Secretary's Advisory Committee on Human Research Protections

October 4 and 5, 2004 Meeting
Alexandria, VA

Summary Minutes

MONDAY, OCTOBER 4

Welcome and Opening Remarks

Dr. Prentice welcomed members of SACHRP, ad hoc members, and members of the public.

The Chairman reviewed the SACHRP charter. He observed that there is one vacancy on the Council, left by the departure of Dr. Nigel Harris, to be filled. He acknowledged the importance of the Council's close working relationship with Dr. Bernard Schwetz, OHRP Director; Cathy Slatinshek, Executive Director of SACHRP; Kelley Booher; and other OHRP staff in helping it accomplish all it has been able to do so far.

Report on Issues

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

Dr. Schwetz noted that the Government is operating on a Continuing Resolution until the new budget is approved, which will not occur until November 20 at the earliest. In the meantime, all major new initiatives are on hold.

The charter for OHRP has been approved within the Department of Health and Human Services (HHS) and is now being reviewed by legislators.

Two letters from SACHRP, one on research related to children and one related to the Health Insurance Portability and Accountability Act (HIPAA), are in the office of the Secretary of HHS under review. OHRP awaits the Department's response.

At the last meeting, SACHRP requested that OHRP develop guidance on Subpart B that would address issues discussed at that meeting (see minutes for July 26 and 27, 2004, pages 35-37). These included the interpretation of the requirement that pregnant women cannot participate in behavioral and social science studies unless the studies lead to "important biomedical knowledge" that "cannot be obtained by any other means," the conditions for study continuation for women who become pregnant after enrollment in a study approved under Subpart B, and the appropriate use of exemptions related to pregnant women. OHRP continues to address these concerns and hopes to have definitive comments for the committee by its next meeting.

Dr. Schwetz reported that OHRP has developed a fellowship program during the past year that will become a formal budget item in 2005. OHRP is interested both in new investigators seeking exposure to a regulatory office such as OHRP and notable people in the field who are able to spend 6 months to a year on a "sabbatical" stay. In 2004, fellows have included Cathy Hanna, Dr. Ivor Pritchard, and Dr. Christina Chou, physician from Taiwan. Dr. Schwetz said he would welcome members' recommendations for OHRP fellows.

The Acting Director reported that OHRP now has a contract in place with the Institute of Medicine (IOM) to establish the ethical foundations for a new Subpart C.

OHRP raised the question of priority issues related to human resource protection with the various agencies under the Common Rule. Issues identified were related to the following areas:

- *Confidentiality,* including mandatory reporting requirements, privacy of genetic information, information on drugs, and third-party issues. This area has both Federal and State requirements, which are poorly understood.

- *Multi-center trials*, including the local context and IRB consistency, as well as concerns related to central IRBs.

- *International research,* including the relative lack of interest in and attention on social and behavioral research at this level.

Ex officios are working on common definitions for adverse event reporting, as well as standard format and content for these reports and policies for report dissemination. They are also discussing issues related to central IRBs, but will probably wait to determine SACHRP's position before taking any action.

Dr. Schwetz reminded those present that the 25th anniversary of the Belmont Report will be celebrated on November 16.

Approval of Minutes and Overview of Charges to Subcommittees

Ernest Prentice, Ph.D.

Minutes for the previous meeting of SACHRP were approved unanimously

The Chairman provided an overview of charges to existing SACHRP committees. In regard to the Subcommittee on Research Involving Children (Subpart D), he noted that the subcommittee's recommendations on how the 407 panel review process should be structured have been expressed in a letter that has been relayed to the HHS Secretary. He is optimistic that these recommendations will result in changes in guidance.

The Subpart C subcommittee is working on short-term strategies to address the serious problems with Subpart C; in the longer term, a rewritten version will be needed.

The Chair invited comment from members of the public. There were no requests to address the Council at this time.

Report of the Subcommittee on Research Involving Children

Celia B. Fisher, Ph.D.; Susan Kornetsky, M.P.H.

Dr. Fisher, subcommittee Co-Chair, presented the subcommittee's fourth report to SACHRP. She noted that the subcommittee has been focusing on issues related to "nonbeneficial" research. Beginning with §404, which covers minimal risk research, she reviewed the subcommittee's proposals:

- **Proposal 1: Uniform Standard.** The proposal to adopt a uniform standard received contingent approval at the previous SACHRP meeting. This standard was proposed by the National Commission in 1977 and persisted until the 1981 preamble to the regulations stated that that "HHS has reworded the final regulation to reflect its intention that the risks of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research."

  Dr. Fisher reviewed "justice" arguments supporting uniform and relative standards. She stated that while the justice argument for the relative standard contends that a uniform definition would deprive less healthy or less advantaged children from participating in research, this is spurious since such children can still participate in higher-risk studies that offer the possibility of direct benefit (§46.405), are likely to yield generalizable knowledge about the child's disorder or condition (§46.406), or provide an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§46.407). She cited the justice argument that children should not be subjected to greater research risk simply because their daily lives are filled with greater risk than healthy children or those living in safe environments. It is not acceptable or ethical for researchers to introduce risks experimentally that some children face routinely (such as unhealthy levels of lead).

  Since §46.404 is the gateway to high-risk nonbeneficial research for children, a conservative standard is appropriate; it offers no protection besides parental permission and child assent, leaving IRBs a "very significant" role in assuring that protections are fair.

- **Proposal 2: Reference Point for Uniform Definition.** The reference point is "risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests." This definition is consistent with proposals from the National Commission in 1978), National Human Research Protections Advisory Committee (NHRPAC) in 2002, and the Institute of Medicine (IOM) (2004).

- **Proposal 3: Minimal Risk Should be Age Indexed**. Risks faced in daily life change with age, as do components of children's routine medical and psychological evaluations.

- **Proposal 4: Upper Limits of Risk and Harm.** The concept of minimal risk should be an upper

limit that takes into account the fact some children face greater risks in daily life than others because of physical, medical, environmental, or psychological reasons. Because of this variance in risk exposure, risks might be underestimated or overestimated in specific instances. Dr. Fisher gave two examples:

- *Case 1:* Small puffs of smoke may be minimal risk for healthy children, but greater than minimal risk for severely asthmatic children. The risk to the asthmatic children might be *under*estimated.

- *Case 2:* The risks of exposure to a small amount of Dextroamphetamine by normal children to image the effect on the brain and compare it to the effect on the brain in children with ADHD. In this instance, risk might be *over*estimated. Noting that exposure to dextroamphetamine is not part of a normal child's daily life or a well child visit (though it might be compared to drinking several caffeinated sodas), investigators might feel coerced into inappropriate decisions (e.g., use of §46.405 or §46.407).

If these guidelines are accepted, IRBs will need to ensure they are both protecting children *and* permitting the conduct of good and important minimal risk research.

- **Proposal 5: Equivalent Procedures.** In evaluating the magnitude of harm and probability of risks, IRBs should consider only risks that may result from the research. These need not be the exact instances that occur in the children's lives or the exact procedures used in a well-child visit. Rather, they should be defined as "equivalent in probability and magnitude of harm to risks of daily life or to routine physical or psychological examinations or tests experienced by average, healthy, normal children living in safe environments."

- **Proposal 6: Equivalence Criteria.** These are referenced to risks encountered in daily life or routine examinations. Considerations include the duration, reversibility of harm, and cumulative characteristics of the specific event. *Duration* means the length of time the child will be involved in the experimental procedure: is it equivalent to the length of time a child would be involved in a daily life activity or well child procedure? C*umulative characteristics* refer to the number of procedures included in a protocol or the number of times that an individual procedure is repeated in a given period of time. For example, venipuncture may be considered minimal risk, but repeated over time, there is a cumulative effect that must be taken into account. *Reversibility* of the procedure's harm may occur spontaneously or through actions by the investigator that moderate the impact of the event (e.g., a child who feels faint after a blood draw receives juice).

- **Proposal 7. Well-Child Visit: Referent for Routine *Medical* Examinations or Tests.** Several examples were given of well-child medical examinations or tests. The risk posed by questions included in a social behavioral survey might be assessed by comparison to the kinds of questions a child might be asked on a routine visit to a physician (questions that would vary according to the child's age).

- **Proposal 8. Well-Child Visit: Referent for Routine *Psychological* Examinations or Tests.** Examples given of typical well-child psychological examinations or tests included routine child

or family history questions that probe potential health risks. For adolescents, this could include some exploration of sexual behavior, smoking, or use of illicit drugs.

- **Proposal 9. Index Routine Psychological Tests to Standardized Screening or Assessment Measures.** Several examples were given of measures that might be used either for children who have not been referred or for those who do not yet have a diagnosis. These are not in-depth probes, but rather the type of questions that might be posed to children who may or may not have a problem. Dr. Fisher noted that, for some populations, certain measures may constitute greater than minimal risk. An example might be a question related to suicide or child abuse. The IRB always would have the right to question whether a specific population might have a higher level of risk.

- **Proposal 10. Criteria for Possible Exceptions to Routine Psychological Tests.** Dr. Fisher presented additional guidance for gauging whether or not greater risk is involved in some questions. These included duration of testing, the possibility of persistent post-experimental reactions suggested by an established body of evidence, and the existence of plans to identify, follow-up, and remediate adverse reactions. She noted that it is not the responsibility of the IRB to do research on these topics itself, but rather it is the responsibility of the investigator to educate the IRB so that it can make an informed decision.

- **Proposal 11. Possible Exceptions to Daily Life Equivalence.** Some risks in the daily lives of normal, healthy, average children may not be minimal in probability and magnitude of harm. An example would be playing football. Even though associated risks are socially acceptable in the context of a sports program, risks equivalent to these activities could not be introduced solely for the purposes of nonbeneficial research.

- **Proposal 12: The Uniform Standard Must Apply Internationally.** Justice and beneficence arguments underlie this proposal. However, it is possible to study greater than minimal risks when they occur naturally, rather than as part of the imposed research protocol. For example, an experimental intervention would never be allowed that permitted a child to engage in prostitution, but ethnographic research on children that are doing this might be permitted.

DISCUSSION OF PROPOSALS 1-12

Discussion points included the following:

- The explanation of the meaning of "living in safe environments" (Proposal 2) will be revised, at the suggestion of the Chairman, to insert the word "particularly." It now reads: "Children living in unsafe environments may be exposed routinely to socially permitted risks (i.e., exposure to unhealthy levels of lead), but such risks are neither socially desirable nor ethical, *particularly* when introduced through experimental procedures defined as minimal risk."

- Dr. Prentice pointed out that the concept of "minimal risk" applies to both beneficial and nonbeneficial research. He specifically noted that §46.404 encompasses interventions that might be beneficial. Dr. Fisher agreed.

- In regard to international application of the uniform standard, Dr. Carome indicated that under the Federal-wide Assurance (FWA), Subparts B through D do apply to research at overseas sites. Speaking for the Food and Drug Administration (FDA), Dr. Lepay explained that most international research is submitted to FDA outside the Investigational New Drugs (IND) process. It is therefore governed by separate regulations based on Institute of Child Health (ICH) or world-accepted standards for good clinical practice and conduct, not on FDA's regulations.

- A member raised the question of how the findings of the Kennedy-Krieger case apply. Mr. Barnes explained that the intervention in this case implemented different lead abatement interventions for three different categories of families. Dr. Fisher added that what is proposed by the subcommittee is that researchers be permitted to observe existing conditions (for example, prostitution or lead exposure) but not impose them.

- Dr. Weiner expressed concern that exceptions were presented to routine psychological tests (proposal 10), but similar exceptions were not presented for routine medical procedures. Dr. Fisher agreed. However, Dr. Gyi stressed the importance of information on persistent post-experimental reactions being provided to the IRB by the investigator. He felt guidance should make it clear that the responsibility for presenting existing evidence lies with the investigator, not the IRB. Ms. Kornetsky saw the need for educating the IRB in this instance to be consistent with general practice. Dr. Fisher noted that in many cases, no literature exists to provide evidence of the level of risk for a particular experimental procedure.

- Dr. Fisher clarified, in response to a question from Dr. Hauser, that parental permission may be waived when this is warranted in the judgment of the IRB.

In response to a query from the Chairman, Co-Chairs clarified that it is indeed the IRB's role to probe specifically how magnetic resonance imaging (MRI) would be done. This would include how children would be prepared for the experience of the MRI and whether sedation would be used.

ACTIONS on PROPOSALS 1-12:

Committee members reviewed each of the 12 proposals to determine whether it could receive contingent approval with the understanding that, when all work is completed, the Committee will have another opportunity to review proposals as a whole before they are relayed to the Secretary. All proposals were approved with the following exceptions or qualifications:

- Proposal 7 will be amended to assert that the procedures listed are *one* reasonable basis for equivalence.

- It was noted that Proposal 9 is not a complete list of standardized screening or assessment measures. Dr. Weiner asked whether educational as well as psychological tests might be included.

- Following discussion, proposal 10 was withdrawn as duplicative of Proposal 4. Dr. Gyi stressed that guidance should emphasize the importance of grounding risk estimates in evidence. He also felt strongly this should not be a burden on the IRB.

- Following discussion, this proposal 11 was also withdrawn.

- ***MOTION AND ACTION:*** Mr. Barnes moved that SACHRP give contingent approval to all proposals except 10 and 11, which were withdrawn, with the understanding that there would be an opportunity to revisit particular recommendations at the end of the process. Mr. Adams seconded the motion. Approval was unanimous.

Dr. Fisher continued with the presentation of proposals related to §46.406. This section encompasses situations in which the IRB finds that more than minimal risk is posed by the procedure or intervention and that it has no direct benefit for the individual subject. The Co-Chair observed that greater protections were clearly required under these circumstances, also noting that this category of research is the regulatory threshold for independent IRB approval. The subcommittee agrees with the National Commission that foreseeable benefit to an identifiable class of children may justify a minor increment of risk to research subjects; however, it also holds with the Commission, the National Human Research Protections Advisory Committee (NHRPAC), and IOM that the fact that children have a disorder or condition does not mean it is fair to expose them to procedures with higher degrees of risk and no prospect of direct benefit.

The Co-Chair stressed the need for guidance to make the meaning of "minor increment" as transparent as possible, with the aim of creating a greater consensus on its meeting. Underestimation of risks would lead to potential exploitation and unacceptable research risk, while overestimation could deprive children of research necessary to their health and welfare, move investigators to overestimate direct benefits to try to make the study fit a §46.405 classification, or push IRBs into submitting a study as a §46.407 that could have been approved as a §46.406.

- **Proposal 13. Uniform Standard.** The choice of a uniform or relative standard must be made in regard to the minor increment itself. The subcommittee recommended a uniform standard that indexes the minor increase to the minimal risk criteria recommended for §46.404, comparing risks of research to the risks of daily life or routine medical or psychological examinations or tests that may be experienced by the normal, average, healthy child living in a safe environment.

- **Proposal 14. Minor Increase Equivalent Criteria**. The subcommittee identified five factors to take into account in determining whether a procedure is a minor increase over minimal risk: magnitude of pain or discomfort, probability of risk, duration, cumulative effect, and reversibility of harm. Past precedent has been to define "minor increase" by simply using synonyms for "minor" and leaving the determination of what minor means to each IRB. Dr. Fisher particularly stressed the importance of reversibility, but noted that in instances such as a Phase I housing study to determine toxicity, there may not be sufficient evidence to determine whether or not the effects of exposure are permanent.

- **Proposal 15: Index "Minor" Increase to Common Medical or Psychological Diagnostic Procedures.** In order to define what constitutes a "minor" increment, the subcommittee proposed comparison with the probability and magnitude of harm or discomfort ordinarily encountered in

minor procedures that are routinely performed to diagnose medical or psychological conditions. The subcommittee gave several examples of minor procedures, including radiation exposure, lumbar punctures, and repeated blood draws. A minor increment would *not* apply to procedures that require in-patient monitoring or follow-up evaluation or to those that have an appreciable risk of death, disability, or serious adverse effects.

- **Proposal 16: "Condition."** Only children with a "condition" can be exposed to research in this section. Dr. Fisher presented **a**n interpretation of the term that was a modification of IOM proposal 4.: "The term condition should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health and wellbeing or to increase their risk of developing a health problem in the future." Dr. Fisher stressed that the assertion that characteristics amount to a condition must be anchored in scientific evidence. Also, there must be a risk that something negative might happen to the population with the condition. However, this understanding of the term would not exclude a normal average healthy child from participating in research on a disorder or health problem that affects all children. An issue for SACHRP to decide is whether it is appropriate to allow an IRB to independently judge that a normal healthy child can participate in such research, so long as there is a ceiling on what "minor increment" means.

- **Proposal 17. Vital Importance.** Criteria were proposed with the intent that "fishing expeditions" be ruled out. To be considered vitally important, the subcommittee proposed, knowledge gained through the proposed research should have clear implications for understanding the etiology, prevention, diagnosis, pathophysiology, or amelioration of the condition; for developing treatment for the condition; and/or determining future directions for research on the condition.

- **Proposal 18. "Commensurate."** Approvable interventions, according to the regulation, present experiences "commensurate" with those in subjects' "actual or expected" medical, dental, psychological, social, or educational situations. The intent of the term is to ensure that parents or guardians (and children, when feasible) are able to make an informed decision about whether or not to participate. The actual or expected situation used as a point of comparison need not be the same as the proposed procedure, but it should be equivalent in magnitude and probability of risk. An area of controversy related to Proposal 18 is whether "their actual or expected…situations" should include vicarious experience, such as the subject observing a similar procedure undergone by a sibling. Ms. Kornetsky observed that the issue of what this term means comes up frequently in IRB deliberations and has become extremely problematic.

- **Proposal 19. Sequential Steps in §46.406 Decision-making Algorithm.** Co-chairs presented an algorithm anchored in the notion of a uniform standard, noting that the choice of a standard becomes a reference point for key definitions. Decision points were as follows:

  - Is the research risk a minor increment over minimal risk? If not, refer to §46.404 or §46.407.
  - Does the proposed child research population have a disorder or condition? If not, refer to §46.407.

- 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 §46.407.
- 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 §46.407.
- Are parental permission and child assent procedures adequate?
- If yes to all of these, classify as §46.406.

DISCUSSION OF PROPOSALS 13-19:

Observing that the only proposal that would require an amendment to Subpart D to be implemented was the uniform definition of minimal risk, Dr. Prentice asked whether the subcommittee felt that with interpretations and a possible amendment the existing subpart would "accommodate the modern era of pediatric research." Dr. Fisher said the subcommittee was not yet ready to make that determination. First, a consensus must be reached on whether normal children should be exposed to a minor increment over minimal risk with independent IRB approval. Dr. Fisher stressed that this is a key issue because the existing interpretation limits controlled baseline studies on issues of importance.

Discussion focused on the conditions under which children without a "condition" should be able to participate in nonbeneficial research that poses a "minor increase over minimal risk." Dr. Polan argued that if there are clear limits and a ceiling on minimal incremental risk, there could be a value for all children being able to participate in control groups, since findings sometimes benefit the population in general. Control groups, she stressed, are important for good science. Dr. Jones added that there is no review or system of "checks and balances" to ensure that an IRB's decision in such cases is appropriate. Dr. Weiner observed that a child is "normal" only up until the time a condition is diagnosed in that child; there is a continuous dimension shading from normal to having a "condition." In some instances, whether or not a child is subject to a condition is not known. Mr. Barnes suggested that the subcommittee take the position that parents ought to be able to consent and children assent to this type of research, knowing that parents and IRBs may choose to make tougher and more protective decisions.

The committee focused much attention on the use of minor diagnostic procedures as an index for what is meant by a "minor" increase over minimal risk. Dr. Prentice asked whether the subcommittee had discussed limiting the minor diagnostic procedures to those that would either be encountered or expected for a subject with a specific condition. Dr. Fisher pointed out that would make the standard a relative one, which was not the subcommittee's intent. Dr. Prentice suggested it could be thought of as a "limited relative standard." Co-Chairs were uncomfortable with this approach. Dr. Prentice then suggested the committee to "bring the bar down" by developing a reasonable list of "minor procedures." However, Dr. Weiner noted that the guidance will inevitably list procedures that may be old before they are published. Mr. Barnes suggested this problem could be addressed by providing illustrative examples rather than an exclusionary list and clearly explaining the *reasoning* behind classifying a procedure as minor so that newer procedures can be analyzed in a similar way.

Additional discussion points included the following:

- Dr. Weiner asked whether the case mentioned earlier in which normal children were exposed to

small amounts of Dextroamphetamine would be ruled out in this formulation. Dr. Fisher felt it would not be ruled out because of the concept of "equivalence." The definition of "condition" would also be important in the determination.

- Mr. Barnes questioned whether it was possible to hold a uniform objective definition for a "minor increment" of minimal risk (Proposals 14 and 15), given the language surrounding "commensurate" (Proposal 18). It is possible that part of the regulation would need to be changed to accommodate this interpretation.

- Dr. Hauser pointed out the difficulty of applying uniform criteria to an experimental procedure for which the risks are unknown. He suggested it might mean that such a procedure cannot be used under §46.406.

- Dr. Prentice and others questioned which of the procedures used to index a "minor" increase to common medical or psychological diagnostic procedures could really be considered minor (Proposal 15). Dr. Fisher explained that the subcommittee had not yet flushed out and discussed each procedure and agreed that the subcommittee would give further consideration to the specific procedures listed.

- Also in regard to Proposal 15, Dr. Prentice noted that an "appreciable risk of death" is "a bit far removed from what a minor procedure ought to be"; he suggested that this language be reconsidered.

- Mr. Barnes asked whether a geographic area in which there is a high incidence of disease would be considered a "condition" (Proposal 16). Dr. Fisher said it would. Mr. Barnes added, however, that in some cases there is no established body of evidence that could be cited to show that the condition exists; research might be driven by intuition.

- Dr. Jones asked under what conditions it would be possible to say a child is susceptible to a condition. Ms. Kornetsky said current thinking is that predisposition is viewed as a potential condition, regardless of whether there is a 10 percent or 50 percent chance of developing it. This point might need to be clarified.

- Dr. Prentice stressed that the best way to ensure consistent interpretation across IRBs is to provide education to support the guidance.

ACTION ON PROPOSALS 13-19:

- ***MOTION:*** Dr. Polan moved that SACHRP ask the subcommittee to give further consideration to the implications of requiring a subject enrolling in a §46.406 trial to have a disorder. Should a healthy child be allowed to participate? If so, under what circumstances? The motion was seconded by Mr. Adams.

- ***DISCUSSION ON THE MOTION:*** Committee members continued to explore the topic of what type of research would be permitted under the current proposals. Dr. Gyi asked whether phase I

types of studies could be done under §46.406; Dr. Polan again stressed the importance of having a control group for valid research. However, Dr. Prentice held that it would not be possible for a Phase I clinical trial to be approved as a 406 study – it would have to be done under 405 or 407 – though some pharmacokinetic studies in normal children would be permitted under the new guidance. Dr. Fisher rejoined that she would like to see a 406 category for which some Phase I trials would indeed be appropriate. Dr. Prentice observed that this degree of flexibility does not exist in the current recommendations.

ACTION: The motion was unanimously approved.

Dr. Prentice reminded the subcommittee that as it begins to address §46.405, its task will become even more difficult. Currently, a study might be approved under 405 using one analysis method and referred as a 407 under another.

Report of the Subcommittee on Research Involving Prisoners

Mark Barnes, J.D., LL.M; Nancy Dubler, LL.B.

Mr. Barnes prefaced the subcommittee's presentation by explaining that it is seeking approval for its recommendations so that it can prepare a final report for SACHRP. Ms. Dubler stressed that Subpart C ultimately needs to be rewritten. However, the subcommittee seeks some "quick fixes" that the subcommittee understands could be addressed through guidance on a short-term basis.

- **Recommendation 1. Definition of a Prisoner.** The subcommittee proposed retaining the narrow definition of prisoner in Subpart C and developing guidance related to "persons with restricted liberty and compromised ability to provide informed consent" in Subpart A that would specifically apply to a broader population, including those in "halfway houses." This guidance would be placed at §111(b), which refers to subjects who are vulnerable to coercion or undue influence. Guidance would note that prisoners in these categories have restricted liberty and compromised ability to provide informed consent, even though they do not fall under the language of Subpart C. Such guidance would have an impact on institutions that have chosen not to include Subpart C in their assurance (regardless of the source of funding). As Mr. Barnes noted, it would address a "huge gap" in protection for this vulnerable population.

DISCUSSION/ACTION ON RECOMMENDATION 1:

Dr. Gyi suggested that it would be important to ensure that the various Federal agencies under the Common Rule would feel comfortable with this direction. Dr. Carome said no conversations on this issue have occurred to date with sister agencies. Ms. Kornetsky was concerned that "regulatory creep" would be unfair to institutions that have specifically chosen not to have their assurance include Subpart C. She also noted that other populations, such as elderly persons in institutions, would potentially be entitled to the same protection. However, Mr. Barnes rejoined that Subpart C applies to a particular group with a history of abuse and this history provides a compelling reason to provide these protections for them. Further, Subpart A already identifies prisoners as a vulnerable population; what the subcommittee would be doing is developing questions and guidance to assist the IRBs in fulfilling their obligation to protect

this particular group. Dr. Prentice added that work is being done on defining reasonable protections for other populations; for example, OHRP is working with FDA to identify appropriate protections for decisionally impaired individuals.

Dr. Fisher said she would need the subcommittee to "flesh out" the guidance for this population under Subpart A before approval, though she recognized the subcommittee's concerns as important and legitimate. She was concerned that the proposed approach constituted an "end run" on the inadequacies of Subpart C, a contention that Ms. Dubler disputed. Instead, Ms. Dubler said, the proposed strategy was simply a recognition of the severe limitations of Subpart C, both in intellectual content and in jurisdiction. Dr. Fisher continued with the observation that there are major differences between prisoners in penal institutions and those in various programs outside of prison. Ms. Dubler said the IRB would make a determination based on each protocol and each specific situation. Both co- chairs assured Dr. Fisher that the subcommittee did plan to offer distinctly different guidance for the different groups involved.

Dr. Prentice expressed concern that additional protections provided under Subpart A and additional protections under Subpart C might not be congruent. Ms. Dubler stressed that every IRB would have to look at local conditions, a process in which the current language of Subpart C is not helpful. She said the subcommittee would make every effort, however, to ensure their recommendations were not contradictory to Subpart C. Mr. Barnes added that in some situations they might imply a "parallel universe," but he could see not any reason they would be contradictory.

- ***MOTION AND ACTION:*** Dr. Hauser moved to approve the definition of prisoner found in Recommendation 1. The motion was seconded. The proposed definition and "pathway" were approved by a vote of 6 to 3 with no abstentions.

- **Recommendation 2. Subpart A Review for Subsequently Incarcerated Persons.** In cases in which some individuals are unforeseeably incarcerated after beginning participating in a study, the subcommittee proposed requiring a straightforward, case-by-case analysis under Subpart A rather than a full Subpart C review. This "focused inquiry" would take into account the individual's changed circumstances. However, for a study involving a "significant cohort" persons who can be identified in advance as likely to be incarcerated (such as active IV drug users who have been previously incarcerated), the IRB should be advised to apply Subpart C to the study prospectively. Mr. Barnes argued that this approach would ease the regulatory burden on IRBs *and* have the effect of increasing protection for this population. The effect, he said, would be to increase appropriate foresight and planning by researchers who are planning studies in which many of those enrolled are likely to become incarcerated.

  Ms. Dubler added that the Bureau of Prisons and Department of Justice informed the subcommittee that the proposed practice is one they follow when dealing with a protocol in which subjects are likely to become incarcerated.

Specific subparts of Recommendation 2 included the following:

(a) When it is not reasonably foreseeable that some portion of the research subjects will subsequently be incarcerated, during a study that was not designed to include any prisoners at the time of its initiation, Subpart C review is not required. However, additional

safeguards for vulnerable populations, including prisoners, are required pursuant to section 46.111 (b of Subpart A "to protect the rights and welfare of these subjects."

(b) Subpart C review is required only when the study clearly involves persons subject to the definition of a prisoner, or when it could reasonably be anticipated that the subjects might become incarcerated, such as persons with intravenous drug use (IVDU) histories who have been incarcerated in the past. Populations whose prospective incarceration is reasonably foreseeable should be entered into protocols only after the protocol has been passed by the appropriate IRB in accordance with a full Subpart C review, including the participation of a prisoner representative.

(c) When any research subject is subsequently incarcerated, whether or not the protocol has been reviewed under Subpart C, there must be a focused inquiry regarding the risks and benefits to that particular subject of continuing in the protocol as an incarcerated person.

(d) For medical intervention protocols there is no clear rule on whether the subject should or could continue. That determination requires a focused evaluation of the specific protocol and the specific circumstances of the inmate. This analysis is required in any case under Subpart A, with its requirement for special focus on an increased vulnerability of the subject.

DISCUSSION/ACTION ON RECOMMENDATION 2:

- Ms. Odwazny explained that prospective review under Subpart C would require a regulatory amendment, since Subpart C is being applied to people who are not, at the time, prisoners who would fall within the scope of that regulation. She observed that in a study with a high likelihood that many subjects will be incarcerated, existing options are either to include additional people to allow for attrition or make accommodations so that the people who are incarcerated can continue. It makes sense to tell the investigators to consider this possibility at the outset.

- Dr. Prentice identified an apparent justice issue, in that a subject at risk of being incarcerated might be denied ability to participate in a protocol because of the requirement for Subpart C review. He noted that the approvability of protocols under Subpart C is limited. Mr. Barnes said the alternative would be to attempt to avoid the heightened protection of Subpart C when it is clearly relevant. In addition, Ms. Dubler observed that incarceration would likely result in having to drop subjects from the protocol, which could make study data less useful.

- Dr. Prentice questioned the need for section b of Recommendation 2, which calls for a full Subpart C review for populations "whose prospective incarceration is reasonably foreseeable". Instead, he suggested a review under relevant provisions of Subpart A. Ms. Dubler and Mr. Barnes agreed. However, Ms. Dubler stressed the importance of including guidance on the questions to be asked and findings to be made in this circumstance.

- ***MOTION AND ACTION:*** Dr. Hauser moved to approve sections a, c, and d of Recommendation 2, with parts of b appropriately incorporated into c. The motion was seconded and approved

unanimously.

- **Recommendation 3. Multi-Site Studies.** The subcommittee proposed that guidance state that even though, formally, one IRB suffices for multi-site study review, the local IRB is still responsible for exploring and determining what the specific risks are in the local prison or jail before approving the protocol for the local site. Mr. Barnes explained that Subpart C language, one IRB could approve a study for 100 sites, even though each would be conducting the study under very different circumstances.

DISCUSSION/ACTION:

- Dr. Gyi asked what would occur if there is no local IRB. Mr. Barnes said there would have to be an IRB with jurisdiction. However, Dr. Gyi pointed out this IRB could be remotely located. Mr. Barnes said he would then expect the IRB to access the expertise and resources needed to make its determination. *Co-Chairs agreed to amend existing language to refer to "the IRB responsible for each site" rather than "the local IRB."*

- Dr. Fisher and Dr. Gyi pointed out that there are many ways that information on local conditions could be forwarded to the responsible IRB. Dr. Gyi encouraged the subcommittee to consider mechanisms that would allow the IRB to make a determination based on consultation concerning local attitudes and issues. Various members raised questions about how the recommendations would apply under a range of circumstances – for example, central or independent IRBs, IRBs with satellite sites, sites with and without local IRBs, and instances in which investigators do not attach to particular institutions. Members agreed that the co-investigator located at the site in question ought to be able to provide essential information.

- Dr. Fisher suggested that more clarity on the type of information needed for approval would be helpful.

- Dr. Hauser suggested the following alternate wording: "OHRP guidance should state that even though formally one IRB suffices for multi-study review, the local or responsible IRB is still accountable for exploring and determining what the specific risks are in the local prison or jail before approving the protocol for the local site." Ms. Dubler, however, stressed the importance of ensuring that someone at the local site is able to speak to the conditions there. She felt the alternate wording should be presented to the subcommittee.

- The subcommittee agreed to give this recommendation further consideration. Dr. Prentice encouraged the subcommittee to consider the central IRB model and how the subcommittee's recommendations would apply in this case. He also suggested that the subcommittee contact Dr. Felix Gyi for more information on the operations of an independent IRB.

Recommendation 4. The Prisoner Representative. OHRP Guidance should provide assistance to IRBs searching for a prisoner representative and should suggest persons who may qualify.

DISCUSSION/ACTION:

- ***MOTION AND ACTION:*** A motion was made and seconded to approve Recommendation 4. It was approved unanimously.

Co-Chairs plan to do additional work on Recommendation 3. They plan to return at the next meeting to present their work on that recommendation and on recommendations 5-8, which were not presented. Mr. Adams suggested that holding over the discussion on those recommendations for the next meeting might provide an opportunity to hear from other penal institutions that may have concerns and input. Dr. Fisher requested that the subcommittee present proposals separately, rather than presenting a proposal with several subparts, to facilitate voting.

Public Comment

The Chairman invited members of the public to comment.

- Dr. John Mather of the University of Michigan requested that SACHRP consider the purpose of the public comment sessions and their timing. He suggested providing an opportunity for public comment immediately after proposals are presented.

  Dr. Mather also expressed concern that some proposals under consideration would make IRBs' deliberations more complicated.

  Dr. Mather informed SACHRP, in regard to the presentation on prisoner protection, that the University of Michigan has determined that all subparts may apply, regardless of whether the research is federally funded. He observed that there is a potential for two different definitions of prisoners under Subpart A and C. He also stated that persons subsequently incarcerated are reviewed under Subpart C on an individual basis.

  Dr. Mather quoted Section A, §46.111(b): "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects." Dr. Prentice asked whether, if given the option of reviewing cases of subsequent incarceration under A rather than C, it would increase the IRB's regulatory burden. In response, Dr. Mather reflected that guidance is probably going to be written up for the other named populations as well as prisoners, opening the possibility that this section of Subpart A might actually be able to substitute for Subpart C.

- Dr. Gyi informed Dr. Mather that SACHRP is concerned to minimize the workload for IRBs. Dr. Mather further explained that the decision making process is becoming more difficult "in the absence of some crisper definitions." He pointed to the complexity of making determinations using the procedures suggested as references for minimal risk; for example, the same procedure may be a much higher or lower risk depending on the subject's age.

- Dr. Gyi also invited Dr. Mather to comment on how and whether input may be solicited from multiple sites when a prisoner protocol is reviewed. Dr. Mather said his institution would not generally be inclined to try to oversee research that is being done at a distance. He believes the local IRB should be geographically close.

Closing Discussion

Dr. Prentice reviewed the agenda for Day 2.

Ms. Kornetsky asked Dr. Schwetz for more information on the process used by OHRP in issuing guidance and on decision-making by other agencies related to new guidance. Dr. Schwetz responded that OHRP begins by discussing the planned guidance with the agencies most closely associated with that area and determining whether, for example, FDA might be developing parallel guidance. Then, it approaches other agencies under the Common Rule through the Human Subject Research Subcommittee (HSRS) of the Committee on Science. Concerned agencies are offered an opportunity for input. The process continues by issuing notices and getting input from the public.

Mr. Adams reinforced Dr. Mather's comments on the need to provide an opportunity for public comment after key presentations. He did not feel this was necessary after panel presentations, but did feel it would be useful after proposals have been presented. Dr. Prentice agreed the agenda could be structured accordingly.

Dr. Prentice closed with a summary of the day's activities. He said he finds the deliberations fascinating; both at the subcommittee and the main committee level, and believes progress is being made. He reminded members that the process of issuing guidance can be lengthy, and patience is needed. He predicted that the Subpart D subcommittee will probably need to continue work for 2 years, while the Subpart C subcommittee will probably end its work in two or three more meetings as it comes to the end of what can be accomplished through short-term remedies. He noted that the committee's charter has been renewed, which suggested satisfaction with its work.

TUESDAY, OCTOBER 5

The Chairman provided an overview of the day's activities and introduced the first panel of the day, which focused on issues related to Subpart A.

Subpart A Issues Panel

Remarks by Ada Sue Selwitz, M.A.

Ms. Selwitz chose to focus her presentation on the risks vs. benefits of revising Subpart A. She began by providing a potential "hit list" of requirements that she believes have proven problematic. These included the following:

- *The assurance requirement* (§46.103), which she believes does not add protections for subjects but does provide an unnecessary regulatory burden. This is especially problematic in dealing with sites engaged in research but without legal ties to the institution.

- The *cooperative research provision* (§46.113), which, in contrast to the FDA version, requires written agreements. Managing assurance and other site requirements may soon require her to hire a full-time person just for this purpose.

- The *continuing review requirement* (§46.10[e]), which she believes is applied too broadly and could benefit from more effective and innovative approaches to assessing implementation. She questioned whether studies that are less than minimal risk or have no subjects enrolled really require re-review, with all the associated paperwork, on a yearly basis.

- *Procedures for waiving informed consent* (§46.116[d], which she believes are somewhat unclear (e.g., the meaning of "practicably" and how to avoid adversely affecting the "right" to informed consent when waiving it).

- *Reporting requirements* (§46.103 [b][5]), a section that is problematic because of the interface with other regulations.

- *Definitions* that can be clarified through guidance, including "legally authorized representative," "human subject," and "research."

- *Exemption categories* (§46.101 [b]) are the source of a great deal of confusion, much of which she believes can be addressed through guidance.

Ms. Selwitz also noted that there are problems in applying Subpart A in a social science setting, though sometimes she feels this difficulty reflects fear or confusion on the part of IRBs.

However, on the "risks" side of the equation, Ms. Selwitz felt that Subpart A avoids prescriptive detail and is relatively straightforward. In general, it has provided a sound framework for decision-making. She held that it is not really possible to eliminate the "grey" in sound ethical decision-making; nor is it

possible to adequately anticipate new questions or ethical challenges that may surface in the future. She therefore urged caution in revisions. Among her concerns was the potential for even less harmony among Federal regulations, since there is no guarantee other agencies will revise their regulations to harmonize with changes in Subpart A. This is especially important because one of the most significant regulatory challenges facing IRBs and the research community today is the lack of harmony among Federal funding and regulatory agencies in interpretations of Subpart A.

Remarks by David G. Forster, J.D., M.A.

Mr. Forster structured his presentation to address the question of whether Subpart A protects subjects and whether it poses too much regulatory burden. In this regard, he held that Subpart A was not "broken" but could be improved by modifications. He said he had difficulty seeing where the regulatory burden that does exist could be reduced; something like Subpart A is definitely needed. Mr. Forster believed guidance could address most of the problems could be addressed through guidance, though a rewrite would be welcome.

Major concerns related to the following:

- *Exemption criteria* (§46.101 [b]) are presented in a "confusing, awkward structure" with many undefined terms (such as "normal educational practices").

- Several *key definitions* (§46.102) are unclear. These include:

  - "Legally authorized representative," which becomes more difficult in relationship to State definitions. He said that current OHRP guidance is difficult to interpret. Mr. Forster suggested a Federal regulation that would include a definition but would not override "stricter" State laws.

  - "Research," which is not clearly defined and which is interpreted differently by various agencies. Guidance would be helpful.

  - "Human subjects" became more complex when OHRP introduced the idea of "secondary subjects." It is not clear whether they exist and, if so, what to do about them. This issue is being interpreted inconsistently across the country.

  - "Minimal risk" is sometimes demonstrated using a "differential risk" argument that Mr. Forster believes should be explicitly ruled out. An example would be "a study of an investigational new formulation of an approved drug for asthma is minimal risk because the risk of the intervention is the same as for the approved drug for asthma." He argued that almost anything could be shown to be minimal risk using this type of reasoning. He held that the concept needed an "objective, tied-down" definition.

- *IRB Actions* (§46.109). Many IRB actions, such as tabling and deferring, are not listed as among IRB authorities.

- *Continuing review* (§46.10[e]). Like Ms. Selwitz, Mr. Forster questioned whether this is required for minimal risk review. However, the definition of minimal risk should be tied down before making a change.

- *Expedited review* (§46.110). Some regulatory burden is created by the fact that reviewers cannot disapprove research without full board review. Simply saying no to an advertisement or minor changes to research can be time consuming.

- *Criteria for IRB approval* (§46.111). Mr. Forster observed that this important material is buried in its current location. Instead, it should appear at the beginning of the regulation. He also questioned whether the estimation of reasonable risk should include scientific validity and value to society. In regard to long-range effects, he wondered whether publication of study results, sex selection techniques, and public registries are beyond the boundary for consideration. He also noted that the meaning of "vulnerable subjects" is not clearly defined. He commented that the word "vulnerable" is not in the Belmont report. There is also no referent for "additional safeguards." Finally, a variety of issues such as financial conflict of interest, transparency, and new technologies are not explicitly addressed.

- *Suspension or termination* (§46.113). It is not explicitly clear that IRBs have the authority to suspend research when regulations are violated or when there is unexpected serious harm to subject. The speaker noted that liability issues are a concern; could an investigator conceivably sue the IRB for exceeding its authority?

- *IRB records (§46.115).* Subpart A does not take into account the modern use of computers for storage. For example, could disapproval forms not be stored in the computer rather than in the minutes themselves, a procedure that creates 400-page minutes? Must minutes really contain all the information required in the regulation? He also pointed to the need to capture lengthy e-mail chains of correspondence between the IRB and investigator, which results in extensive duplication.

- *Waiver of informed consent* (§46.116). Like Ms. Selwitz, Mr. Forster found the regulation about not waiving "rights" problematic. He also raised the question of whether the use of private information for research could be held to violate subjects' dignity and asked whether ownership of intellectual property resulting from the research would be considered a "right." He agreed with Ms. Selwitz that the term "practicably" has no clear meaning (§46.116[d]). He suggested eliminating the short form for consent, which he said was not useful. He strongly recommended removing the requirement that the subject will be asked whether they want to sign the consent document even though the IRB has waived it, which he said can be awkward to implement. In the case of interviews with participants in a needle exchange program, for example, it might lead subjects to suspect the interviewer is really associated with law enforcement.

Finally, Mr. Forster called attention to the "Funding Catch-22," in which the investigator cannot get finding prior to IRB review, but the IRB does not have the complete project to review until funding has been secured. IRBs have developed mechanisms such as "approval in principle," but sometimes funders do not accept this. Guidance would be welcome.

Remarks by Daniel K. Nelson, M.S., C.I.P.

Like other speakers, Mr. Nelson felt Subpart A was, on the whole, "not broken" and has weathered well. He said that problems related to Subpart A lie in the realms of implementation, application, and interpretation. While these problems can be addressed through guidance, he also noted that assimilating guidance is difficult in practice. Internal memos, letters, OPRR reports, determination letters, opinions and readings, and many other sources exist, but many IRBs are not aware of sources of guidance important to their work. He suggested that an updated "User's Guide to the Regulations" might tie together all these sources. However it is addressed, a key question is: "how can we take all this good guidance that we desperately need, keep it integrated and current, and really apply it to our daily routines?"

Mr. Nelson observed that we now have "single-site regulations in a multi-site world." He advised that the new multi-site framework must be reflected in guidance and education. For example, the assurance mechanism needs to be adapted for multi-site studies.

In regard to the issue of whether Subpart A inappropriately forces social and behavioral research into a biomedical model, he held that the regulations are not at fault in this. Problems lie instead in the way the regulations are being applied. He recommended continuing education efforts as the best remedy.

The speaker echoed Ms. Selwitz in pointing to harmonization of requirements as a major concern, pointing to discord among "the regulatory agencies' interpretations, IRB interpretations, and the interpretations of funding agencies." He reported that most of the "tugs of war" his IRB has experienced have been with funding agencies.

Mr. Nelson pointed out some specific "trouble spots" in Subpart A:

- *Exemption criteria* (§46.101 [b]). Like Mr. Forster, Mr. Nelson found provisions relating to exemptions problematic. As is, he said, the exemptions create an "awkward no-man's land somewhere between not-human subjects research and what really constitutes expedited review," in that IRBs must review them in order to determine they are eligible for exemption. He pointed to what he called a "technical discrepancy" in regulations related to demonstration projects (§46.101 [b] [5] and (§46.101 [c])[1]). He also observed that some exempt research projects – for example, many of those carried out by students, studies of organizations, and case studies – pose the same risk to human subjects as nonexempt research.

- *Definitions* (§46.102). Mr. Forster held that it is difficult to apply the "minimal risk" definition in practice, though he had no suggestions on how to improve its usability.

- *Assurance requirements* (§46.103). IRBs need encouragement to share the review process with other entities, despite barriers posed by legal issues and institutional interests. He acknowledged the work OHRP has already done to improve the process as useful. However, more guidance is needed on issues such as the use of IRB Authorization Agreements and unaffiliated investigator agreements.

- *Written procedures* (§46.103 [b]). Mr. Nelson questioned how many IRBs are actually aware of this part of the regulation and trying to apply it.

- *IRB membership* (§46.107). Mr. Forster suggested that requirements for community representation are not sufficient to ensure adequate representation on larger IRBs.

- *Convened meeting review* (§46.108). This provision, the speaker held, is a source of regulatory burden, since there is no good reason for many minor items to be reviewed by the full board. When entire studies and consent forms can be handled through expedited review, it is not clear why such modifications always require action by the full board.

- *Expedited review* (§46.110 [b] [2]). Mr. Forster found some "minor confusion" in determining how requirements may apply to minor amendments.

- *Procedures for waiving informed consent* (§46.116[d]). The speaker reported that some reviewers interpret the waiver as applying to retrospective reviews, which creates a dilemma when a mix of retrospective and prospective data exists. He suggested guidance would be helpful. He also questioned the intent of providing "additional pertinent information after participation."

Remarks by Stephen Peckman

Mr. Peckman stressed the "enduring quality and flexibility" of Subpart A. The regulations provide a template for addressing ethical issues. He noted, however, that while the regulation outlines the responsibilities of the institution (and, by extension, the IRB) it does not address the responsibilities of the principal investigator. He also observed that many social and behavioral researchers feel it inhibits their work and primarily reflects a biomedical model.

- *Exemption criteria* (§46.101 [b]). The meaning of "normal educational practice" is not defined. Other unclear terms in this section are "public behavior" and "publicly available."

- *Definitions* (§46.102). Mr. Peckman agreed with others that key definitions need work. He considered the definition of research to be the most poorly written section of the regulations (for example, what is "generalizable knowledge"?). The definition of a human subject is blurred by the words "about whom." When, he asked, is research "about" a person? Mr. Peckman gave the example of a survey in which he is asked what it is like to work at his institution. Is that "about" him or the institution? Also, when a teacher responds to questions about students, are there any "human subjects" in the study? He agreed with others that "minimal risk" is also unclear, in part because it is not clear *whose* daily life is intended to be the referent.

- *Assurance requirements* (§46.103). Mr. Peckman felt the required document was an important one that "holds the institution's feet to the fire" on critical issues, defines responsibilities, and identifies key institutional officials. However, it is not clear what happens if the institution fails to discharge its responsibilities. He stressed the importance of the sponsoring institution having an "ethical ethos" that supports decision-making. He suggested that expectations of the institutional official responsible for building this ethos might be defined in guidance, as well as acceptable

qualifications, location in the chain of command, and execution of authority. It is also not stated what constitutes conflict of interest for this key individual. For example, should the person responsible for brining in research dollars serve in this capacity?

- *Institutional support* (§46.103 [b][2]). Guidance is needed on how what constitutes sufficient support.

- *IRB membership* (§46.107). Mr. Peckman questioned whether the composition of modern IRBs met the intent of the National Commission, which wanted a balanced representation of scientific, individual, and community concerns. He pointed out that IRB members are overwhelmingly white (92 percent) and mostly male (58 percent); most are institutionally affiliated. He appeared to support the National Bioethics Advisory Board's (NBAC) recommendation that at least 25 percent of the IRB should be unaffiliated with the institution, with a primary concern in nonscientific areas. Such persons give a voice to the community and potential subjects.

- *Expedited review* (§46.110 [b] [2]). Mr. Peckman questioned whether use of the short form created "two classes of subjects." He also advised that guidance allow for the use of new methodologies and flexible strategies, such as audio taping or videotaping the consent process and providing subjects with a copy for reference.

- *Suspension or termination* (§46.113). Mr. Peckman felt the IRB should have the authority to suspend an investigator but allow a study to continue when the problem lies only in the investigator and an alternative is available.

- *Informed consent* (§46.116 and 117). Mr. Peckman questioned how the emphasis on a signed consent form protects the subject. He held that insistence on a written document was often culturally or situationally inappropriate. He argued for more flexible requirements for ensuring informed consent. In cases where the IRB finds that a signed document might place the subject at risk, he asked why subjects would be given this option. He also suggested the process would be illogical in much international research, for example in research with a nomadic tribe that has no access to modern communications. Finally, he noted that the process allows subjects to participate in biomedical research at their own risk without treatment or compensation – a "large loophole" in the fabric of human subject protection.

DISCUSSION OF SUBPART A ISSUES

Dr. Prentice agreed with Mr. Nelson that the need for clarifications and modifications to return to the full IRB board is problematic. Noting that in his experience this requirement adds to the workload of IRB members and delays research initiation, he asked whether other panelists agreed this was a problem. Ms. Selwitz said she agreed. Mr. Peckman, however, stressed the value in giving an investigator very specific guidance from the IRB as a whole, which better "grounds the investigator in a place to make decisions." Both Mr. Peckman and Ms. Selwitz pointed out that the problem was caused primarily by guidance as opposed to the regulations themselves.

In light of the problems sometimes created through guidance, Ms. Kornetsky wondered about the balance between flexibility and specific guidance that "corners" the IRB. Mr. Peckman responded that guidance is indeed needed in some basic and fundamental areas for which guidance has never been issued, such as the definitions of "human subject" and "research." Ms. Selwitz agreed with Ms. Kornetsky on the need for caution, noting that the system "is being undermined with too much detail." She said she did not agree with her colleagues that all the problems they identified are ones in which guidance is the solution. Mr. Forster added that much of the need for guidance is driven by the fact of agency oversight and the resulting need to be as sure as possible of compliance.

Dr. Prentice focused on the requirements for documentation that have ballooned minutes from 4 pages in the "old days" to 100 or more. He asked what guidance from OHRP might address the problem. Mr. Peckman stressed the need to document the IRB decision-making process adequately, noting that it is possible to go too far in the opposite direction: "3-page IRB minutes for the review of 20 protocols" would hardly be sufficient. Ms. Selwitz agreed with Dr. Prentice that the pendulum has swung too far toward inclusion and suggested there may be alternative ways of demonstrating the quality of work done without focusing on the minutes documents. Mr. Peckman noted that many minutes largely consist of a lengthy recitation of the protocol and not the IRB's own deliberations. Dr. Weiner and Mr. Peckman both felt minutes would be much shorter and more functional if they focused more specifically on the IRB's decision-making process.

Dr. Gyi noted that lengthy minutes are, in part, defensive documentation for litigation purposes. Sometimes the extent of documentation is driven by determination and warning letters rather than across-the-board guidance. He asked if panelists had suggestions on how OHRP might provide useful guidance on this subject. Mr. Forster suggested that OHRP could assist by outlining a range of ways documentation could be accomplished and indicating what options are acceptable. Mr. Peckman suggested that outlining a range of options would also be helpful in regard to consent documentation.

Mr. Barnes proposed that the solution to the various problems described might not be to generate more guidance about it, but rather to consider revising Subpart A in a way that achieves more uniformity among Federal agencies. He suggested that the best approach would be to determine what should be achieved "thematically" and then leave it to IRBs to find their own paths to the identified goal. The most serious problems in compliance, he stated, lie with investigators and not with IRBs. In response, Mr. Nelson commented that while IRBs enjoy the flexibility that comes from having an apparently loose framework, they also see determination letters effectively creating case law and holding other institutions accountable. Ms. Kornetsky agreed with Mr. Barnes that it would be more effective to approach future guidance in a performance-based rather than prescriptive way. She also pointed out that determination letters may not be properly interpreted by IRBs. An appropriate model may be the performance-based guidance given by accreditation agencies that ask IRBs to prove they are meeting a stated principle or intent.

Dr. Polan said that in her experience principal investigators do want to do the right thing and have an inadequate understanding of requirements. She asked panelists what changes might be made to assist investigators and also ensure that research is conducted ethically and protects patients. Mr. Peckman agreed with her that the irresponsible investigator Mr. Barnes referred to is an "outlier" and suggested that most investigator problems result from lack of guidance and problems in the regulations themselves. He noted that social-behavioral researchers are in the "biggest bind." Another concern is the power of money,

rather than ethics, to "rule the game."

Dr. Jones agreed with Mr. Barnes that investigators' lack of understanding of the nuances of ethical research is a key problem. She suggested that education might be used to build a better knowledge base of the principles of human subjects protection. Dr. Weiner asked panelists whether some of these education issues might be addressed through the accreditation process. Mr. Forster said that the accreditation process had resulted in more paperwork, procedures, and guidance for his institution, but not necessarily in education.

Mr. Adams asked panel members for additional comments on the need to compile guidance and the methods that might be used to accomplish this. Mr. Nelson observed that much guidance exists, but IRBs are unaware of it. OHRP has done a good job of compiling it on a single Web page, but there is still a gap in the ability of IRBs to translate this guidance into its daily operating procedures. Mr. Peckman added that the Web site was useful and user friendly, but that IRBs still use the 1993 guidebook as a primary training source. This important source, he said, needs an overhaul. Ms. Selwitz commented that the need was really to make guidance from all sources, not just OHRP, easier to find. In response, Dr. Schwetz commented that a new Guidebook would be quickly out of date; for this reason, OHRP has focused on creating Web-based information instead.

Dr. Schwetz continued with the reflection that the human subject protection system, unlike systems to inspect imports or meat, is built almost entirely on trust. There will not be an inspector at every research site to see if guidance is really being followed. Given this system, it is difficult to provide the right amount of guidance to maintain trust and allow the system to work as well as possible.

Public Comment

The Chairman invited public comment.

- Mr. Ira Prichard noted the regulations do not contain the complete list of categories of human subject involvement referred to in Subpart A and which are relevant to the exemption process (§46.101[b]). He asked how IRBs could judge whether the subjects' "only involvement" is in these categories in the absence of this list.

- Ms. May Ann Makeba of the Society for Research in Child Development drew attention to what she called fundamental issues with the developmentally appropriate use of assent regulations. She protested the practice of requiring written assent from very sick children. She also noted inconsistency across IRBs on how children give assent (oral or written) and highlighted the challenge of offering an option for assent appropriate to the child's cognitive level. Dr. Prentice agreed this was an important issue and expressed confidence that the Children's Research Subcommittee would address it.

- Dr. John Mather said that having all existing OHRP guidance codified and available on the agency Web site would be extremely useful. Finally, he affirmed the importance of written assurances, which become governance documents that can be used to hold institution officials accountable. He said more needed to be done to mentor faculty members on the IRB process and provide accurate guidance. Investigators are often referred to Department Chairs, who usually "do not have a clue" about requirements related to human subjects protection.

SECOND DISCUSSION PERIOD, SUBPART A

Dr. Prentice thanked panelists for their insightful presentations. He commented that IRBs are clearly overinterpreting, underinterpreting, and inconsistently interpreting the regulations. He asked SACHRP members what next steps would be appropriate.

Dr. Fisher commented that many investigators, especially social-behavioral scientists, are frustrated that IRBs fail to use expedited review when it would be appropriate. She also said that many of them see the informed consent procedure as something that is not participant friendly, hampers good research, and limits the randomization or breadth and generalizability of the sample tested. She commented that the short form is reportedly misused, though it is more participant friendly than the long form. She also highlighted the problem of overestimating sociobehavioral risk by focusing on populations rather than procedures (i.e., assuming anything done with a vulnerable population is above minimum risk). She pointed to a need to clarify the extent to which an investigator's attempts to take actions that minimize risk should affect categorization of risk.

In response to a question from Mr. Barnes, Dr. Prentice clarified his own perspective on next steps. Dr. Prentice said he felt it was important to identify all issues that plague IRBs and investigators, contribute to regulatory burden, and do not contribute to the protection of human subjects. He suggested it would be useful to establish a subcommittee to analyze Subpart A and identify what can be done to make it work better, as subcommittees have been doing for Subpart B and C. While the regulation is "masterfully written," some parts of it do cause confusion and should be addressed through guidance. For example, appropriate criteria for waiving informed consent are needed. Dr. Schwetz agreed that a subcommittee would be the best way to help OHRP set priorities and convert "information into action." He noted that SACHRP has high credibility and can help ensure that Subpart A issues are prioritized and addressed effectively.

MOTION: Mr. Barnes moved that a subcommittee should be established to address issues related to Subpart A systematically. The subcommittee was asked to bear in mind that the best answer may not always be specific prescriptive guidance; rather, it should also consider that in some cases general guidance that gives IRBs greater flexibility may be more effective. Ms. Kornetsky seconded the motion.

DISCUSSION: Dr. Polan suggested that about 50 percent of the proposed subcommittee should be investigators. As a compromise, she agreed that at least one-third of the members should be active PIs, some of whom might also be IRB members. Mr. Barnes accepted the friendly amendment. Dr Weiner added that there should also be representatives of the public on the subcommittee. In response to a question from Dr. Gyi, she clarified that their role would be to provide a perspective on areas of subject protection in which they would and would not be willing to yield. They might also bring ideas from other

sectors that might contribute to problem solving. Mr. Barnes observed that it would be important to find community representatives who have enough background to participate effectively. Dr. Polan added that a broad ethnic and socioeconomic background in community representatives would be helpful.

ACTION: The motion carried unanimously.

Definition of Research vs. Nonresearch: Issues Panel

The Chairman introduced the second panel of the day, which focused on defining what activities may and may not be considered research.

Remarks by Michael Carome, M.D.

HHS regulations apply to research involving human subjects conducted or supported by HHS that is not otherwise exempt, as well as to non-exempt human subjects research at an institution holding an applicable Assurance of Compliance. When assessing a particular activity, Dr. Carome said, it is important to ask three questions in a specific order:

- Does the activity involve research?
- If it does involve research, does it involve human subjects?
- If it does involve human subjects, is the activity exempt?

The regulations define research as "as systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (§46.012[d]). Deciding whether an activity involves research according to this definition does *not* depend on the risk/benefit balance, the specific type of design, the presence of testing or evaluation, whether research is the primary objective, or whether results are published.

In answering the first question – does the activity involve research? – Dr. Carome stressed that overlap exists between research, as defined by the regulations, and other activities. The activities described are considered research regardless of whether or not they are conducted or supported under a program considered research for other purposes. For example, human subject research may overlap with other activities such as public health surveillance, quality improvement, and clinical practice. As a result, regulations that pertain to research and nonresearch activities may also overlap. The Belmont Report also notes that research and practice may be carried on together, with an element of research that requires review occurring within an activity that, as a whole, does not.

In addressing the question of whether or not the research involves human subjects research, key considerations include whether the activity is designed to test a hypothesis and reach conclusions that can then contribute to generalizable knowledge. Researchers often document this process in a formal protocol. To assess the intent of those conducting the activity, IRBs may consider these protocols, the prior academic or research record of the investigators, research records, and documentation such as abstracts, manuscripts, and publications.

Remarks by James Hodge, Jr., J.D., LL.M.

Mr. Hodge reported on the work of a panel established by the Council of State and Territorial Epidemiologists (CSTE) to identify the essential features of public health research and core public health practice activities. Like Dr. Carome, he began by emphasizing that the same activity can often be described either as research or nonresearch. Undoubtedly, some of the ways in which epidemiologists collect and disclose human subjects' data can look and feel like human subjects research. However, he said, an important distinction between such epidemiological activities and research is that public health research is intended to generate knowledge that will primarily benefit those *beyond* the participating community. While both research and practice take steps to protect individuals, their methodology and objectives, as well as their underlying legal support and ethical frameworks, are very different. Many of these activities have unique designs that distinguish them from research.

The panel defined public health *practice* as follows: "The collection and analysis of identifiable health data by a public health authority for the purpose of protecting the health of a particular community, where the benefits and risks are primarily designed to accrue to the participating community." In contrast, public health *research* was defined as "the collection and analysis of identifiable health data by a public health authority for the purpose of generating knowledge that will primarily benefit those beyond the participating community who bear the risks of participation." While public health practice is grounded in the constitutionally-approved authority of the government to protect the public's health, safety, and general welfare, public health research is grounded in the principles of the Federal Common Rule that focus on protecting individuals in the pursuit of knowledge. It is a duty of public health practitioners to conduct certain activities.

Unlike research, public health practice has specific legal authorization from government, is driven by the duty to protect public health, has government oversight, may legitimately involve persons who do not provide informed consent, and focuses on populations, while respecting human rights. Also, data may be collected regarding living or dead individuals, while research involves living individuals who volunteer to participate or who do so with the consent of a parent or guardian (unless this is waived). Functional criteria for use in identifying a public health practice activity include:

- The presence of general legal authority for the activity (usually absent in research), such as a direction for the state to collect information on HIV status
- The specific intent (research is about testing a hypothesis, while public health practice is driven by the duty to protect public health)
- The locus of responsibility for participant protection (the PI in research, but a larger government entity in public health activities)
- Participant benefits (public health activities always intend to confer a benefit to participants, while research may not)
- The presence of experimentation (a hallmark of research), and
- Subject selection (random for research, but self-selected for public health practice).

The panel did not find the following to be meaningful criteria for distinguishing research and nonresearch activities:

- Who is performing the activity (a private agency may be contracted to do work for the public health authority)
- Intent to publish (both researchers and practitioners may publish results)
- Urgency
- Funding, and
- Data collection methods (tools may look similar).

Mr. Hodge noted that because the Health Insurance Portability and Accountability Act (HIPAA) does not provide meaningful guidance on how to distinguish public health and research activities and gives public health activities *carte blanche,* there is a strong incentive to describe activities as public health practices.

Remarks by Mary Ann Baily, Ph.D.

Dr. Baily reported findings from an ongoing project by the Agency for Healthcare Research and Quality (AHRQ) and the Hastings Center that addresses ethical issues in improving health care quality and safety. Her presentation focused on the distinction between quality improvement (QI) activities and research. The genesis of the project was the difficulty reported in applying the research regulatory framework to QI activities.

Dr. Baily described QI as encompassing a broad range of activities of varying degrees of complexity and methodological and statistical rigor through which health care providers improve clinical practice. To accomplish this, they develop, implement, and assess repeated small-scale interventions, identify those that work well, and implement them more broadly. Examples include retrospective data reviews, limited innovations in work patterns in small teams, and large-scale data analysis of prospectively determined interventions across multiple sites.

Thousands of small changes are made routinely as health care methods adapt to changing background conditions, especially technology. The role of QI is to make this continual adjustment more self-reflective and systematic, ensuring positive change. The close linkage between QI and the implementation of change in the care delivery context is one of the features that distinguish it from research. Other contrasts between QI and research include the following:

- QI activities are part of normal health care operations; research is a distinct enterprise.
- QI is funded by clinical care resources, while research is funded from a separate research budget.
- QI is not completely optional, while conducting research is a choice.
- Subjects have an ethical obligation to participate in QI activities, but not in research.

Like research, QI can produce generalizable knowledge. However, while research does this regardless of whether the knowledge gained can be implemented immediately by others, knowledge produced by QI always has the goal of effecting immediate local improvements. QI is led by people who work in the clinical setting where changes will occur. Another distinguishing feature is that while research may implement a fixed protocol over a period of years, QI methods expect changes in the protocol over the

course of the activity. QI is an integral part of the ongoing management of the system for delivering health care – not an independent, knowledge-seeking enterprise.

A major conclusion of the project is that requirements for ethical QI differ from requirements for ethical clinical research, justifying a different approach to oversight of QI. Most notably, while formal informed consent is not required from a human participant in a QI activity, consent to receive health care should include consent to a minimal level of cooperation with ongoing QI activities of the care provider. Only when the QI activity imposes a burden of greater than minimal consent should an explicit consent be required.

Dr. Baily held that requiring IRB review of QI creates a disincentive for systematic monitoring and evaluating of change, since it is always possible to make the change *without* systematic monitoring. Encouraging this approach, she said, benefits no one. Management of the quality of a core management function should not be "outsourced." Problems with IRB review of QI include high transaction costs, a structure that is a poor fit for QI activities, and differing ethical standards.

However, ensuring ethical conduct of QI does require guidance on interpreting and applying ethical standards, when informed consent is required, and what kind of ethical review process is appropriate, as well as an economic and regulatory environment that supports ethical conduct and accountability. For this purpose, Dr. Baily proposed importing a system for protection of human participants in QI activities into the accountability system for clinical care rather than exporting QI to the IRB-based system for protecting human research subjects.

Remarks by Margaret E. O'Kane, M.H.D.

Ms. O'Kane spoke as a representative of the National Committee for Quality Assurance (NCQA), a nonprofit organization that measures and reports on health care quality with the aim of improving the quality of health care. Through the Partnership for Human Research Protection, it also works with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to accredit research programs on their treatment of human subjects.

She noted that at the time of the Belmont Report, the paradigm of health care was a one-on-one transaction between a health care provider or physician and a patient – a model that she said often results in a gap between the care provided and the most beneficial treatment. A recent article (McGlynn et al, 2003) [1] indicates that patients in the U.S. receive recommended care only about 55 percent of the time. This quality gap – a result of providers failing to apply beneficial treatment and do so effectively, applying a treatment that is not clearly beneficial, or failing to address patient needs – results in avoidable deaths, medical costs, and sick days. Today's paradigm is a more complex one that applies systemic interventions in an effort to prevent medical errors and avoidable medical costs and ensure optimal care. Quality improvement systems may design processes of promoting adherence to standards of care, conduct monitoring to detect variation from standards, do surveillance of patient outcomes, and report on findings to health care professionals and the public.

[1] McGlynn, E.A. et al.The quality of health care delivered to adults in the United States. N Engl J Med. 2003 Jun 26;348(26):2635-45.

An example of a study with the aim of improving quality is a study of administration of biotics related to surgery by Brent James. Through data mining at Intermountain Health Care, he was able to systematically examine the different processes and outcomes of care related to administration of antibiotics (for example, what antibiotic was given and when it was delivered). He was able to ascertain that the 2-hour window prior to surgery was the most effective point at which to administer the antibiotics. This has now become a standard of care. This case, Ms. O'Kane stressed, underlines the ethical responsibility to conduct this type of surveillance activity.

Like research, such quality improvement efforts clearly do result in generalizable knowledge. As in research, an intervention group is identified; there is an observation or intervention with individual patients, staff, or systems; systematic data collection; and statistical analysis. However, she agreed with Dr. Baily that this is not a reason to subject them to IRB deliberations. Unlike research, quality improvement efforts occur in the context of health care provision; they are closely linked to operations and supported by leadership. They involve patients who have already consented to treatment with a provider who has access to patient information as a necessary part of providing that care.

While QI does need review and oversight, Ms. O'Kane, like Dr. Baily, does not believe IRBs are suited to assess QI efforts. IRBs are not familiar with operational issues and do not appreciate operational time pressures. Instead, she said, what is needed is the development of an appropriate capability within the quality infrastructure to protect patients' interests.

DISCUSSION

Dr. Prentice described a hypothetical example in which an IRB Chair receives a call from an investigator who wants to do a systematic study to improve care that randomly assigns patients to two standard methods or procedures. In deciding whether this is research, he asked whether intent to publish is an appropriate determining factor. Ms. O'Kane said that while publication has been used to make this determination, she believed strongly it should not be a "threshold issue." Dr. Baily said the effort may be research, but it is also clearly quality improvement. She did not see the issue of publication as a potential dividing point, since it would be helpful to share findings in either case. She did not feel that an IRB would be the best option for having this project reviewed, however. Mr. Hodge added that while the activity is apparently research and there is justification for IRB involvement, the intent to publish is inconsequential, since findings of work done through public health practice are routinely shared. Dr. Fisher agreed that using publication as a criterion did not make sense.

Ms. Kornetsky observed that journals are increasingly concerned about publishing results of QI activities on the grounds that IRB review may have been required. Dr. Baily concurred, noting that AHRQ and the Hastings Center are trying to address this issue.

Dr. Carome responded that Dr. Prentice's example was clearly research and the type of activity IRBs are qualified to handle. He noted that the fact that the therapies are both accepted standard practice is irrelevant in the determination. Mr. Barnes commented, however, that Dr. Carome's comments lead to the conclusion that almost every activity could be classified as research. He pointed out that public health practice routinely takes actions that are essentially experiments (for example, locking up and civilly

detaining people who are recalcitrant in taking their anti-tuberculosis medications). He believed the lines between research and practice are permeable.

Dr. Fisher questioned Dr. Baily's contention that a justified omission of informed consent is one of the distinguishing factors between research and QI. Since Dr. Baily said this omission would hold only for minimal risk research, she found that problematic. She questioned Dr. O'Kane's assumption that QI always has the patient's best interest at heart and suggested that patients may not always see best practices in this light. Dr. Fisher suggested that one important criterion that could be used to distinguish research from pure QI activities might be whether or not the patient is receiving a procedure he or she otherwise would not receive. Records reviews such as the Intermountain Health Care study do not affect patients differently and therefore could not be considered research. In response, Dr. Baily reiterated the importance of informed consent when a person is subjected to an intervention above minimal risk. An example would be when an intervention is tested that is not a part of normal health care, in which case there is no prior consent. Ms. O'Kane suggested that whether or not an intervention group gets a higher degree of care is another distinguishing factor between pure QI and QI that is also research. However, she acknowledged that paradigms for thinking about research do overlap significantly with ways of thinking about systematic delivery of high-quality care.

Dr. Carome stressed that this discussion could not be framed by only one example; it would be possible to lay out 100 distinct examples of QI that might or might not be considered research by OHRP. He gave two examples to distinguish QI that is not research from a research activity:

- *QI that is not research*: After a chart review showed that only 50 percent of patients who had heart attacks went home with beta blockers (a proven means of reducing mortality), a computer flag was added asking the nurse to confirm that a beta blocker has been described and, if not, to document the reason why. A chart review is done again after a year to determine whether or not the computer flag led to improvement. Whether or not the results are "written up" would not affect the determination.

- *Research:* Managers of a hospital system want to find the best way to make sure a patient goes home on a beta blocker. Using two similar hospitals within the system, they institute a study to compare the efficacy of the use of computer flags for nurses vs. physicians.

Dr. Baily and Ms. O'Kane differed, however, with the contention that the second example should be classified as research. Dr. Baily described it as the "essence of QI." She further argued that a result of classifying it as research might be that the hospital simply decides to implement one method for one period of time and another later for a comparable period. The organization can then do a chart review and determine which works best. She held that the need for this type of thinking wastes time and resources that would be preserved in a system in which IRB review and normal ethical oversight of QI are more closely integrated.

Dr. Hauser, however, felt nervous about the possibility of integrating research and QI, which he held were two distinct activities. He commented that the example Dr. Prentice gave is clearly research and supported Dr. Carome's classification of the two examples involving the prescription of beta blockers. He observed that if QI processes were submitted to IRBs, it would deter the effort to find and correct problems in a timely way. As a member of the Quality Committee of a health system, he reported that

almost all the cases that come to the committee's attention are root cause analyses or sentinel event analyses that must be addressed immediately. While activities done to identify and understand problems such as adverse drug reactions or wrong patient surgery should be classified as QI, he said experiments could be considered research.

Public Comment

The Chairman invited public comment.

Dr. Robert Levine of the Yale University School of Medicine said he once served as a special consultant to the National Commission for the Protection of Human Subjects, where his assignment was to define research and distinguish it from practice. He said the Commission rejected the criterion that research could be defined by the intent of the person is doing it; the word "designed" was used instead because intent could not be clearly seen. A second criterion rejected by the Commission was whether or not publication was a goal.

Dr. Levine advised SACHRP against continuing the many efforts to define research. He recommended "going the exemption route" instead. He pointed out that an agency so exempted is not absolved from ethical responsibility.

Models of IRB Review

Dr. Prentice acknowledged Dr. Susan Weiner, a SACHRP member and Ms. Amy Patterson as organizers for this panel. Dr. Weiner commented that from the perspective of a public representative, it is vital to find ways of making appropriate ethical review more efficient. She observed that time has a different meaning from the patient's perspective.

Remarks by Michael Carome, M.D.

Dr. Carome pointed out that HHS regulations (45 CFR §46.114) provide for "cooperative research projects" by two or more institutions. In this case, each institution retains responsibility for "safeguarding the rights and welfare of human subjects and for complying with the HHS regulations." Further, the regulations allow any institution participating in a cooperative project to "enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort."

Under the most common assurance process, the Federal-wide Assurance (FWA), the ability to do cooperative research is relative streamlined. Multiple institutions can designate the same IRB and document their arrangement in an IRB Authorization Agreement. However, when the designated IRB is geographically distant, mechanisms must be in place that ensures that the IRB is knowledgeable about the local research context. A guidance document already exists that outlines methods for accomplishing this, including provisions for a shared review process. In Dr. Carome's view, there is no regulatory obstacle to

cooperative review, since specific provisions and alternatives already exist.

Remarks by David Lepay, M.D., Ph.D.

Dr. Lepay, FDA's Senior Advisor for Clinical Science and Director of Good Clinical Practice Programs, stated that FDA has always allowed cooperative review arrangements. He observed, however, that "central" and "local" IRBs do not appear in the FDA regulations. FDA accepts reviews of research by wide range of IRBs that meet regulatory requirements. The regulations define identical expectations from any IRB arrangement, and it is the clinical investigator's responsibility to select an IRB that is able to comply with these expectations.

Dr. Lepay stressed that any IRB can serve as a "central" IRB. However, no local IRB is ever required to enter into a cooperative research agreement for centralized IRB review. Cooperative agreements also may apportion part of the review responsibilities between a central IRB and a local IRB, allowing for a wide range of possible constructs. When this option is chosen, the local IRB with jurisdiction must agree to the arrangement. Written agreements must be executed that document cooperative arrangements, especially between the local institution and central IRB. Dr. Lepay stressed that to be effective, this documentation must be shared with the local IRB; unfortunately, this sometimes does not occur. Other expectations include maintaining subject protections and assuring that the reviewing IRB is appropriately constituted and adheres to all applicable US Federal, state, and local laws.

FDA regulations and guidance highlight the need for IRB members to have adequate knowledge of community attitudes, institutional policies, and state and local laws that apply at the research site or sites. However, FDA has never established local IRB review as an explicit regulatory requirement.

While both central and local IRBs can provide equal protection of subjects' rights, performance data are needed to determine whether or not they are doing so do not yet exist. In order to determine how well systems are performing, data are needed on a range of indicators, such as efficiency and transparency. FDA conducts approximately 300 IRB surveillance inspections annually, but it currently does not subclassify IRBs by type. However, the agency has found it necessary to take official action in only 2 to 3 percent of cases reviewed in its annual inspections.

FDA expects to provide additional guidance in the near future related to use of a centralized IRB process in multi-center trials. The goal will be to address the issue of how flexible systems can best be employed. Proposed guidance will be shared with colleagues at OHRP and NIH before it is released for public comment.

Remarks by Susan Kornetsky, M.P.H.

Ms. Kornetsky observed that IRBs are not generally aware that the regulations provide for "cooperative research." Such arrangements exist in an environment in which the way research is conducted is changing in many significant ways. Multi-institution research is more common, for many and good reasons. Relationships between academics and industry are increasing, and funding is shifting from Federal to corporate sounds. There is a general increase in clinical research and technology continues to advance at a rapid pace. Also, mergers among institutions are increasingly common.

Even in this changing environment, local "protectionism" and "territoriality" can be obstacles to cooperative research. There are concerns about liability and legal implications that give institutions pause when they think of relinquishing the review process. Some IRBs distrust others or maintain that they best know their research participant community. Also, the regulatory environment has sometimes been over-reactive, stifling creativity. Some also fear the loss of "business" to other IRBs.

Using a centralized review process may help remove conflict of interest concerns, attract sponsors, and facilitate timely reviews. It also can eliminate duplicative reviews. Ms. Kornetsky suggested that while the need for "local knowledge" in a geographic sense is sometimes a legitimate concern, in many cases it makes sense to consider the "community" not as a physical location, but as a group of individuals with a shared condition participating in research. In fact, she argued that autonomous institutions with their own IRBs may sometimes be acting in their own interest in a local context, which can be a conflict of interest.

Ms. Kornetsky highlighted multiple review models. For example, the Multi-Center Academic Clinical Research Organization (MACRO) has five sites with an alternating lead institution for each review; the Biomedical Research Alliance of New York (BRANY) has a central IRB with members from surrounding academic institutions; and the National Cancer Institute (NCI) reviews a protocol through an IRB composed of representatives of cooperating groups, followed by a focused review to determine if there are local concerns related to the approved protocol. A similar two-tiered system is now being considered for the pediatric oncology group as well. Central IRBs (CRBs), which are independent and usually, but not always, for profit, are another viable option.

Ms. Kornetsky pointed out that the National Bioethics Advisory Commission has recommended the use of alternatives for multi-institutional review (2001). To accomplish this, the Commission suggested designating independent scientific review and research ethics committees and connecting IRBs with the lead IRB through the use of effective communication tools, such as Web sites. Similarly, the Institute of Medicine recommended streamlining multi-site research. The most recent report in the pediatric group emphasizes this need as well, since in children's research it is usual to work with multiple institutions in order to access sufficient numbers of participants.

Ms. Kornetsky stressed the growing need to consider alternatives and let go of "baggage." She observed, however, that there are legitimate concerns to be addressed in moving toward such alternative models. For example, finding a way to work with informed consent forms across institutions is important. Some IRBs that work together have shared templates with sections that can be individualized. Whatever the approach, improving communication among IRBs about review outcomes should be a priority.

Remarks by Robert Levine, M.D.

Dr. Levine recalled that in 1978, when IRBs were established by the National Commission, they were supposed to balance the needs of science with the welfare of the subject. The local Commission expected them to work closely with investigators to assure that the rights and welfare of the subjects were protected and that the application of polices was fair to the investigators and contributed to the education of the research community and the public. IRBs were held to have the advantage of familiarity with the actual conditions surrounding the conduct of research. Their relationship with investigators was seen as collegial, whereas IRBs are now viewed as "guards" for the subjects. During the 1970s and 1980s, students competed for appointment to IRBs, and senior and respected members of the faculty served on

them willingly.

Today, the speaker maintained, the credibility of the IRB as an institution and the motivation to serve has eroded. Members of the faculty have been held responsible for OHRP closings, and institutions have been portrayed by the media as incompetent or worse. Also, members' energy is often sapped by low-yield chores. A driving factor is that medical centers are facing financial crisis, and salaries are often linked to revenue generated – pressures that decrease motivation to serve on IRB. These factors raise concerns about the wellbeing of the local IRB as an institution, since in order to function well, any IRB requires motivated members who wish to be of service to the discipline and the institution and receive the institution's respect.

Dr. Levine held that, in terms of measurable activities that indicate literal compliance with regulations, there is nothing the local IRB can do that cannot be done equally well by a CRB. Consequently, CRBs fare well on audits and inspections. Nevertheless, he suggested that the "bureaucratic rationality model" is not necessarily equipped to evaluate objectively the deliberations of "wise judges." He stressed that local IRBs do offer something of "immeasurable value" that may be lost as universities and others increasingly turn to CRBs for relief.

Remarks by David Forster, J.D., M.A.

Mr. Forster observed that there are many players in clinical research, including sponsors, contract research organizations (CROs), institutions, institutional review boards, investigators, site management organizations, and subjects. There may be numerous participating sites, each of which has a different structure. As a result, multi-site research can be "incredibly complex."

Sponsors are interested in independent IRBs because they want to ensure consistency in review for multi-site trials. Sometimes, IRBs outside the institution sponsoring the research are positioned to apply pressure when internal ones might not be able to do so because of conflict of interest (for example, when a lucrative patent could be the outcome) or other concerns. Independent IRBs also may offer some economy of scale. Large IRBs are able to develop deep infrastructure and expertise, afford high-maintenance sites and a proactive site visit program, and stand to lose any one sponsor or institution as a client.

From the perspective of sponsors, independent IRBs are a means of providing consistency of review for multi-site trials. They can offer consulting services on IRB issues and give opinions on draft protocols and consent forms. They are often able to apply pressure on noncompliant investigators and sometimes are used to provide review services in instances where the institution has a conflict of interest. From the perspective of institutions with their own IRBs, many of the same considerations apply. In addition, independent IRBs are able to provide timely review of research, freeing up IRB staff resources for other tasks (such as site visits). Usually, sponsors are willing to pay for the cost of an independent IRB.

Mr. Forster identified many issues that must be worked out when an institution chooses to work with an independent IRB:

- How will the external IRB mesh with the institutional bureaucracy and other institutional committees?

- How will the institution assign protocols?
- How will the independent IRB be compensated?
- How will communication be conducted?
- How will investigations of noncompliance be organized and conducted?
- How will the independent IRB learn about community attitudes and local conditions?

In regard to the latter issue, the speaker observed that independent IRBs have developed many strategies for getting input on local attitudes. For example, they ask the investigator and institutional representatives for input, do interviews, conduct site visits, and conduct searches of the Internet and other media. Mr. Forster suggested that media coverage is generally a good indicator of local values. Also, local representative board members can provide a great deal of information on local attitudes.

Although responsibility and liability are a frequently cited concern, Mr. Forster asserted that an institution may actually reduce its liability by outsourcing in some instances, assuming they are using a high quality IRB; however, an institution does not completely relieve itself of responsibility by outsourcing to an independent IRB. Independent IRBs do have responsibility and liability for the studies they review, regardless of what other parties may be involved; they can be sued.

A significant issue in the use of independent IRBs is their obvious conflict of interest: "the IRB is paid by sponsors and investigators to protect subjects from sponsor and investigators." Means of addressing this issue include the institution of controls to minimize the likelihood of bias as a result of conflict of interest, such as carefully choosing Board members and insulating them from issues such as financial loss or gain. Mr. Forster recommended that a majority of Board members should be unaffiliated with the corporation and none should hold corporation equity. He also recommended ensuring that none of them rely on the Board as a primary source of income. Members should be educated to focus on subject safety as opposed to business issues. Disclosure of the conflict of interest to affected parties is another partial solution.

While "IRB shopping" among investigators is a serious problem, Mr. Forster held that it was one not limited to independent IRBs. Sometimes PIs submit a single study to multiple sites and keep the ones that say "yes." FDA has addressed this problem by requiring IRBs to report disapprovals to others. It is also possible to gather information on prior approvals by directly requesting this information on the application form.

Remarks by Lowell Schnipper, M.D.

Reporting for a task force assembled by the American Society of Clinical Oncology (ASCO), which has conducted extensive review of literature and extensive interviews with IRBs across the country in order to inform policy development, Dr. Schnipper said IRBs appeared to be overwhelmed with the volume of review requirements. The task force learned that it was difficult and time consuming to analyze adverse events, there was variability in the oncology expertise available, IRBs were often under-funded, and there was significant variability in reviewing protocols.

Dr. Schnipper said that after many "heated discussions," the task force chose to issue a policy statement supporting centralized review. He said this approach offered a way of concentrating expertise and promoting efficiency, allowing the local IRB to focus its resources on monitoring the onsite trial after rigorous scientific review has been done. Centralized review has the potential to reduce costs, eliminate

duplicative reviews in multi-site trials, and ensure consistency across trial sites. He suggested that centralized review is best suited for trials that have undergone rigorous scientific review, such as the NCI Cooperative Group trials. He saw the study of "orphan diseases" as especially suited to this model.

Nevertheless, Dr. Schnipper held that the role of the local IRB should be preserved. For example, he sees it as the best site to assure the qualifications of the investigator leading the trial, ensure that needed resources are in place, and maintain overall responsibility of proper conduct of the trial.

As this model is used more frequently, buy-in of local institutions is important. It is important to articulate clearly the division of responsibilities between central and local IRBs. Dr. Schnipper suggested that it would be useful for the Federal government to provide "clear and uniform" guidance on the role of the local IRB when a central IRB is used. It might also want to say a CRB is actually "preferred" for certain situations, such as specific trials. He noted that a recent study reported in *Academic Medicine* (July 2004) found that despite widespread fears of litigation and a lower quality standard, almost all institutions who actually used a central IRB were pleased by their services. They reported that the time for turnaround was much shorter. However, academic medical centers were not sure that using a CRB helped them attract additional industry trials.

While OHRP and FDA have both endorsed this strategy, Dr. Schnipper felt this support might be even more emphatic.

DISCUSSION

Noting that the volume of business carried out through independent IRBs has increased dramatically, Dr. Prentice said he was struck by Dr. Levine's comment about the need for concern related to the wellbeing of local IRBs. He asked what the IRB or Human Research Protections Program was likely to look like at an academic health science center in 10 years time – and what, in Dr. Levine's opinion, it should look like. Dr. Levine responded that there is likely to be ever-increasing difficulty getting people to serve on IRBs. He said he was actually in favor, under the circumstances, of turning over the responsibility for primary review of multi-site trials to regional groups or consortia.

Dr. Prentice invited panelists to suggest steps that SACHRP should take. There were multiple responses:

- Dr. Schnipper advised categorizing types of clinical trials and identifying preferred review methods.

- Dr. Levine suggested finding ways to reduce the excessive burdens on the IRB system, including applying sanctions with less visibility and more clarity about the specific reason for the closing, as well as ensuring that the "other side of the story" is told.

- Mr. Forster proposed an examination of the root causes of the movement, which involve funding and resources. He reported that centralized IRBs in some European countries are slow and all-powerful. Consideration should also be given to the implications for small, investigator-initiated studies.

- Dr. Lepay said that he would be interested in hearing more about any concerns and advice that pertain to FDA.

- Dr. Carome noted that it would be helpful if the Subpart A subcommittee established earlier in the meeting could give some attention to §46.114.

- Mr. Barnes suggested that SACHRP could play an advisory role to OHRP and other agencies as increasing implementation of central IRB review occurs. He reported that, intuitively, he believes this change will offer better subject protection, expedite research, improve analysis of adverse events, and provide better oversight of research. He suggested it would be useful to identify the variables that should be considered in assessing how the process is working in specific areas.

- Dr. Jones stressed the importance of educating researchers and institutions. He was especially concerned about maintaining a culture capable of supporting underlying ethical principles, regardless of the model used. Dr. Levine, however, said it is not possible to "turn it all around right now." There is too much fragmentation; the ethos of the 1960s will not return.

Dr. Gyi stressed that there are existing models and pathways for efficient conduct and review of research. He noted that the European system offers both good and poor models, including some that can result in paralysis of the research review process.

Noting that regulatory barriers do not exist to centralized review, Dr. Schnipper commented that he was still unable to identify the real barriers to the more common use of a review mechanism such as the NCI program. Ms. Goldberg commented that from the NCI perspective, the project is going well and about 2000 local sites are making good use of central view. Under this system, the National IRB reviews the protocol before it is distributed to participating sites, which can use a subcommittee or single review as opposed to a full board review. In fact, the process can take a matter of days. So far, 184 IRBs have approved 49 protocols using a "facilitated review" process. However, turf issues are still a hurdle. People have become "set in their ways" and change takes time. Liability issues are a continuing concern.

Ms. Goldberg suggested that a strong message from regulatory agencies that such approaches are acceptable would be useful. Dr. Prentice concurred that specific guidance might be useful. He also felt that spelling out the responsibilities of local and central IRBs and how they are handled (for example, managing informed consent and adverse events) would be a useful step. Dr. Carome confirmed that OHRP has not provided a formal guidance document on central IRBs or cooperative review. However, OHRP did issue a letter to sites on their responsibilities in participating in the NCI protocol. Dr. Levine added that it was important to share the stories of cases in which liability issues have been tested in court.

Dr. Weiner suggested, based on her work with Dr. Patterson that NIH might be willing to sponsor a workshop for the purpose of analyzing issues related to central IRBs. Such a workshop could provide a means of grounding SACHRP guidance with more data and evidence than it currently has available.

Mr. Barnes suggested that a useful option might be for SACHRP to issue a statement as a committee regarding the use of CRBs. This might be a useful step to take before formally asking OHRP or FDA to issue a statement that might not even be necessary. To do this credibly, however, members need more information. Dr. Weiner supported the idea of proceeding in this direction. In response to a question from

Dr. Prentice, Mr. Barnes clarified that he was suggested that a workshop be convened to provide a basis for a SACHRP guidance document. He envisioned the workshop as exploring "a panoply of mechanisms to achieve central review." Dr. Schnipper added that ASCO would be interested in as much data as possible on the economic implications of "business as usual" as opposed to other structures.

MOTION: Mr. Barnes moved that SACHRP recommend to NIH, FDA, and OHRP that they consider holding a coordinated workshop focused on central review mechanisms, that members of SACHRP attend this workshop, and that SACHRP use the workshop experience and other processes as a means of gathering information and moving toward a consensus statement. Dr. Weiner seconded the motion.

DISCUSSION: Mr. Adams suggested leaving open the possible outcome. The friendly amendment was accepted, leading to the following revision: …..and that SACHRP use the workshop experience and other processes as a means of gathering information and moving toward future committee action, possibly consisting of a consensus statement.

ACTION: The motion was approved unanimously.

The meeting was adjourned.

Secretary's Advisory Committee on Human Research Protections
October 4-5, 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.

Original Signed January 31, 2005

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