether the prisoner would be subject to coercion or unable to give voluntary consent in the new context, the likelihood of violations of confidentiality and the potential for harm from such violations, and the likelihood of secondary harms (such as stigma or segregation from other prisoners).

The subcommittee believes that when there is little risk to the individual and little involvement of the correctional institution is required to continue the study, analysis under Subpart A should be sufficient. However, the greater the risk to the inmate and the more enmeshed the protocol is with levels of correctional administration, the less likely it is that the person would be allowed to continue. No person who was in a protocol and subsequently incarcerated would be allowed to continue in the study without a focused review.

The subcommittee believes this process would result in a richer and more beneficial review that would not be constrained by the four narrow categories available under Subpart C, which are not applicable. For medical intervention protocols, determination of whether the subject should or could continue would require a focused evaluation of the specific protocol and the inmate's specific circumstances (which would be required in any case under Subpart A). This type of analysis would set a tough standard under Subpart C.

Subsequently incarcerated persons as prisoners. Dr. Fisher expressed concern that these subsequently incarcerated individuals are not considered prisoners, despite satisfying every criterion stated earlier for being considered as such. Ms. Dubler responded that one reason the subcommittee considers them a separate group is, as mentioned earlier, that their consent was not coerced while in this setting. Also, it would detract from the validity and usefulness of much useful research. Dr. Fisher suggested it would be more appropriate to frame the guidance to indicate that the individual is to be considered a prisoner, but that there are situations in which the four classifications could be waived. Mr. Barnes responded that this would be a possible long-term solution, but at present cannot be accomplished without rewriting the regulation.

Consent. Ms. Kornetsky saw a need for the prisoner's consent to continuing participation, observing that consent is understood as a continuing process. Mr. Barnes pointed out that the investigator is not aligned with the correctional institution. Dr. Fisher emphasized that reconsent should nevertheless be required, since it was originally given in different circumstances. Ms. Dubler responded that the first step would be to go to the research subject and ascertain the individual's desire to continue. However, Dr. Fisher felt this should occur only after the research was found to be approvable.

Prisoner representatives for focused reviews. Dr. Prentice commented that the focused review should always require a prisoner representative. Mr. Barnes said the subcommittee agrees; however, if correctional expertise already exists on the IRB, an additional prisoner representative would not be required for this purpose. The expertise needed to evaluate risks and benefits would be required under Subpart A.

Little risk/minimal risk. Ms. Kornetsky questioned the meaning of "little risk." Dr. Prentice asked whether the term "minimal risk" could be substituted. Ms. Dubler felt this would not add clarity, since Subpart C has its own definition for the term, which is not clearly understood. The definition in Subpart A is also

unhelpful. Dr. Fisher was concerned that the extent of risk appeared not to be indexed to a healthy person, resulting in decreased protection. Mr. Barnes held that the minimal risk concept was not applicable to the analysis, which applies only if a waiver is requested under Subpart A. Ms. Adams remarked, however, that it was important to define "little risk" in a way that both the prisoner and the IRB can understand. Dr. Prentice supported the Co-Chairs' position, noting that the concept of minimal risk does not apply because the IRB has already made a determination of the risk classification in a non-incarcerated context, and the issue is whether that determination has or has not changed. The question is therefore not whether there is little risk, but whether there is little *additional* risk. The Co-Chairs agreed with this explanation and Dr. Fisher said it answered her question.

IRB workload. Ms. Kornetsky raised the question of the additional workload this procedure places on the IRB. Mr. Barnes said the subcommittee felt this approach would be less onerous than a complete new review under Subpart C. This vulnerable population deserves the benefit of a review, and the subcommittee believes that analysis under Subpart A will be more protective that review under the "almost moribund" four categories. Dr. Prentice added that there is a justice issue: if Subpart C is applied, many incarcerated persons will simply be dropped from the study. (Mr. Barnes and Ms. Dubler said there was anecdotal evidence that this is the option most investigators choose.)

Precedent. Ms. Kornetsky was concerned as to whether a precedent was being established that would apply to other populations, such as the mentally incapacitated. Mr. Barnes believed that this would set a precedent only for this particular population. Ms. Dubler added that children are the only other similar population for which special protections have been established. She also pointed out that an investigator who recognizes a reasonable chance that some subjects may be subsequently incarcerated could have the protocol reviewed under Subpart C at the outset.

"Good science." Dr. Fisher held that continuing a protocol with a prisoner when that possibility was never envisioned by the investigator is likely to lead to bad science. Ms. Dubler said the investigator needs to make this call, but there should still be a review by the IRB; continuation in the protocol might even be ethically required. Dr. Fisher did not feel this should be the sole province of the investigator, who would be under pressure to maintain the required power projected for the study. Dr. Prentice, however, said the investigator would be more likely to drop the prisoner because of the hassle posed by continuing the study in prison.

Interpretation of Follow-up Requirements

The regulation language is as follows: "Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of the individual prisoner sentences and for informing participants of this fact" (§46.306[a][7]). The subcommittee considered whether this required follow-up applies to persons released from prison while a study is in progress or to subjects who remain incarcerated after the study ends. The subcommittee believes that the safety and welfare of subjects would have to be considered in each eventuality.

Payment. Dr. Prentice asked who would be responsible for paying for this care. Ms. Dubler said that since prison health services do not cover study interventions, this care should be built into the cost of the study. A researcher conducting research with this population would have to address this issue in advance. Mr. Barnes agreed with Ms. Kornetsky that this could result in having a prisoner dropped from a drug study that might be beneficial; however, the existing language of the regulation requires this provision.

Application. In response to a question from Dr. Gyi, both Co-Chairs held that this provision would apply only to protocols reviewed under Subpart C and not to those who are subsequently incarcerated.

Regulations 45 CFR 36 vs. 312. Dr. Gyi observed that many IRBs apply both 45 CFR 46 and 312 (Food and Drug Administration [FDA]). Ms. Dubler said the intent of Subpart C is to block the applicability of §312. Mr. Barnes commented that the analysis would be basically the same under either regime. FDA has not signed onto Subpart C, however.

Dr. Gyi said that some subjects who were incarcerated have been dropped from studies under §312 because even when the investigators wanted to continue the protocol with those subjects, sponsors were unwilling to support it. Mr. Barnes said this would require further thought on the part of the subcommittee. Ms. Dubler suggested posing a question to FDA concerning the number of approved studies in a given period of time that involved subjects who were subsequently incarcerated.

Identification of a Prisoner Representative

The subcommittee addressed the issue of who would be an appropriate prison representative to fulfill Subpart C requirements. They felt the selection should be based on a functional analysis rather than on the simple fact that an individual is an ex-prisoner. Some ex-prisoners might not be well prepared to participate on an IRB; advocates who work with the population could be more knowledgeable. An appropriate representative should be able to understand and appreciate the needs of inmates, understand the relevant correctional health and mental health delivery systems, have an affinity for the incarcerated populations, be an effective voice and not a token, understand the potential for coercion in prison settings, and know the configuration of the relevant prison settings, populations, and administrations. This individual should function as a part of the IRB at all times, not simply when prison issues are discussed.

The subcommittee also saw a need for guidance from OHRP that underlines the responsibility of investigators – not just IRBs – to ensure that ethical issues in prison-based research are addressed the investigator should communicate problems and propose solutions to the IRB that will protect the subjects' interest. The subcommittee also recommends, in regard to multi-site studies, that each IRB overseeing a study should include a prisoner representative – not, as current guidance requires, only one for the study as a whole.

Full-time IRB membership. Dr. Prentice questioned the feasibility of having a full-time prisoner representative on the IRB. He noted it is especially hard to find qualified persons for this role. Mr. Barnes said it might be difficult, but the important thing is to have someone able to participate constructively in the discussion, and this is one way to make this more likely. Dr. Prentice felt that should be some "wiggle room." Ms. Kornetsky agreed. She suggested the subcommittee state the desired outcome, but not prescribe the method. Mr. Barnes said he would take this feedback to the subcommittee.

Representatives for multiple sites. Dr. Weiner asked whether there was enough state-to-state variation to

justify the requirement for multiple prisoner representatives. The Co-Chairs said there was "enormous" variation.

Subsequently incarcerated. In response to a question from Dr. Gyi, Ms. Dubler said a prisoner representative supporting this process would not need all the characteristics required for a Subpart C review. Such an individual could provide expertise on the specific issue and leave.

Control Group vs. Placebo

Ms. Dubler said that Subpart C regulations provide special protections for "control groups which may not benefit from the research." OHRP guidance presently holds that a "standard of care" research arm is a condition of the research that confers no benefit; therefore, such designs require HHS Secretary review. This position was first taken 4 years ago; it constitutes a departure from previous OPRR positions that only research that involves a placebo requires Secretarial review. The subcommittee holds that an inmate who is receiving standard of care is receiving a benefit, and no review should be required. Analysis should be based on whether "clinical equipoise" exists between the two arms.

Placebo. Dr. Prentice asked whether under current regulations, the use of a placebo triggers the review automatically, even if clinical equipoise is found. This was understood to be the case. Ms. Kornetsky asked how many studies have been referred to the Secretary for this reason. Mr. Barnes said there were three, but the real problem was the studies that did not make it that far.

Clarification of the Meaning of "Minimal Risk" in the Regulation

Co-Chairs pointed out that Subpart C clearly intends the comparator for "minimal risk" to be healthy, normal functioning people as opposed to inmates. This has been done in order to provide additional protection.

National Prisoner Research Review Board

The subcommittee discussed whether there should be a national review board for prisoner research, but members did not agree and are unlikely to develop a recommendation on this topic.

Future Work on these Issues by the Institute of Medicine

Ms. Barnes explained that the subcommittee strongly believes that Subpart C does not achieve its purpose and needs to be reworked to respond to legitimate concerns and to be more protective of subjects. The subcommittee supports the idea that an Institute of Medicine committee examine these issues and make suggestions for rewriting Subpart C. This might result in more Federal agencies being willing to sign on to its provisions.

The subcommittee now intends to finalize its draft report and present the final report to the committee.

DISCUSSION

The Chairman invited members to give the subcommittee feedback on its presentation. At this point, Dr. Fisher requested that the subcommittee develop a rationale for broadening the definition of "prisoner" to other populations that are not in penal institutions. Dr. Gyi said that additional work was needed to help members understand the ramifications of some issues. For example, he felt the role of the prisoner representative should be designed in the context of the focused review for the subsequently incarcerated.

Public Comment

The Chairman invited members of the public to comment.

- Sharon Hill Price from Copernaica's Group (an independent IRB) said she was "blown away" by the meeting and wanted to emphasize the need to rewrite the regulations. She has heard members discussing short-term fixes, but the process can only be improved in the long term through rewriting. In response to a question from the Chairman, she said that she believed all the regulations, including Subpart A, may need to be rewritten. Ms. Price also emphasized a need for consistency in regulations between FDA and OHRP. She observed that in a sense, any individual advised to participate in a study by his or her primary care physician could be considered vulnerable because of that relationship.

- John Mather, head of the Office of Research Compliance Review at the University of Michigan, commented that the Association for the Accreditation of Human Research Protection Programs (AAHRPP) has put out very helpful documents to guide self-assessment for accreditation. He emphasized the need to clarify and update HHS guidance. Harmonization between OHRP and FDA would help the university's seven IRBs reach decisions more comfortably. Collecting best practices for IRB reference would also be useful.

NIH's Harmonization Program
Amy Patterson

Ms. Amy Patterson provided basic background on the harmonization program of the National Institute of Health (NIH), which was the subject of discussion at the March SACHRP meeting. She offered six clarifying points:

1. The initiative is known as the Clinical Research Policy Analysis and Coordination Program. Located in the Office of Science Policy, which is within the NIH Director's Office, it represents a long-term commitment and is considered a standing program.
2. The initiative did not occur in response to a Congressional mandate. Rather, it is a response to the expressed need of the research and research oversight communities for harmonization of policies and requirements.
3. The goal of the effort is not to reduce research protection, but to enhance protections by clarifying and streamlining policies and requirements.
4. The program is not focusing exclusively on modifications to the Common Rule, but it is interested in this committee's work.
5. The program's first priority is adverse event reporting, but it is also exploring other issues, such as the responsibilities of IRBs and Data and Safety Monitoring Boards (DSMBs) in evaluating safety information and the feasibility of various central review mechanisms. They are also looking at challenges related to the Health Insurance Portability and Accountability Act (HIPAA).
6. The program is working closely with its "sibling" agencies but has not established a formal advisory group. It does intend to engage its constituencies in focus groups to provide input into the process.

In response to a question, Ms. Patterson clarified that the effort has both an external and an internal face; NIH is engaging in dialogue with other agencies, many of which are also looking at establishing new regulations and policies.

Recommendations of SACHRP Regarding HIPAA and Human Subjects Research

Mark Barnes, J.D., L.L.M.

Mr. Barnes presented highlights of a 16-page draft letter with several recommendations intended for delivery to HHS Secretary Thompson. The content of the letter is derived from presentations at SACHRP's March meeting. However, although the committee endorsed the approach of the Association of American Medical Colleges (AAMC), he and Dr. Weiner did not incorporate the AAMC's recommendation that HIPAA should not apply to human subjects research because they did not think it was likely to happen, whether it ought to or not.

Accounting of Disclosures

HIPAA requires that when information is disclosed under one of the specified exemptions, a note must be made in the patient file as to who received the information**.** This requirement is taxing in large retrospective medical records research. There is also a treatment disparity in that similar notes are not required for internal disclosure. A limited modification that provides an exemption for research involving over 50 subjects has not proved helpful, in that it creates other burdensome requirements. Compliance is so time consuming, in fact, that some prefer to risk a sanction from the Office of Civil Rights. The American Association of Medical Colleges (AAMC) proposes that research disclosures be exempt from accounting requirements. Instead, researchers would be required to explain the conditions under which subject records might be accessed in a notice given to all subjects.

In response to questions, Mr. Barnes said the number of requests for accounting under HIPAA is unknown. The requirement encompasses any disclosure of medical information outside the workforce. The only exception occurs if the individual has signed a HIPAA authorization for the study.

- **Draft Recommendations:** Research disclosures should be expressly exempted from the accounting requirements. Covered entities should be required to inform patients in the Notice of Privacy Practices that their patient health information (PHI) may be used and disclosed for research purposes without authorization where additional safeguards are in place.

De-Identification Standards

HIPAA requires that data must be stripped of 18 separate categories of information. Persons doing exempt research already anonymize data, and Mr. Barnes was unaware of any harm to subjects that resulted from this strategy. In some types of research, information such as the birth date is an important part of the research. The Office of Civil Rights has said that such information should be included only if a data use agreement is signed between the data giver and recipient. Mr. Barnes proposed that three identifiers – zip codes, geographic subdivision, and treatment dates – be deleted in order to align de-identification standards with the historic Common Rule standard for identifiable private information. Dr. Prentice suggested adding birth dates, and Ms. Kornetsky suggested broadening that to any dates. Mr. Barnes said he would add this recommendation to the letter.

- **Draft Recommendations**: Standards for de-identification under HIPAA should be more closely aligned with the historic Common Rule standard for identifiable private information. The following categories should be considered for deletion: zip codes, geographical subdivisions, and [treatment] dates.

Subject Recruitment

Mr. Barnes said the history of HIPAA regulations in this area has been one of inconsistency and frequent "moving the goal posts." The draft letter points out these inconsistencies, which Federal personnel sometimes say do not exist. Examples of troublesome areas include:

- For unknown reasons, NIH guidance (February, 2004) allows internal researchers to use retrospective records review to identify and contact potential subjects. However, external researchers are allowed to use such records only to identify subjects, resulting in added steps.
- The same guidance permits researchers to access and individual's Patient Health Information (PHI) from the data base of a covered entity if the individual signed an authorization allowing this. This, however, contradicts a response from the Office of Civil Rights to NHRPAC 18 months ago.

These regulations, Mr. Barnes asserted, are not more protective of subjects. They actually allow all directly employed researchers to identify and contact subjects they have never seen before in a treatment relationship. Under the Common Rule, most IRBs do not allow persons who have no direct relationships with a patient to contact them.

External researchers have approached this dilemma by routinely getting a complete or partial waiver of authorization from the IRB. An alternate approach is to draft a "business associate agreement" between the disclosing and receiving entities, which is also typically boilerplate. Because of such complexities, hospitals that do not want to run afoul of HIPAA sometimes refuse potential researchers. Mr. Barnes presented a recommendation that research (both identifying and contacting potential subjects) should be considered "health care options" of a covered entity. Alternatively, he suggested additional formal guidance from DHHS confirming that no separate permission is required to contact potential subjects. Another alternative would be that the provision for disparate treatment of internal vs. external researchers would be discarded.

Dr. Prentice confirmed with Mr. Barnes that someone performing preparatory activities for research activities would typically have a protocol for this phase of the project reviewed by the IRB. This, Mr. Barnes said, does not contradict OHRP's current position. Dr. Prentice questioned the need for the alternative recommendations, and Mr. Barnes concurred that the first recommendation was preferable. Ms. Kornetsky pointed out that the alternatives were inconsistent with what is done under the Common Rule. The agreed-on recommendation then stood as follows:

- **Draft Recommendation:** Research recruitment (both identifying and contacting potential subjects) should be considered "health care operations" of the Covered Entity. The requirement not to remove PHI from the Covered Entity's premises should be modified.

Additional discussion points included the following:

- Mr. Barnes said that internal researchers contacting potential subjects are viewed as part of "health care operations."
- Dr. Fisher asked how an external researcher could be considered part of the health care operations of the covered entity. Mr. Barnes gave the example of a voluntary medical staff member at Hopkins who is not directly employed. Such an individual is not legally internal. Mr. Barnes stressed that IRBs should be paying attention to records access by persons who are truly external.
- Dr. Fisher pointed out that not all research comes under the Common Rule, so the Covered Entity might be allowed to give out data to people with no protections. Mr. Barnes responded that other sources of law would require physicians to exercise appropriate fiduciary duties over patient information.

Research inside/outside Common Rule. Dr. Weiner said she was not comfortable with the recommendation, partly because it would abrogate her rights as a parent to control access to her child's records. Dr. Fisher felt that such access would be potentially distressing to parents who would receive calls from unknown persons who are aware their child has a particular disease. She wanted to add language about expectations under the Common Rule and additional language for research that does not fall under the Common Rule. Mr. Barnes suggested that for research activities that do not far under CFR Part 46, there should be no changes.

Business associate. Several members, however, remained uncomfortable with the option of access through the "business associate" agreement. Dr. Fisher suggested adding language that would require the covered external researcher and the Covered Entity to protect confidentiality. Dr. Polan sought language that would ensure the association was a real one. Mr. Barnes suggested this could be approached structurally by broadening the concept of an Organized Health Care Arrangement (OHCA) in a way that basically abolishes the distinction between internal and external researchers. Dr. Fisher found this option acceptable and Mr. Barnes agreed to make this modification.

Removal of PHI. Dr. Gyi questioned the recommendation to modify the requirement related to removal of PHI from the premises, which contradicts the need for review preparatory to research. Mr. Barnes said the requirement was problematic as stated because the meaning of "premises" is unclear for entities that may have several "premises." Dr. Gyi clarified that the intent of the recommendation is to modify the requirement so that a researcher who is part of the OHCA can remove the PHI.

Databases and Tissue Banks

Future use. Mr. Barnes explained that a discrepancy exists between HIPAA and the Common Rule in regard to future uses of databases and tissue banks. HIPAA does not allow blank research authorizations for "future unspecified research"; subsequent authorization will be required, even if the subject has given informed consent to both the primary study and future uses. The Common Rule does allow the IRB to review and approve a form that seeks consent for future uses. For example, Mr. Barnes explained, tissue deposited for future use might be placed there with a general understanding that it would be used for cancer research. The researcher who wants to access it later would get a waiver of informed consent from the IRB.

The draft recommendation to address this situation was as follows:

- **Draft Recommendation:** When the IRB has considered and approved a consent form that permits consent to certain future uses under the Common Rule standard, HIPAA should likewise permit subjects to authorize the use and disclosure of their PHI for the same future uses without invalidating the research authorization.

Dr. Fisher and Dr. Prentice, however, wanted modified language that ensured the specificity required under the Common Rule was brought out. Dr. Prentice noted that IRBs waive informed consent too often under §116(d), and there is no real documentation of how the waivers meet requirements. Mr. Barnes stated that he believed it would be possible to craft an informed consent that met all the requirements of the Common Rule.

Compound authorization rule. Mr. Barnes explained that under HIPAA, it is not possible to combine authorizations for two separate research studies in the same document. As a result, even if there is one consent form for a primary and secondary study, two separate authorizations are required. It is not possible to have an explanation of the intended study sequence in one document. The draft recommendation presented was as follows:

- **Draft Recommendation:** HIPAA's compound authorization rules should be revised to permit the combining of research authorizations into one form when researchers seek to bank data and materials as part of an underlying clinical trial.

Dr. Weiner pointed out, however, that "opt out" provisions are needed to separate the decisions patients are required to make. It is not a problem if they are on the same physical piece of paper (prohibited under HIPAA), but it should be clear that the patient can authorize one use and not the other.

Research exempt under common rule. Mr. Barnes explained that some "minimal risk" research is considered exempt under the Common Rule but is nevertheless subject to HIPAA requirements. This means that researchers are forced to seek waivers of authorization from IRBs for research that is exempt. The proposed recommendation was:

- **Draft Recommendation:** Revise the categories of research for which authorization is not required to include research determined by an IRB to be exempt form the requirements of the Common Rule.

In addition, there are transition provisions that specify that a study that received a waiver of informed consent prior to the specified compliance date would not require a waiver of authorization. However, the provisions did not state that this would also apply to a study exempted from the Common Rule prior to that date. The result is that many exempt studies are underway that are exempt from the Common Rule but, as of the specified compliance date, are violating HIPAA because they do not have a HIPAA waiver of authorization. To address this, Mr. Barnes proposed the following:

- **Draft Recommendation:** Revise the transition provisions to grandfather not only research that received an IRB waiver of informed consent prior to HIPAA's compliance date, but also research that did not receive IRB review or oversight as a result of meeting an exemption under the Common Rule.

International research. When a researcher from an American covered entity goes to another country to do

research and collects PHI, Mr. Barnes explained, "whatever they touch turns into protected health information." This means that every international subject is technically required to sign the same five-page authorization that Americans sign, even through it may not be meaningful to them. He therefore recommended:

- **Draft Recommendations:** Give clear guidance in the near future on the scope of HIPAA's application in the international context and restrict that application as much as possible; clarify, if legally possible, that PHI collected from foreign nationals outside the U.S. by researchers who are affiliated with Covered Entities is not subject to HIPAA's requirements solely as a result of the researcher's affiliation with the Covered Entity or clarify how international research can be insulated from HIPAA's applicability; clarify that the IRB may waive authorization in the international context because foreign subjects would be overwhelmed due to cultural and language barriers. Alternatively, clarify that the IRB may approve an alteration of the authorization requirement to provide a truncated version of the authorization elements.

The following points were discussed:

- Dr. Fisher objected to the language allowing a waiver of authorization, preferring to emphasize the need for a culturally appropriate authorization process. Dr. Polan also wanted to delete the assumptions, which she felt sounded patronizing. Dr. Fisher proposed deleting the language, "restrict that application as much as possible," given that there is a reason HIPAA exists in the U.S.
- Dr. Fisher asked why the words "if legally possible" were needed. Mr. Barnes responded that HIPAA contains the concept of a "hybrid entity," which might be used to carve out some international activities.
- Ms. Kornetsky and Dr. Fisher wanted to remove the words, "or clarify how international research can be insulated from HIPAA's applicability," which are not needed.

Public health research. The problem in this area, Mr. Barnes said, is that state hospital associations and individual providers have not wanted to hand over public health data to government agencies because they do not see a HIPAA exemption for surveillance activities. Public health authorities, which are allowed to access data, are defined as those responsible for public health matters as part of their official mandate. An agency such as the Agency for Healthcare Research and Quality (AHRQ) does not meet this definition and has therefore been denied the data it needs. Mr. Barnes therefore recommended:

- **Draft Recommendations:** Revisit the definition of public health authority and the exception for uses and disclosures for public health activities and broaden them sufficiently to ensure that Federal and State agencies that have as their primary purpose the prevention or control of disease, injury, or disability, or the analysis of data in alliance with public health and public benefits agencies, fall under this exception, even if the legal authority establishing such agencies failed to authorize them to compel the collection of PHI in the course of their duties.

DISCUSSION

Ms. Kornetsky and Mr. Barnes agreed to work on a new draft of the recommendations that incorporated the comments received. The committee considered approving the recommendations as presented in

principle, taking into account suggested revisions. However, members ultimately decided to wait to approve the recommendations after reviewing the letter to the HHS Secretary and the revised recommendations.

Closing Remarks

The Chairman thanked everyone for a productive meeting.

Secretary's Advisory Committee on Human Research Protections

July 26-27, 2004 Meeting
Washington, D.C.

Summary Minutes

TUESDAY, JULY 27

Welcome and Business Items
Ernest Prentice, Ph.D.

Dr. Prentice welcomed everyone to the second day of the meeting and provided an overview of the day. He noted that the next meeting of the committee would be October 4-5, 2004.

The Chair invited a motion to approve the previous meeting's minutes.

MOTION:

Mr. Barnes moved to accept the minutes of the March 29-30, 2004 meeting. Dr. Weiner seconded the motion.

ACTION:

The motion was approved unanimously.

The Chairman informed the group that Dr. Nigel Harris has accepted a position as Vice Chancellor at the University of West Indies and will no longer be available to serve on SACHRP. Dr. Prentice read a letter of appreciation from Secretary Thompson acknowledging Dr. Harris's contribution. He also presented a plaque with Dr. Harris's name and service dates. Dr. Harris thanked members for the opportunity to contribute.

Social and Behavioral Research Issues: Panelists and Presentations

Dr. Prentice explained that the purpose of this panel is to address concerns by investigators engaged in social and behavioral research that the Common Rule is being misinterpreted and applied in ways that inhibit research. He noted that researchers were all nominated by organizations of which they are members, including the American Psychological Association (APA), the Federation of Precognitive and Behavioral Sciences ("the Federation"), and the American Sociological Association.

Remarks by Michael Fendrich, Ph.D.
Dr. Fendrich began with the observation that the average person is bombarded with surveys on a daily basis. He noted that these surveys contain both harmless and potentially sensitive questions, such as those routinely asked of blood donors: "Have you ever used needles to take drugs, steroids, or anything not

prescribed by doctors?" Noting that such questions have been answered by millions of people, he reminded members that the definition of minimal risk relies on a comparison with daily life and routine physical or psychological exams and tests. He then posed the question, "are surveys, interviews and research using such questions considered more than minimal risk because they include such questions?" He argued that because such questions are common, exposure to them cannot be above minimal risk. He therefore recommended:

- **Suggested guidance:** Sensitivity of question content should never be the sole basis for IRB determination of risk level in a research study.

Turning to the issue of informed consent, Dr. Fendrich noted that many of the elements of informed consent described in the regulations are irrelevant to most behavioral survey research, and even counterproductive. An example of an irrelevant requirement is the obligation to disclose "alternative procedures or courses of treatment" for a survey that is not intended to contribute to the health of the participant. He argued that provisions for confidentiality of records are also not relevant to much survey research. Also, the mere presence of the obligatory statement that child abuse may be reported may sound threatening; since the incidence is so rare, he suggested, it is not necessary.

Dr. Fendrich also cited statements frequently found in consent documents about possible adverse effects of the questions. He observed that reactions to sensitive questions vary, and there is little systematic research on these reactions. He believed such warnings did not really protect subjects, who always have the option of leaving questions blank. His experience is that extreme discomfort or embarrassment are very unusual reactions. Therefore, when the declining rate of survey participation is a concern, it is a mistake to "frontload" surveys with warnings that may decrease participation.

Finally, Dr. Fendrich pointed out that a recent National Research Council (NRC) Report (2003) found that 18 percent of IRB Web sites, representing 47 major research institutions, do not indicate that irrelevant elements of informed consent may be omitted. He suggested that templates following best practices for securing consent in social/behavioral research should be developed and disseminated. He proposed the following:

- **Suggested guidance:** IRBs should be reminded that in minimal risk social/behavioral survey research it is often most appropriate to waive elements of informed consent (NRC, 2003). Unnecessary specific statements relevant to clinical research settings should be omitted wherever possible. In the absence of relevant empirical evidence, specific statements about question risk/reaction should generally be omitted from consent documents.

Remarks by Karen Hegtvedt, Ph.D.

Dr. Hegtvedt began with two examples of studies reviewed by the IRB committee she has chaired for 4 years. First, in the "dark ages" of the committee, she described putting a historian going to Brazil to study ethnic groups "through the ringer" because he did not want to get written documentation of consent (ultimately waived). A second study was carried out by a woman studying distress in rural Mongolia who brought in beautiful formal consent forms. However, after making inquiries, Dr. Hegtvedt learned that in this largely illiterate, post-Soviet country, such forms would be culturally inappropriate. In fact, Dr. Hegtvedt argued, having people sign a written document they may not understand could actually increase harm to subjects. She therefore emphasized the benefits of regulatory flexibility, both to PIs and to

participants.

Social and behavioral research methodologies are diverse and often complementary; it is important to be sensitive to the nuances of their characteristics and differences. Most of them, whether qualitative or quantitative, pose minimal risk to subjects. Quantitative methods create and test models and hypotheses, using methods such as surveys, censuses, and experiments. Behavioral research seeks to illuminate the complexity of the social world through observations, interviews, oral histories, and focus groups. In some cases, both quantitative and qualitative research may be used in a complementary way.

Dr. Hegtvedt offered the following insights pertaining to review of qualitative research by IRBs:

- Determine whether it is research. Much qualitative research falls short of the standard of generalizability.
- Where human subjects are involved, pay attention to confidentiality issues.
- Be mindful that this type of research is typically about "two people talking to each other." Pay attention to the purpose and potential benefits, the context (which is relevant to the suitability of the proposed approach), and the data collection methodologies.
- Data collection methods must ensure benefits (though these are usually not benefits to the individual) and minimize risk and harms.
- Informed consent procedures must be appropriate for the context (including culture) and method.

Observation in public and private places raises many specific issues. In a public space, the study may fall under the exempt category, but if the observation is in a private space it may be expedited or may require full board review. The privacy of those observed and the sensitivity of the research topic must be considered. She offered the following guidance:

- **Suggested guidance:** For research that proposes observation in public and private places, delineate and define the "openness" of the observation place to determine if it is public. Attempt to gauge whether attendees and users think of this as a public place. Also, determine the criteria for when it is appropriate for the researcher to identify himself or herself as a researcher.

Oral histories also raise significant issues. Some histories meet the criteria of generalizability, and some are not intended to reach general conclusions. The Oral History Association (OHA) has extensive guidelines for this method, and NRC recommendations are also relevant. She suggested the following:

- **Suggested guidance**: Oral history projects should be reviewed by a third party to maintain high ethical standards. Criteria should be developed for presenting oral history projects to IRBs and to help IRBs determine the appropriateness of exclusions. Regulatory flexibility should be appropriate to the risk level, subject characteristics, purpose, and other considerations.

Concerns related to *international contexts and local review* relate to time delays in research start-up and to the challenge of determining the most appropriate locus for review (which may not be the U.S.). Dr. Hegtvedt suggested:

- **Suggested guidance**: Rely on IRB or university expertise for minimal risk studies. IRBs need to

assess whether lack of contextual knowledge may increase risk, in which case review local review (i.e., in the country where research will be done) may be needed.

Photo or video documentation raises the issue of subjects' consent to researchers taking and using images. It is increasingly easy to publish digital images on the Web, raising issues of privacy and confidentiality. Special consideration is needed to cultural attitudes about taking and displaying images. Guidance includes:

- **Suggested guidance**: Subject consent is required when images are taken for research analysis. Criteria should be developed for when consent is needed, including consideration of the intended use of the images and whether they will be released to other researchers. Some subjects want to be known, while others do not; the issue of when masking is appropriate should be addressed.

Issues related to *waivers* are at the crux of workability. They may create "overkill" for minimal risk studies, and sometimes create an inappropriate focus on the individual as opposed to the group (in a tribal society, there may a single leader whose consent is required, and individual consent is not culturally relevant). In addition to taking into account NRC recommendations, the following is proposed:

- **Suggested guidance:** Publicize the implications of the "exempt" category (not all consent elements are required). Recognize different forms of consent (individual vs. group). Encourage IRBs to use regulatory flexibility to create consent procedures appropriate to the purpose and context of the study.

The speaker drew the following overall conclusions:

- IRBs need to consider the purpose and context of the study to determine the most appropriate way to protect participants. Models are needed that illustrate the required sensitivity.
- We need to teach investigators how to write proposals and how to make reasonable requests.
- It is important to make sure the relationship between IRB members and staff and investigators are characterized by mutual respect and trust.
- Flexibility should be modeled in published guidance and in the government's response to queries.

Remarks by Joan E. Sieber, Ph.D.
Dr. Sieber stressed that privacy and confidentiality issues are distinct. Privacy refers to a person's interest in controlling the access of others to himself or herself, while confidentiality refers to data and agreements about how data will be shared. Cultural context is important when considering privacy and confidentiality issues. For example, in Sri Lanka health is discussed publicly, and private discussions of health make people uncomfortable.

Respecting privacy and ensuring confidentiality are not always simple tasks. Using the example of a 30-year study of family styles in many cultures, Dr. Sieber highlighted the following issues:

- The meaning of signing a form varies culturally. Many Native Americans are suspicious of forms, for example, and suspect that the form protects someone other than the subject. Unfortunately, many IRBs refuse to use the waiver of signed consent.
- Regulations do not require destruction of data. They require protection of confidentiality. Even so,

IRBs often insist on destroying data, such as videotapes, that funders would prefer to have archived and shared. Sophisticated means of protecting confidentiality in such cases are available, but not widely known. (Some sources include the Web sites of NIH, the American Statistical Association, and the Census Bureau.)

- Subpart B was broadened 2 years ago to encompass anyone who becomes pregnant during the study period. In the case of the study used as an example, many families would have to be dropped for this reason. Families in which someone went to jail might also have to be dropped.

Dr. Sieber gave a second example, a study of smoking cessation with high school-age participants who do not want their parents to smoke. The benefit is high, and there is no risk. However, 13 percent of IRBs *never* waive parental permission, and 57 percent would waive it only for older children, for a normal school intervention, or for non-sensitive research – not for a study of this type. Again, if a teenage girl became pregnant or a participant was jailed, they might have to be dropped from the study.

Dr. Sieber closed by emphasizing the need for flexible solutions that impose a minimal regulatory structure. Common sense and good science are both essential in crafting effective solutions.

Remarks by Philip Rubin, Ph.D., Chief Executive Officer (CEO, Vice President, and Senior Scientist, Haskins Lab, New Haven

Dr. Rubin observed that behavioral and social sciences are a broad group that includes, for example, psychology, linguistics, economics, sociology, political science, and geography. He urged SACHRP to take advantage of the work of the various professional societies that have addressed these issues, such as the American Psychological Association (APA) and the Federation. He also advised SACHRP to coordinate its recommendations with the Human Subjects Research Subcommittee, in which ex officio members of SACHRP are represented. He said SACHRP was well positioned to take advantage of the NRC report, the Social and Behavioral Sciences Working Group (SBSWG), and NHRPAC. He urged SACHRP to consider working cooperatively with SBSWG. Dr. Rubin then highlighted some key recommendations from each of these, stressing the underlying importance of facilitating a non-adversarial relationship between IRBs and investigators.

- *The NRC Report*: Recommendations include enhancing informed consent through detailed guidance for IRBs and researchers on procedures for different populations; enhancing confidentiality protections; facilitating effective review of minimal risk research (i.e., through flexible approaches to addressing minor changes); studying the operations of IRBs; and facilitating the review process at the system level by helping IRBs distinguish between design changes that should be required to protect participants and those that should be advisory.
- *SBSWG:* Several illustrative examples of recommendations were given. One was that institutions should develop guidance for researchers about project eligibility for expedited review, including the IRB's interpretation of minimal risk.

DISCUSSION

Questions and panel responses included the following:

- *How prevalent is the problem of IRBs applying a biomedical model to behavioral/social science*

research in unreasonable ways? (Dr. Prentice). Dr. Sieber commented that a major problem resulting from experience with unreasonable IRBs is that researchers may settle for a trivial study that is non-problematic. Dr. Rubin said that when he was in charge of National Science Foundation (NSF) funding for behavioral and cognitive science from 1999 to 2003, he saw a "sharp increase" in inappropriate applications of the biomedical model over that period.

- *Is it helpful to have behavioral and social science IRBs or encourage more behavioral and social scientists to participate on IRBs? Also, please elaborate on the import of the declining response to social survey research (Ms. Kornetsky).* Dr. Fendrich stressed the importance of having the necessary expertise on a case by case basis; unfortunately, it appears threatening when a researcher questions whether an IRB has the needed capacity. The importance of the declining response rate was that the increasing number of "warning labels" on research can discourage participation in an already difficult environment for this type of research. Dr. Hegtvedt said, speaking as the Chair of the Social Behavioral Humanist IRB at Emory, the new IRB has been welcomed by investigators and has facilitated some important work that was previously denied because the medical review boards did not understand it.
- *The presentations suggest a need for guidance and education, but not necessarily regulatory change (Dr. Harris).* Dr. Rubin stressed the importance of SACHRP leveraging its position to endorse or otherwise further the work of other groups.
- *Is there some way that SACHRP could help medically oriented IRBs understand non-quantifiable research and appreciate that it has validity? (Dr. Polan)*. Dr. Sieber said this was a difficult question. Even on a social and behavioral IRB, members have strong opinions about what is and is not good science.
- *What constitutes an adverse event in this type of study and how should IRBs measure and manage such issues? (Dr. Gyi).* Dr. Sieber said the term is typically limited to pharmaceutical research. A more relevant term is "unexpected problem," which is simply something the IRB needs to be informed of that may require follow through. Dr. Rubin said the potential for harm usually involves breaches of privacy or confidentiality. Another possible harm, unrelated to the research itself, stems from safety issues, such as fall hazards.
- *What percentage of this type of research falls under the Common Rule? Is it mostly publicly or privately funded? What percentage of IRBs comes from a biomedical environment? Is this issue systemic or cultural in nature? (Dr. Jones)*. Dr. Sieber noted that most IRBs violate the regulations by their unwillingness to call in an appropriate expert. She considered this a very serious and common problem. Dr. Rubin suggested approaching NIH or APA to ask for a ballpark estimate. The bulk of research is quantitative research in the social and behavioral sciences field. Dr. Jones said there is much unfunded research in the university environment, but there are also federally and privately funded studies.
- *Would it be advisable to get information from the former chair of NHRPAC on what recommendations and decisions were made to help SACHRP identify next steps? (Mr. Barnes)*. Dr. Rubin supported the suggestion, suggesting that a member interact with the chair, Felice Levine (present in the room).
- Dr. Fisher highlighted issues raised by speakers: examples of minimal risk, the fact that IRBs are not using their right to waiver, overstatement of risk or misuse of regulations, the use of local review, and the fact that this crisis may be pushing social and behavioral research into the realms of the safe and trivial.
- *What associations are looking at the problems around these issues? (Mr. Adams).* Dr. Fendrich said

there is an APA task force on Research Regulation, but it has not begun its work. Good data cannot be expected until about a year from now. Mr. Adams expressed an interest in seeing the results of any research done by affected professional societies.

- Dr. Weiner observed that while SACHRP needs to examine these concerns in the larger context of regulation, direct and active advocacy is needed on the part of affected groups.

Dr. Schwetz informed SACHRP members of the existence of the Human Subjects Research Subcommittee (HSRS) of a Committee on Science under the umbrella of the Office of Science and Technology (OSTP) of the White House. The same ex officio members who work with SACHRP are represented on the committee. In response to the NRC report, a subcommittee of HSRS was formed not only to review its recommendations, but also to pull together all recommendations from other groups who have looked at this issue and to organize, analyze, and prioritize them. The next step will be to determine what agencies should "own" which recommendations and which should be dropped because they are either impossible or no longer relevant. Dr. Schwetz co-chairs this committee with Dr. Peg Barrett from NSF.

Dr. Rubin expressed appreciation for Dr. Schwetz's leadership in addressing these issues.

HIPAA Presentation on Issues

Mark Barnes, LL.M.; Susan Kornetsky, M.P.H.

Ms. Kornetsky explained that, in regard to conveying the Subcommittee's recommendations to the HHS Secretary, staff members have explained that this is done in a formal way, and the 16-page letter will not be used in its present form. However, she and Mr. Barnes will ensure that the letter reflects agreed-on changes.

Mr. Barnes reviewed the recommendations:

- In the area of "Accounting of Disclosures," the original recommendations were unchanged.
- In the area of "De-Identification Standards," the term "treatment dates" was broadened to "dates."
- In the area of "Subject Recruitment," the following revised recommendations were presented:

  Revised Recommendation: Distinctions and requirement related to recruitment that would include identification and contact of potential subjects should distinguish between researchers affiliated with covered entities and truly external researchers, but should treat similarly all researchers who are affiliated with the covered entity either as workforce members or as those who are subject to the covered entity's policies and procedures.

  Revised Recommendation: Researchers should be allowed to remove PHI from the Covered Entity's premises as part of the reviewers' preparation for research, so long as appropriate precautions are taken.

Dr. Fisher suggested revising the second recommendation to clarify that the same researchers, the ones affiliated with the covered entity, are intended. Mr. Barnes agreed to this change.

- In the area of "Data and Tissue Banks," there were no changes.
- In the area of "Compound Authorization Rule," the "opt out" provision was added:

  Revised Recommendation: HIPAA's compound authorization rules should be revised to permit the combining of research authorizations into one form when researchers seek to bank data and materials as part of an underlying clinical trial. Compound authorization rules should require an "opt out" option for the tissue or data banking portion of the protocol.

- In the area of "Research Exempt under the Common Rule," there were no changes.
- In the area of "International Research," there were a number of changes:

  Revised Recommendation: There should be clear guidance in the near future on the scope of HIPAA's application in the international context, since there is no guidance at the present time. Clarify if legally possible under the regulations that the PHI collected from foreign nationals outside the U.S. by researchers who are affiliated with Covered Entities is not subject to HIPAA's requirements solely as a result of the researchers' affiliation with the Covered Entity.

  Revised Recommendation: Clarify that the IRB can waive authorization in the international context, assuming all the waiver requirements are met. Clarify that an IRB may approve an alteration of authorization requirements to provide a truncated version of the authorization that is culturally appropriate for the particular international study.

- In the area of "Public Health Research," there were no changes.

MOTION

Dr. Fisher moved to accept the recommendations of the subcommittee for HIPAA and to permit OHRP and the Chair to make appropriate clarifications. Dr. Polan seconded the motion.

DISCUSSION

Mr. Barnes assured Dr. Harris that implementing the proposed recommendations would not allow a truly external researcher to call the patient. Dr. Harris said he felt strongly that the person who contacts a patient should be the treating physician, which he understood to be a requirement of the Common Rule. He wanted to ensure there were no changes to this provision. Mr. Barnes observed, however, that there is no formal guidance from OHRP that the Common Rule should be interpreted this way. In fact, he is aware of a university that lets "anybody on earth call anybody up." If the Common Rule were revised to specify that contact should be made only by the treating physician, a host of legal questions would arise about who could be considered a treating physician. He suggested an alternate approach was to stress the discontinuity and encourage the HIPAA drafters to coordinate the regulations with ethical practice.

Dr. Fisher was concerned that an overly restrictive rule on patient contact might restrict research, since full-time clinical faculty and private clinicians usually have little time for recruitment. Dr. Harris, however, said there were certain patients that he felt only he should contact. Dr. Prentice said his institution has introduced a concept called "ethical professional access to the prospective subject population" which allows members of the research team in the study area (such as pulmonary medicine) to contact patients. However, other staff in oncology or psychiatry would not be authorized to make contact with the patients for this purpose. Dr. Harris said he would be comfortable with that approach.

Members accepted the following suggestions by Mr. Barnes:

- He will point out this discontinuity in the letter to the Secretary and note that there are significant ethical concerns related to who is allowed to contact the patient under HIPAA.
- The letter will also recommend a guidance document from OHRP concerning this issue.

Mr. Gyi advised that examples given in the guidance document should bear in mind the situation of researchers who are not affiliated with institutions.

ACTION

The motion was unanimously approved.

Next Steps

Dr. Prentice explained that OHRP personnel will brief the Secretary's staff and make any clarifications required to convey the recommendations. After that, staff members take the letter to the Secretary.

He noted that the Secretary's staff was briefed last week on the previous letter sent by the committee.

Proposed SACHRP Guidance on Publications, Presentations, and Media Interviews

Dr. Prentice explained that while members of the media sometimes request interviews with members of SACHRP and many members write papers on a broad range of issues discussed by SACHRP, there are apparently no guidelines about how Federal advisory committees should handle media contact. He stressed that members are encouraged to publish and remain active on the national scene, but that a policy was needed.

Dr. Prentice presented a series of proposed policy guidelines as follows:

1. SACHRP members *identified as such* who are effectively representing the Committee may give presentations and write articles on any topic that SACHRP has discussed. Members are, however, encouraged to ensure that any paper that contains specific SACHRP recommendations is not published *prior to* receipt of those recommendations by the Secretary of HHS.

2. SACHRP members *identified as such* who are effectively representing the Committee may give presentations on any topic that SACHRP has discussed. In situations where SACHRP has

adopted recommendations but the official letter to the Secretary of HHS has not reached the Secretary's office, the status of those recommendations should be made clear.

3. SACHRP members who are effectively representing the Committee should notify the chair of SACHRP or OHRP in advance about publication/presentation activities related to SACHRP.

4. SACHRP members who are not representing the Committee may give presentations or write articles on any topic that SACHRP has discussed but should include a disclaimer, when appropriate, that states that the member is not acting on behalf of SACHRP. Members are encouraged to consider the potential impact on SACHRP of any presentation or publication containing controversial opinions that may politicize the Committee or otherwise compromise its effectiveness. Advice concerning impact should be sought from the Chair of SACHRP and OHRP as necessary.

5. SACHRP members are free to grant interviews with the press and other media. Members are, however, encouraged to refer post-SACHRP meeting requests (which normally occur within the first 5 days after a SACHRP meeting) to the Chair of SACHRP, who will act on behalf of the entire Committee.

The following questions and key points were raised in the ensuing discussion:

- Dr. Prentice agreed that the document should be called "guidance" rather than "policy."
- In regard to 1 and 2, Dr. Prentice agreed with Mr. Adams that the Secretary may well learn of SACHRP deliberations and recommendations before they are formally conveyed to him. However, putting this information in an article before the Secretary has seen it would be "putting the cart before the horse." He agreed that it would be helpful to let members know when recommendations have been conveyed to the Secretary. In addition, members who anticipate making public comments who need to know the status of recommendations should contact the Chair or OHRP as provided under 3.
- In regard to 4, Mr. Barnes wanted to confirm that it is not necessary to explain that a member is not representing SACHRP when no one would expect this to be the case. Dr. Prentice said a disclaimer is needed when the member is discussing something SACHRP is doing and mentions SACHRP by name.
- In regard to 4, Dr. Jones asked for more clarification, since she frequently discusses a controversial topic as one of her academic interests. Dr. Prentice responded said the intent was not to infringe on academic freedom, but to avoid having that opinion linked to SACHRP in a way that might have a negative impact on the committee. He suggested contacting OHRP for advice if needed and simply being aware of the possible consequences for SACHRP when expressing a controversial opinion in a public forum.
- In regard to 4, Dr. Prentice agreed to strike the following: "…containing controversial opinions that may politicize the Committee or otherwise compromise its effectiveness. Advice concerning impact should be sought from the Chair of SACHRP and OHRP as necessary."
- In regard to 5, Dr. Prentice explained that if a reporter comes up after the meeting and asks a member to explain something he or she said in the meeting, that media contact does not need to be referred to the Chairman. This policy is intended to cover contact at a later time.

MOTION

Mr. Adams moved to accept this as guidance. The motion was seconded.

ACTION

The motion carried unanimously. .

Subpart B. Overview

Ernest Prentice, Ph.D.; Nancy Jones, Ph.D.; Mary Lake Polan, M.D., Ph.D., M.P.H.

The Chairman acknowledges the contributions of Dr. Jones, Dr. Polan, and Ms. Irene Stith Coleman in helping to interpret the provisions of Subpart B, which provides additional protections for pregnant women, human fetuses, and neonates, who are involved in research. He noted that the Committee's charge is to determine whether Subpart B "*appropriately* protects pregnant women, fetuses, and neonates."

The Chairman reviewed the history of Subpart B and its provisions. Among the key points made in the presentation are the following:

- The original report was issued in 1975 after only 4 months of work in the aftermath of several well-publicized, unethical studies.
- The amendment to Subpart B was partly intended to recognize a woman's autonomy and the parents' joint interest in the health of their fetus or neonate.
- From 1981-2001, no research was allowed that involved pregnant women.
- Basic definitions include pregnancy (implantation to delivery), fetus (product of conception from implantation to delivery), viable neonate (a neonate after delivery which can survive to the point of being able to independently maintain heartbeat and respiration), and nonviable neonate (a neonate after delivery which is not viable).
- Requirements are more stringent if there is no prospect of direct benefit.
- Research must hold out the prospect of helping the neonate achieve viability with the least possible risk.
- The only requirement for research after delivery involving the placenta, dead fetus or fetal material, fetal tissue, fetal cells, or fetal stem cells is that it be conducted as required by applicable Federal, State, and local laws and regulations.
- Research that does not meet Subpart B requirements is reviewed by a 207 panel convened by OHRP. (There have been no reviews for this category.)

Issues highlighted by Dr. Prentice include:

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1. *How should minimal risk be interpreted when the subject is a pregnant woman or fetus – by an absolute or relative standard?* The answer to this, Dr. Prentice said, is unknown.

2. *Can behavioral/social science studies that involves pregnant women where there is no direct*

benefit to the woman or fetus and minimal or no risk to the fetus meet the requirements of §46.204(b)? This regulation requires that research leads to "important biomedical knowledge" that "cannot be obtained by other means." OHRP interprets biomedical knowledge as including knowledge gained through social and behavioral research, if it has a biomedical component. As a result, traditional behavioral social science research projects cannot involve pregnant women. This is a justice issue. The current interpretation of "cannot be obtained by other means" is that the inclusion of pregnant women in the research is necessary to obtain data required to pursue the objective.

3. *Does Subpart B regulate human embryonic research performed ex utero?* Based on the definition of fetus, only implanted embryos are covered, so embryos "frozen" as byproducts of in vitro fertilization (IVF) are not covered.

4. *If a woman becomes pregnant after enrolling in a study not approved by the IRB under Subpart B, must she be involuntarily withdrawn? If not, what conditions must be met to permit her to continue in the research?* OHRP's current interpretation permits the IRB Chair to permit her to continue if the research is in her best interest. ("Best interest" is not defined.)

Dr. Prentice said he felt the additional protections for pregnant women, fetuses, and neonates were appropriate. However, he was concerned that the strict requirements for continuing research with no prospect of benefit to the pregnant woman or fetus pose a justice issue and appear to be unjustified.

DISCUSSION

A discussion of Subpart B was chaired by Mr. Barnes.

Use of Exemptions

Dr. Jones noted there appears to be a presumed risk for the fetus, whether or not the risk has been demonstrated. These provisions may keep women from being involved in broader studies of great importance. She raised the question of whether it is possible to facilitate use of exemptions when there is no risk. Dr. Prentice stated that some IRBs are being overly protective and do not apply the exemptions when they could.

Exclusion of Pregnant Women/Revision Options

Dr. Polan observed that if the fetus and woman are appropriately protected, there is no reason to exclude a pregnant woman from any research protocol that she has joined prior to becoming pregnant. Dr. Fisher noted the group was in apparent agreement that if there is minimal risk to the woman and fetus, the stringent requirement of biomedical significance is not relevant. She asked what options were available to clarify this. Dr. Prentice asked Ms. Odwazny to comment on what would be required to remove the section that refers to "biomedical knowledge" and "data that cannot be obtained by any other means."

Ms. Odwazny responded that these changes would require a notice of proposed rulemaking followed by public comment. They could not be done without issuing guidance. She noted, however, that OHRP has interpreted biomedical knowledge as broadly as possible. Dr. Fisher asked if OHRP could not simply give examples that clearly include the social and behavioral fields. Ms. Odwazny responded that there may be some types of social and behavioral research that could not be construed to fall within the meaning of

"biomedical." Observational studies or surveys would be examples. Mr. Barnes suggested that a longitudinal study of a number of families and family interactions to validate psychoanalytic concepts would be another example. Dr. Polan noted, however, that a hard line between behavioral and biomedical activity no longer exists; she said she had difficulty thinking of a study that would not fit. Dr. Prentice rejoined that many traditional studies would not be able to meet the criterion. Dr. Weiner added that disciplines such as linguistics and geography would also not yield "biomedical" knowledge.

Mr. Barnes commented that he had seen studies add a pseudo-medical component simply to meet this requirement. Dr. Prentice said he had not seen this and suspects most IRBs are not aware of these requirements.

Recommended Action

Dr. Prentice observed that there is no official guidance from OHRP with regard to these Subpart B issues. He therefore recommended that OHRP issue guidance regarding how to interpret biomedical knowledge in the broadest possible sense, including the requirement that data cannot be collected any other way than by enrolling pregnant women. The appropriate use of the exemption clause could also be stressed.

For the long-term rewording, however, he believed the purpose of the research should explicitly include social/behavioral knowledge and the requirement that it be "not obtainable by other means" should be dropped.

Dr. Polan asked how long it would take OHRP to hold the necessary consultations and move forward. Dr. Carome responded, "at least several months."

MOTION

> Dr. Prentice moved that OHRP be requested to develop guidance on Subpart B that would address the issues SACHRP discussed at this meeting. Dr. Polan seconded the motion.

ACTION

> The motion was approved unanimously.

Dr. Prentice commented that he would ask for OHRP to advise SACHRP on the status of this request at the next meeting.

Dr. Jones suggested that an ethical review by the Ethical Advisory Board (EAB) might be considered if the issues involve attract broader public concern.

Discussion of Issues

Dr. Prentice opened a discussion on future topics and next steps for SACHRP.

Letter from ASCO
Dr. Prentice reviewed a letter from the American Society of Clinical Oncology (ASCO), which is frustrated by the need to deal with multiple IRBs, each of which has its own application or review form and its own required consent templates, to gain approval for a single multi-centered clinical trial. ASCO is requesting SACHRP to look at this issue.

The Chairman noted that a central IRB, or CIRB, has been established for the National Cancer Institute (NCI) and a pediatric central IRB is planned. It is not clear to what extent this will alleviate the problem, since it is unknown how many institutions will sign onto the central IRB and there has been difficulty getting the necessary buy-in.

Initial comments from committee members included the following:

- Dr. Weiner observed that institutional review times can vary from 3 weeks to 18 months.
- Dr. Weiner noted there have been discussions of alternative models, such as regional IRBs. However, liability issues are a concern; if something goes wrong, the IRB is at fault. Dr. Prentice rejoined, however, that blended models are available in which IRBs do not have to totally relinquish their authority. An example is the relationship of the University of Rochester with the Western IRB. There is an individual who is the liaison between the two, and all protocols still undergo review in some form. Adverse events are reported to both entities.
- Mr. Barnes observed that there are some problems with central IRBs that should be critically examined. For example, an IRB may have a history with a particular investigator that is helpful.
- Dr. Gyi questioned the appropriateness of SACHRP addressing issues that affect free market enterprise. Dr. Prentice responded that the letter does not call for guidance related to the use of independent IRBs, but rather guidance that encourages the exploration of co-op or central IRBs as an option.

Prioritization of Issues
Mr. Adams was concerned that the committee prioritize issues for itself, rather than responding to a "squeaky wheel." Dr. Prentice pointed out that this issue was brought up at the first SACHRP meeting. Mr. Adams still felt there was a need to make an organizational determination as to how issues come before it and how they will be dealt with. He also suggested seeking input from other agencies as to what issues they find to be most important.

Dr. Schwetz commented that the issue of central IRBs is not one that can be considered a "burning issue" based on the likelihood of injury to participants. He said HSRS would be prepared to prioritize a list for SACHRP's consideration. However, he felt it was important for SACHRP to hear from a variety of sources. Dr. Schwetz asked Dr. Carome to articulate some of the issues that seemed to "rise to the top." Dr. Carome highlighted facilitation of central IRBs, as well as the definition of research and its relationship to other activities, such as public health surveillance, clinical practice, quality assurance, quality improvement, and innovative medical care. He said the list from all agencies is likely to include 30-40 topics. He suggested that the definition of research might warrant SACHRP's attention, including the question of whether current Subpart A provisions should be revised, clarified, expanded, or deleted.

Mr. Adams suggested a review of the minutes to see what issues have been raised that have not yet been addressed. He also said a prioritized list of agency concerns would be helpful. Dr. Schwetz observed, however, that some agency priorities can be dealt with among the agencies or within OHRP. This exercise will occur in September, so by October OHRP should have input from that process for SACHRP.

Pursuing Subpart A Issues

Dr. Prentice observed that one way to pursue topics is by a panel, which is a way of airing the issues. Subcommittees are another option. Starting with the October meeting, when the Subpart C committee makes its final report, the committee might have an opening for two committees, since the Accreditation Subcommittee has also completed its work.

Dr. Prentice suggested that a subcommittee could examine Subpart A and incorporate considerations relative to behavioral and social science research. He proposed that 10-12 people look at both short-term and long-term strategies. The committee would help shape guidance that would relieve the regulatory burden and ensure or help minimize the possibility that IRBs are over-interpreting or under-interpreting the regulations.

Dr. Fisher supported this proposal "for consistency and utility." The panel could also provide useful input on what constitutes research. Mr. Barnes, however, noted that Subpart A is "sort of everything": the work would be "huge" because of the number of issues that arise in Subpart A – research, public health surveillance vs. research, public health studies and research, welfare benefit studies and research, etc. He did not oppose the committee, but noted that it is "an odd duck" because of the scope. Mr. Barnes said that while SACHRP should move toward a subcommittee, he believes a panel should be convened to set the agenda and provide a platform for launching the new subcommittee.

MOTION:

> Mr. Barnes moved that a panel discussion be held at the October meeting that would address practical problems and possible solutions related to Subpart A. People who deal with Subpart A on a daily basis would be asked to speak and prioritize concerns. Dr. Jones seconded the motion.

DISCUSSION:

The following points were made:

- Dr. Jones felt the panel would help SACHRP identify and focus on important issues.
- Dr. Weiner thought a substantive topic, such as minimal risk, would be more fruitful to explore.

ACTION:

> Mr. Barnes withdrew the motion.

MOTION:

> Mr. Barnes moved that SACHRP work through Subpart A issues as a committee of the whole,

reaching consensus as they were addressed and developing recommendations. Dr. Weiner seconded the motion.

DISCUSSION:

The following points were made:

- Dr. Prentice said the committee already had too much to do. He felt that focused discussions would set the stage for addressing issues such as minimal risk, modifying existing exemptions and adding exemptions, assurance requirements, modifying continuing review and streaming the process, and modifying the categories of research that could be expedited.
- Dr. Weiner said it was the committee's collective responsibility to debate such issues openly.
- Mr. Barnes said his motion implied picking a series of discrete topics to address, followed by a discussion and, it is hoped, consensus on the issue at hand.
- Dr. Fisher questioned the efficiency of addressing such issues as a panel of the whole. She finds the heterogeneous perspectives that are available on a subcommittee extremely useful.
- Dr. Prentice reminded the committee that it does not have the authority to establish a Subpanel in any case. He suggested agreeing in principle that these topics should be considered by panels and deciding in October whether or not the move to a subcommittee should be made.

Committee members agreed to accept Dr. Prentice's suggestion. There was no formal action on the motion.

Proposed Panels

Definition of Research. Dr. Polan suggested a panel on the definition of research. She highlighted the issue of the line between research and surveillance, which is especially important in the context of the global incidence of infectious disease.

MOTION:

Dr. Jones moved that a panel be asked to address issues of research vs. public health surveillance and quality outcome assessment in the light of all the "nuts and bolts" of research, including IRB and oversight. Four persons would be identified to address these issues at the October meeting. Mr. Barnes seconded the motion. He also strongly encouraged an invitation to Peggy O'Kane, head of the National Committee on Quality Assurance (NCQA)

ACTION:

The motion was approved unanimously.

Mr. Barnes and Mr. Gyi agreed to identify speakers.

Central IRBs. Mr. Barnes observed that issues relating to central IRBs have been "on the table from the beginning" and suggested a panel to clarify issues.

MOTION:

Mr. Barnes moved to have a panel on central IRBs. Dr. Weiner seconded the motion.

ACTION:

The motion was approved with one abstention due to conflict of interest.

Dr. Fisher cautioned that the panel should be balanced and help members get the "full picture." Dr. Prentice agreed, suggesting that it should include someone who is a strong proponent of central IRBs as well as someone who strongly opposes them. A third presentation might be from a legal perspective and include a consideration of liability issues. A fourth might be a presentation on one of the models. Dr. Fisher asked the organizer to arrange the presentations to help move SACHRP in the direction of certain avenues or recommendations that would be actionable.

Dr. Weiner accepted responsibility for organizing the panel.

Public Comment

The Chairman invited comments from members of the public.

- Ms. Amy Patterson, NIH, asked whether the committee would accept help from ex officio representatives in preparing for panel discussions. She noted that central IRBs were of keep interest to NIH. Dr. Prentice said the answer was yes.
- Mr. Ira Pritchard, U.S. Department of Education, commented on the issue of who should contact a person about participating in a study. He noted that an analogous role to the primary physician might be anyone who has a prior relationship with the subject and has provided a service to them, such as a teacher. However, he said the "down side" of having such a person make the contact is that it encourages a therapeutic misconception on the part of the subject. Also, the subject might be tempted to participate in the study to maintain a harmonious relationship with the service provider. As a result, in some cases this contact might best be made by someone independent of the service provider. He urged the committee to "think twice" about this issue in developing recommendations.
- Mr. Pritchard continued by giving several examples of studies that would potentially involve pregnant women, would offer no prospect of direct benefit to the subjects, and would not lead to biomedical knowledge. These included a study of the relationship between relationship aggression among high school female adolescents in academic achievement, a study of how high school students learn algebra concepts, a study of the political preferences of teenagers, a study of different models of decision making in economic choices involving teenagers and their uses of money, and a study of the informal social networks in an urban community. He described all of these studies as potentially useful studies that could involve pregnant women. Also, he said all of them might be considered covered rather than exempt.
- Mr. John Mather, University of Michigan, raised the issue of the responsibility of universities that hold Federalwide Assurances (FWA) for IRBs that are registered to it. He said the accreditation

process asks universities to consider themselves as an institution, and several off-site IRBs might be registered under domain 2. His concern included international research and "quasi-IRBs" or review bodies. He suggested that issues raised by this relationship are similar to those of central IRBs.

- Dr. Philip Rubin, Haskins Laboratories, re-emphasized the number of research fields that are involved in social and behavioral science and affected by the provisions discussed earlier. These include fields such as economics and political science, which engage in research that yields generalizable knowledge but that is not biomedical in nature.

Closing Remarks

Dr. Weiner asked about the process for replacing Dr. Harris. Dr. Prentice said a notice has been placed in the Federal Register and names have been submitted to the Secretary for consideration. However, no decision has been made.

Dr. Prentice said the committee would meet at least ten times in 2005. A list of dates will be e-mailed so that members can coordinate their schedules accordingly.

The Chairman closed by thanking everyone for their participation, including members of the public. The meeting was adjourned.

Attachment A: Proposed SACHRP Guidance on Publications, Presentations, and Media Interviews *(as revised)*

FROM: Ernest D. Prentice, Ph.D.
TO: SACHRP

Rationale:

SACHRP members have been invited to: a) give presentations and write papers on issues which SACHRP has discussed, and b) participate in interviews with the media. OHRP and I are unaware or any guidelines regarding a policy or guidance adopted by other Federal advisory committees. Since we encourage members to be active on the national scene and promote the image and work of SACHRP, it would be advantageous for SACHRP to have a policy in place.

Proposed Policy:

1. SACHRP members *identified as such* who are effectively representing the Committee may give presentations and write articles on any topic that SACHRP has discussed. Members are, however, encouraged to ensure that any paper that contains specific SACHRP recommendations is not published *prior to* receipt of those recommendations by the Secretary of HHS.

2. SACHRP members *identified as such* who are effectively representing the Committee may give presentations on any topic that SACHRP has discussed. In situations where SACHRP has adopted recommendations but the official letter to the Secretary of HHS has not reached the Secretary's office, the status of those recommendations should be made clear.

3. SACHRP members who are effectively representing the Committee should notify the chair of SACHRP or OHRP in advance about publication/presentation activities related to SACHRP.

4. SACHRP members who are not representing the Committee may give presentations or write articles on any topic that SACHRP has discussed but should include a disclaimer, when appropriate, that states that the member is not acting on behalf of SACHRP. Members are encouraged to consider the potential impact on SACHRP of any presentation or publication.

5. SACHRP members are free to grant interviews with the press and other media. Members are, however, encouraged to refer post-SACHRP meeting requests (which normally occur within the first 5 days after a SACHRP meeting) to the Chair of SACHRP, who will act on behalf of the entire Committee.

Secretary's Advisory Committee on Human Research Protections
July 26-27, 2004
Washington, DC

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.

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