Secretary's Advisory Committee on Human Research Protections

January 31 and February 1, 2005
Alexandria, VA

Minutes

MONDAY, JANUARY 31

Welcome and Opening Remarks

Ernest Prentice, Ph.D.

The Chairman welcomed everyone to the meeting. He then welcomed a new SACHRP member, Ms. Ada Sue Selwitz. He reminded attendees of SACHRP's Charter, which comprises protection of vulnerable subject populations. In fulfilling its charge, SACHRP works closely with OHRP staff, who act as liaisons on SACHRP subcommittees and provide expert advice. The Chair specifically recognized the efforts of Kelley Booher and Cathy Slatinshek, who ensure that subcommittee and full committee meetings run smoothly. He also thanked ex-officio members of SACHRP.

Report on Issues

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

Dr. Schwetz informed SACHRP that OMB has approved revised Federal-wide Assurance (FWA) forms, which contain substantive revisions. The Director expected the new forms to be posted on the Web by the end of the week of the meeting. In the future, OHRP will approve only FWAs. Single project assurances will remain in effect to the end of the project for which they apply, but cooperative and multiple project assurances will have to be replaced by an FWA by December 31, 2005.

Under the new system, only three different agreements will be used: FWAs, the IRB Independent Ethics Committee agreement, and the Individual Investigator agreement. The Acting Director also noted that OHRP has enhanced its Web system so that registered IRBs can submit FWA updates and renewals on line, which will make it easier to submit information.

At the suggestion of SACHRP, OHRP is planning an IRB workshop that will explore why central IRBs are not being fully utilized and consider how other alternatives to local IRBs can be used as effectively as possible. OHRP has received input on the program from other agencies and from SACHRP; it is now seeking partners to cosponsor the program.

The members of the Institute of Medicine (IOM) study group on Subpart C are now being selected. Proposed members are posted on the IOM Web site, and input is still welcome. The study group, funded by OHRP, will explore the ethical foundations of Subpart C, providing a basis for a revised regulation.

Dr. Schwetz also noted:

- It has been established that the Department of Homeland Security is subject to §45 CFR 46. It is expected that the Department will begin to participate in relevant interagency meetings. It will also be an *ex officio* member of SACHRP.

- Agencies under the Common Rule have established a working group to identify problems, issues, and possible solutions related to international research involving human subjects.

- The Secretary of HHS has requested OHRP and FDA to follow up on SACHRP recommendations contained in one of SACHRP's letters to the Secretary. Recommendations in a second letter have been referred to the Office of Civil Rights (OCR).

- The 25th anniversary of the Belmont report was celebrated, and many attendees expressed their enjoyment.

- OHRP has prepared pamphlets to be used in outreach to the general public. The pamphlets are intended to help rebuild trust, especially among minority groups, and help people understand what it means to be a research subject.

- Incoming HHS Secretary Mr. Michael Leavitt has been briefed on human subject protection issues, SACHRP, and other aspects of the Common Rule.

Overview of Charges to Subcommittees; Approval of Minutes

Ernest Prentice, Ph.D.

The Chairman provided an overview of charges to existing SACHRP subcommittees and complimented the subcommittees on their work. He highlighted the formation of a new subcommittee on Subpart A, which will review and assess all provisions of Subpart A and consider how to reduce burdens resulting from "regulatory creep."

Minutes for the previous meeting were approved unanimously.

Dr. Prentice then provided an overview of the meeting agenda. He asked whether any members of the public wished to address SACHRP. Hearing from none, the meeting proceeded.

Report of the Subcommittee on Research Involving Children

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

KEY POINTS, §45 CFR 46.404

Dr. Fisher presented the subcommittee's fifth report to SACHRP. She reminded members of the importance of logical continuity from §404 to §407. Recommendations on §407, which deals with research that is "otherwise not approvable" by an IRB, have been sent to the Secretary. She noted that it was important to bear in mind that research not approvable under §404, §405, or §406 might be approved under §407.

The Co-Chair then reviewed recommendations related to **§45 CFR 46.404** (minimal risk research) that have already received conditional approval from SACHRP. These included:

- **Proposal 1: Uniform Standard.**

- **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."

- **Proposal 3: Minimal Risk Should be Age Indexed**. The rationale is that the risks a child encounters will differ depending on the child's age.

- **Proposal 4: Upper Limits of Risk and Harm.** The uniform, age-indexed definition of minimal risk should represent the upper, not lower, limits of risk to which children can be exposed under §46.404.

- **Proposal 5: Equivalent Procedures. Procedures that** are "equivalent in probability and magnitude of harm to risks of daily life or routine physical or psychological examinations or tests experienced by average, healthy, normal children living in safe environments" should be considered consistent with the definition of minimal risk.

- **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.

- **Proposal 7 and 8. Well-Child Visit: Referent for Routine *Medical* Examinations or Tests.** The subcommittee proposed that routine medical examinations do not have a precise, universally accepted definition; however, what is sometimes called a well-child physician visit offers one reasonable basis for comparison to both routine medical and routine psychological examinations or tests.

- **Proposal 9. Index Routine Psychological Tests to Standardized Screening or Assessment Measures.** Examples of such measures include child and adolescent intelligence tests, infant mental and motor scales, educational tests, reading and math ability tests, and measures related to neurological or motor disorders, social development, family and peer relationships, emotional regulation, and feelings of sadness or hopelessness.

- **Proposal 10: The Uniform Standard Must Apply Internationally.**

KEY POINTS, §45 CFR 46.406

Dr. Fisher presented the subcommittee's recommendations related to **§45 CFR 46.406,** which addresses conditions for approving research that poses more than minimal risk to the child without the prospect of direct benefit. The Co-Chair stressed the importance of defining the "minor increase" over minimal risk in a way that is not so broad that it leads to unacceptable risk and exploitation and not so narrow that it deprives children of research that is important to their health and welfare, encourages researchers to

overestimate direct benefits so that their studies may be processed under §45 CFR 46.405, or causes protocols to be submitted under §45 CFR 46.407 unnecessarily.

The subcommittee's proposals were as follows:

- **Proposal 1: Uniform Standard.** IRBs should apply a uniform standard to determine whether the risks of an experimental research procedure represent a minor increase over minimal risk. The subcommittee held that when research offers no probability of direct benefit, it would not be ethical to subject children to greater research risk simply because their daily lives are filled with greater risk than healthy children or those living in safe environments. While some argue that children who undergo procedures such as venipunctures as part of their regular care experience less harm from such procedures when they are used for experimentation, the subcommittee felt that children may be used to such procedures but still find them as unpleasant as any other child. . A second argument for a relative standard that the greater needs of children who share the subject's disorder or condition justifies increasing levels of risk, also failed to persuade the subcommittee. Members felt that a vulnerable child does not have a greater obligation to serve others by participating in research. The uniform standard is also appropriate because it is consistent with the standard for minimal risk.

- **Proposal 2. Determining Minor Increase over Minimal Risk.** The regulation indicates that approvable research must represent only a "minor increase over minimal risk." It is essential to define what a "minor increase" means in a clear and specific way. Methods, compounds, instruments and other research procedures are so variable that a single quantitative unit of increase cannot be uniformly applied. However, a uniform process of evaluation can be used.

  The subcommittee proposed that IRBs use 10 criteria to determine whether research presents a minor increase over minimal risk. These include:

  1) *Minimal risk comparison*. The IRB considers whether the probability and magnitude of harm or discomfort anticipated in the research are greater than those ordinarily encountered by normal, average, healthy children living in safe environments in their daily activities or during the performance of routine physical or psychological examinations or tests.

  2) *Scientific evidence of risk*. Based on peer-reviewed scientific literature, the IRB determines whether or not there is peer reviewed scientific evidence of the risks associated with the proposed procedure for the subject population. It would also be acceptable to demonstrate that the proposed procedure is sufficiently similar to other interventions with well characterized risks that prudent, informed judgments about risks can be made. The subcommittee sees the principle of "evidentiary protection" as an important framing concept.

  3) *Certainty of evidence*. The IRB considers whether the extent and quality of the evidence is such that there is little uncertainty about the range of risks involved. If there is little reliable evidence to enable the IRB to assess the amount of risk, a conservative approach is appropriate. It should be the responsibility of the investigator to present relevant evidence to the IRB and the IRB's responsibility to ask for it.

  4) *Documented harms.* The IRB considers the seriousness of the documented harms for the subject population. Harms are less serious if they are transient (restricted to the time of procedure or short post-experimental period) and reversible through a short-term clinical

procedure.

5) *Equivalence of procedures.* The procedures are judged to be equivalent in risk to documented risk profiles in terms of duration of harm or discomfort and the cumulative effect of the procedures on the probability and magnitude of harm. For example, if a proposed procedure that could be considered a minor increase over minimal risk is done 10 times when an equivalent procedure is done only once, the cumulative harm of the proposed procedure might exceed a minor increase over minimal risk.

6) *Participant perspectives.* The IRB takes into consideration any available data on how the subject population experiences these procedures (e.g., degree of pain or anxiety).

7) *Mitigating factors.* The IRB determines whether mitigating factors known to minimize or exacerbate the risk have been taken into account.

8) *Inclusion/exclusion criteria.* The IRB determines whether criteria for including or excluding subjects reflect consideration of documented subject characteristics that may influence the probability and magnitude of harm of the procedure.

9) *Monitoring.* The IRB assesses the adequacy of monitoring procedures. The Co-Chair noted that this consideration is new, in that safety data monitoring is not typically applied to nontreatment research.

10) *Safety and competence.* The IRB determines whether the procedure will be performed in a safe environment by qualified personnel with experience conducting the procedure with the subject population

- **Proposal 3. Vital Importance**. In order to be considered vitally important, knowledge gained as a result of the research must have clear and significant scientific implications for (a) understanding the etiology, prevention, diagnosis, pathophysiology, or amelioration of the condition; (b) developing treatment for the condition; or (c) determining future directions for research on the condition. Children should not be used as a sample of convenience for this category of research.

- **Proposal 4: Linking Condition and Vital.** The determination of "condition" and "disorder" should depend on whether (a) the research question is vital to the well being of the subject population and (b) it can only be answered by the subject populations' involvement in the study. The subcommittee concluded that there may be pediatric research designs with no prospect of direct benefit that address a question of vital importance to understanding or ameliorating a condition of healthy children that can only be answered if healthy children are involved in the research. An example would be a study that would significantly advance understanding of childhood diseases such as colds or ear infections.

- **Proposal 5: §45.406 Approval of Healthy Comparison Group.** When a healthy comparison group is included in a study that presents a minor increase over minimal risk, the research may be approved under §45.406 if the research is also designed to collect data that is vital to understanding the healthy child's condition. An example would be a study of neonates' natural immune response to maternal HIV.

- **Proposal 6: "Condition."** "Condition" is defined as specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristics that an established body of scientific or clinical evidence has shown to be *either* a characteristic that is unique to the subject population and essential to empirically answer a question *or* of vital importance for the understanding or amelioration of the subject's disorder or condition. The term "unique" is not meant to imply that the population itself is unique, but rather that the population has a characteristic that is unique to them that makes their participation in a particular study vital. The same characteristic might be considered a "condition" for one study but not for another. For example, children with diabetes as a class might be held to have a disorder or condition for a study that is designed to test the pharmacokinetics of a new form of insulin but *not* have one for a study of a potential treatment for iron deficiency.

- **Proposal 7: Defining "Commensurate."** The regulation contains the following language: **"**the intervention or procedure presents experiences to subjects that are reasonably *commensurate* with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." The subcommittee does not see the term as defining a level of risk, which would introduce a relative standard. Rather, it holds that the term "commensurate" is introduced in reference to the parents' or child's understanding of the experimental procedures during parental permission and assent. The fact that a child or parent has not experienced a procedure does not rule it out, since the risk may be compared to something equivalent that is familiar. This interpretation is consistent with the findings of the National Commission (1977).

- **Proposal 8: Equivalent Procedures.** To provide a basis for assent and consent, children and/or their guardians should be familiar with procedures that are reasonably similar in nature and risk proportionality to those the child has or is expected to experience. However, it is understood that what is considered "commensurate" will differ for parents and children because of their differing perceptions and motivation.

- **Proposal 9: Equivalence Criteria.** The extent to which procedures are determined to be similar to those within the subject population's actual or expected experience will depend upon four criteria: (1) the nature of the procedure, (2) the magnitude of discomfort, (3) the duration, and (4) the cumulative effect.

- **Proposal 10. Evaluation of Commensurability.** IRBs should evaluate the commensurability of a research procedure with respect to the experiences that *most children* within the population of interest have experienced or are expected to experience – not simply the individual subject.

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.406

Dr. Prentice commented that he was impressed with the subcommittee's work, noting that Subpart D is "very complicated."

Members raised the following questions and concerns.

Uniform vs. relative standard. Mr. Barnes questioned whether the standard for "minor increase over minimum risk" is intended to be a sliding scale or an objective standard. Dr. Fisher said the subcommittee believes the "uniform" standard should apply to what is considered a "minor" increment. The Chair supported this proposal as essential to providing an absolute ceiling. However, he noted that

variability is still associated with key definitions, such as "vital importance," "condition," and "commensurability."

Dr. Jones suggested that a relative standard might be justified on the grounds that the research question linked to the individual's condition might benefit those who have the condition as a class. Dr. Fisher clarified that the subcommittee contends that what should not be relative is the ceiling for "minor" increment over minimal risk. A particular healthy child cannot justifiably be exposed to that minor increment if the child has no condition and the research does not address something vital to the child. The ten variables identified in Proposal 3, however, acknowledge that the assessment of increased risk is necessarily contextual.

Mr. Barnes observed that while subjects may have been endangered by the use of relative standards in the past, in some cases the potential benefit to children might justify their use. For example, children in Uganda at risk of HIV infection might justifiably exposed to greater risks than would be appropriate for American children and mothers if this is done to prevent transmission of HIV from mother to child *in utero* (which is not a significant problem in the U.S.). Dr. Polan also found it difficult to apply a uniform standard to international research. However, Dr. Kornetsky pointed out that what is at issue in this section of the regulation is research that does *not* have a potential for direct benefit. Dr. Fisher further pointed out that any good study could potentially be approved under §407. Even so, Mr. Barnes was concerned that some useful studies will be "choked off" or delayed if this is the only route for them to go forward.

Dr. Weiner saw the example of the Ugandan study as highlighting another instance of the risk to an individual balanced against benefits to a class of individuals. In her experience, she said, the risk to the individual is likely to constitute abuse. Even when the benefits to the class are substantial, she argued, "it is too great a risk for us to take." She stressed the importance of focusing on what participation means to the "particular kids" who would be involved in the study.

Dr. Prentice did not see a problem in adopting a uniform definition of minimal risk. He reiterated that protocols that do have a prospect of direct benefit to individuals will be approvable under §405. Therefore, only a small subset of protocols are at issue – those that have no prospect of direct subject benefit whatsoever, but a significant benefit to the pediatric population in the country in question. Such protocols could be approved under §407. He stressed the need to agree on a uniform standard, which has already been given conditional acceptance, and move on. He suggested, however, that a better term than "uniform" might be found.

Finally, Dr. Fisher stressed that the term "uniform" really applies to the analytic process. The IRB may conclude, based on identified considerations that the proposed research is of vital importance to a child with a particular disorder. Factors in making this decision are linked to each other and therefore relative. For example, whether or not a procedure is considered a "minor increment above minimal risk" depends on whether people are competent to do it; each procedure may be assessed differently in a specific context. The subcommittee strongly feels, however, that the fact that a child has experienced a harm does not in itself mean it is justified to expose them to that harm again for research purposes. The burden is to be placed on the protocol, not on the child.

Risk-benefit analysis and commensurability. Dr. Gyi asked how risk-benefit analysis and the concept of commensurability could be separated out; he observed that in practice assent and consent issues intersect with discussions of risks and benefits. Dr. Prentice said he could not see this relationship; he stressed that satisfying the requirement for commensurability would not imply that the risk-benefit relationship of the research must be acceptable. Ms. Kornetsky emphasized that the four conditions (Proposal 9) must be

satisfied independently. Dr. Fisher added that the concept of "commensurate" does not allow more risk; rather, it places a limit or final ceiling on what can be done.

Mr. Barnes, however, questioned whether the concept of commensurability is intended *only* to help children and parents understand the procedure.

Healthy children as participants in pharmacokinetic studies. Dr. Gyi noted that there is a need for pharmacokinetic data for children; it is essential to develop profiles for subgroups such as males, females, and adolescents. He wondered whether such studies could be done in the U.S. under these proposals and, if not, if they could be done overseas. Dr. Prentice responded that he had received feedback from a group of pharmaceutical company representatives that most of them do not feel it would be a serious burden if they were unable to include healthy children in pharmacokinetic studies. He also observed that in some cases a pediatric population in a developing country could have unique characteristics that would justify a pharmacokinetic study.

Vital importance. Dr. Weiner noted that the proposal indicates that the standard for "vital importance" would be met if the research procedure determined future directions for research for the condition. She felt this was insufficient and contradictory to other proposals, since every investigator believes his or her study is of vital importance. It was agreed that this language would be removed.

Simplification. Ms. Selwitz highlighted two primary challenges facing the IRB system that are relevant to the discussion:

1. The complexity of the proposals poses a real challenge to the field, even though the work is "fabulous."

2. The balance between regulatory burden and the need to strengthen protections must be taken into account. The ten conditions identified may all, in practice, need to be documented in meeting minutes.

Ms Selwitz asked the Co-Chairs whether it would be possible "to get where you're going without so many conditions, so that the process becomes less complex for IRBs?" Ms. Kornetsky said the subcommittee tried to identify all the considerations that needed to be taken into account, but could explore the possibility of collapsing some categories.

Dr. Prentice commented that he did not believe the minutes would have to document findings for each of the conditions. While the recommendation can be simplified, complex concepts are involved and guidance is needed. Dr. Weiner added that the criteria presented are helpful and will provide support and reassurance to the public.

Minimal risk procedures. Dr. Hauser asked whether the committee had considered specifying procedures that could be considered minimal risk. Ms. Kornetsky said the committee had originally tried this approach, but found it "messy" and inflexible. The proposed process for decision-making offers guidelines without being prescriptive. Dr. Hauser agreed that the process was difficult, but felt that being specific would be helpful in insuring the vulnerable group was protected. Ms. Kornetsky responded that while she did not believe listing procedures that do and do not qualify was a workable approach, she agreed with the need for concrete examples. The subcommittee has tasked members to identify cases that will help illustrate the analytic process. Dr. Fisher also reminded members that when a list of procedures was presented to SACHRP in a previous meeting, the extent to which a procedure was considered minor

was found to differ significantly depending on the context in which it was performed (for example, in a hospital where the procedure is a specialty or in a clinic where it is used infrequently).

Dr. Polan offered the example of a study focusing on prospective diagnosis of a disease such as diabetes, using populations such as American Indian or Middle Eastern children in which the incidence of the disease is high. He suggested that a skin biopsy or venipuncture would be minimal risk procedures that would be appropriate in this instance. Dr. Fisher rejoined that if the procedures are minimal risk, further considerations of conditions would be unnecessary. She saw no barrier to doing a study that is of vital interest to a particular population and is therefore not especially concerned about the unique needs of international populations. Dr. Polan commented that if the investigator and the IRB have the ability and common sense needed to define what is and is not minimal risk, there is no problem. Dr. Prentice noted that common sense should be exercised within clear guidelines and guided by examples.

Next steps. The Chair noted that some "wordsmithing" is still needed, as well as the specifics of qualifying procedures. He added that the subcommittee has much work remaining and will be working "for a long time"; for example, it has not begun to address §46.408, which addresses parental permission and child assent.

MOTION AND ACTION, SUBPART D, §45 CFR 46.406

Dr. Hauser moved that SACHRP **accept in principle Proposals 1-10 related to Subpart D, §46.406 as presented, recognizing that they need some "tweaking" and will be revisited.** This proposal was seconded by Dr. Weiner.

Mr. Barnes then proposed an amendment to the original motion as follows: **because of concerns about the meaning of "uniform" in §404 and in §406, issues related to "commensurate," the need to come up with examples of the definitions of "minimal" and "commensurate," and the need to further clarify "what uniform risk is or isn't," SACHRP requests the subcommittee to devote a portion of its next meeting and its next presentation to SACHRP to these issues. The subcommittee is further asked to illustrate the "triage" of §404, §405, §406, and §407 so that SACHRP is better equipped to assess the subcommittee's recommendations in the context of the entire structure.** Dr. Khin-Maung-Gyi seconded this amendment.

Ms. Selwitz added the suggestion that the subcommittee consider some educational and sociobehavioral examples. She also asked that it attempt to distill each of the four conditions to its essence so that they are as easy to communicate as possible. Her concern was the need for documentation of conditions, which could be a burden on IRBs. She suggested that the final report might clarify that the use of the conditions is intended to be a process but that documentation of the consideration of each condition is not intended to be a requirement.

Dr. Jones suggested it would be helpful to illustrate the process by which an IRB will interpret guidance and make a decision, perhaps using a decision tree. Also, much is being asked of investigators, and consideration should be given to how these expectations will be communicated to them. The Chair then pointed to the need for an unfolding case study that starts as §404 with added components as it proceeds to §405, §406, and §407 so that people can see the continuity as the process is applied. Dr. Fisher commented that schematics such as a decision tree can be extremely difficult to devise, since the process is not linear and many elements are inevitably interrelated.

The motion, as amended, was **approved** unanimously.

KEY POINTS, §45 CFR 46.405

Dr. Fisher explained that this section governs the conditions under which IRBs may approve research in which "more than minimal risk to children is presented by an intervention or procedure that holds out the *prospect of direct benefit* for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being." The risk must be justified by the anticipated benefit to the subject; this is in contrast to **§**406, in which the subject's condition is key. She then presented the subcommittee's recommendations related to **§45 CFR 46.405** as follows.

- **Proposal 1: Acceptable Risk.** When research presents the prospect of direct benefit for the subject, the ceiling on risk is determined by whether it is proportional to the probability and magnitude of benefit. This is a relative statement.

- **Proposal 2: Available Alternatives.** As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be independently approved by an IRB if the anticipated benefits are not at least as favorable to the subjects as available alternative approaches. The investigator must make the argument that anticipated benefits are as favorable to the subjects as other available approaches. An example would be a Phase I study of children with cancer who are nonresponders to available treatments in which there is a 6-10 percent probability of direct benefit from tumor shrinkage and longer survival. Even though the percent who may benefit is small, because there are no effective alternatives, the study would qualify for §46.405.

- **Proposal 3: Evidentiary Basis for Risk-Benefit Assessment.** Evidentiary evidence can be defined in terms of scientific data or comparison to the standard of care for treating or monitoring the subject's disorder. The subcommittee concurs with the National Commission (1977), which held that "the expectation of success should be scientifically sound to justify undertaking whatever risk is involved." If the procedure cannot be shown to ameliorate the subjects' condition or influence their disease management, it would not be approvable under §46.405. An example would be a pure toxicity study using children who are nonresponders to available treatment.

  Proposal 4: Monitoring Procedure. Any benefit listed in a §46.405 application must be an objective of the study. For approval under §46.405, the monitoring procedure must have the intended, not incidental, potential benefit of influencing the child's management of the disease. The subcommittee reasoned that protection of pediatric subjects should discourage "piggy-backing" greater than minimal risk procedures onto treatment trials if these procedures do not in and of themselves have a prospect for direct benefit or the procedures' efficacy is not a focus of the research. An example that would *not* qualify under §46.405 would be a research study that uses conscious sedation and magnetic resonance imaging (MRI) to study basic brain activity in children with attention deficit/hyperactivity disorder (ADHD) in which the investor claims the MR has direct benefit because a nascent silent tumor might be discovered in some children.

- **Proposal 5: Safety Monitoring/Direct Benefits.** Safety monitoring procedures that are required solely to protect subjects from the high risk of the experimental procedures should not in and of themselves be interpreted under §46.405 as providing direct benefit**.** The subcommittee's rationale for this conclusion is that the purpose of these procedures is to reduce risk, not to provide a benefit that is treatment-oriented.

- **Proposal 6: Component Analysis (1):** Each procedure in a treatment study must be evaluated independently in terms of potential benefits and risks to subjects. If a clinical trial also includes a purely investigative procedure that presents more than minimal risk, the research should be approved under §46.406 or §46.407, not §46.405.

- **Proposal 7: Component Analysis (2):** Different procedures in a single trial may be approved or disapproved under Subpart D standards. An example would be a neuroblastoma trial that includes a bone marrow aspirate of greater than minimal risk that does not provide any direct benefit to the subjects. In this actual case, the PI chose to modify the aspirate procedure so that it presented no more than a minor increase over minimal risk and could be approved under §46.406. The study was approved under §46.405, but the procedure under §46.406.

- **Proposal 8: Opt-Out Provision:** If procedures without potential direct benefit are included in a treatment trial, there should be an opt-out provision for parents and children. The subcommittee stressed the importance of informing parents and children of procedures that are not related to the child's direct care.

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.405

Members raised the following questions and concerns.

Direct benefit. Mr. Barnes argued that "if there is information that will help all children with a condition, that is a direct benefit to the child." However, Dr. Fisher noted that the concept of direct benefit to the child as an individual is the central reason for the existence of §45 CFR 46.405.

Component analysis. Mr. Barnes felt it would be "impossible for an IRB to parse through" and apply the component analysis as proposed. He thought there should be a way to get at the same issue "that does not hog-tie the IRB." He also noted that when a research study is designed, it is not always clear what is and is not intended as treatment. The Chair observed, however, that the National Committee supported the use of component analysis to examine risks and benefits. It is important to distinguish procedures performed for research purposes and those that are performed for other, nontherapeutic reasons. Ms. Selwitz added that component analysis is a natural process followed by effective IRBs. However, IRBs do not typically review every procedure individually; they are able to identify what is potentially problematic without the time-consuming approach of examining each procedure one by one and reviewing ten criteria for each.

Dr. Fisher responded that a check off approach was not intended. However, a parent who was not informed about a procedure performed on the child that was not intended to help the child would have a right to be angry. To protect the integrity of the process, IRBs must ascertain which procedures are potentially of direct benefit and which are not. Dr. Weiner agreed; she stressed the importance of parents being able to opt out of procedures that do not offer direct benefit, emphasizing that component analysis is essential to make this possible.

Mr. Barnes suggested new wording for Proposal 6: "A treatment study should be analyzed to identify purely investigative procedures presenting more than minimal risk, as opposed to procedures in the protocol whose purpose is reasonably necessary to monitor the healthy and wellbeing of the subject in the study." He observed that procedures do not divide simply into research and nonresearch procedures: rather, there is standard of care; experimental interventions and increments to the standard of care needed to monitor subject safety and well being; and purely investigational procedures. Dr. Weiner pointed out that the second of Mr. Barnes's categories is not pure research, since it might result in modifications to

care. Dr. Prentice suggested that Mr. Barnes send his proposed revision to the subcommittee for consideration.

Opt-Out Provision. Dr. Prentice noted that there are nontherapeutic interventions that are scientifically integral to the integrity of a clinical trial. He suggested the following new language: "If procedures without potential direct benefit are included in a treatment trial that are not scientifically integral to the treatment trial, there needs to be an opt-out provision for parents and children." Dr. Weiner, however, strongly objected. Dr. Fisher initially suggested that if a study cannot be done without the parent agreeing to both §405 and §406 elements, then the parent is refusing to give consent to the child's participation. However, after considering a hypothetical example suggested by Dr. Hauser, she recognized that in some cases a study would be invalid scientifically without certain procedures that have no direct benefit in themselves.

Other comments by SACHRP members included the following:

- Ms. Selwitz asked whether the subcommittee would be addressing the issue of placebo controlled trials. Dr. Fisher responded that the subcommittee would begin to consider this issue at its subcommittee's next meeting.

- Mr. Barnes questioned the need for differentiating the analysis required under §405 and §406, noting that "it's not like IRBs are out to hurt children." However, Dr. Weiner emphasized the importance of asking specifically what is being done to a specific child and what is the pretext. Asking these questions reduces abuse.

PUBLIC COMMENT, SUBPART D, §45 CFR 46.405

Several members of the public responded to the Chair's invitation to comment.

- Dr. Fred Samaha, Director of Research Compliance at the Cincinnati Children's Hospital, complimented everyone who has worked on Subpart D. He stressed the importance of a standard definition for "minimal risk." He also noted that the proposed process for assessing "minimal risk" and "greater than minimal risk" would benefit his IRB. He appreciated the articulation of the "profound thought processes" needed for IRBs to function.

- Ms. Caroline Minor of the University of Michigan urged SACHRP to give more consideration to social and behavioral science, much of which does not offer the prospect of direct benefit. She expressed concern that the uniform standard, as articulated, might make it impossible to study some things that IRBs might judge to be more than minimal risk.

- Mr. Paul Goebel, with Chesapeake Research Review, suggested that if the committee does not intend that the IRB document the ten considerations (§45 CFR 46.406, Proposal 2), it should say so. He also commented that Phase 1 studies frequently expose subjects to toxic level material and therefore cannot be classified as without risk.

- Mr. Gary Chadwick of the University of Rochester focused on proposal 5, §405. He held that the proposal should be squared with FDA guidance that diagnosis and safety monitoring tests should be considered direct benefits. He also expressed concern about a system in which a single study might have to be approved under three or four different sections in the regulations.

MOTION AND ACTION, SUBPART D, §45 CFR 46.405

Mr. Barnes moved that SACHRP **give preliminary approval to Proposals 1-8 related to Subpart D, §46.405 as presented.** The motion included the request that **SACHRP's concerns be taken back for further consideration, with special care given to phrasing of the two proposals related to component analysis.** Ms. Selwitz seconded the motion, which was approved unanimously.

Remarks by Dr. Cristina Beato
Christine Beato, Acting Assistant Secretary for Health

Dr. Prentice introduced Dr. Cristina Beato, who serves as the principal advisor on health policy and medical and scientific matters to the Secretary of HHS.

Dr. Beato expressed gratitude for the "incredible work" that SACHRP is doing. She informed members that she will be briefing the new HHS Secretary, Mr. Michael Leavitt, on human research protections, which will become a more critical endeavor as HHS attempts to increase the effectiveness, efficiency, and ethics of its clinical research enterprise. Noting that the committee has been particularly productive, she singled out those who have served as Chairs and members of the subcommittees for special appreciation. She observed that many of SACHRP's recommendations have already been implemented. Finally, she reported that the two letters of recommendation sent to Secretary Thompson have been reviewed and accepted. The committee's recommendations on the privacy rule were forwarded to the Office of Civil Rights, and the recommendations related to research on children and adverse event reporting were sent to OHRP and FDA for action.

Report of the Subcommittee on Research Involving Prisoners
Mark Barnes, J.D., LL.M.; Jack Beck, J.D.

KEY POINTS

Mr. Barnes reported that the committee has made some changes in the proposals previously presented to SACHRP, including the first four that were given contingent approval at the last meeting. He introduced co-presenter Mr. Jack Beck, a subcommittee member who was with the New York Legal Aid Society for many years and now works with the Correctional Association of New York.

He reminded SACHRP that the subcommittee has recommended that Subpart C be redrafted, and the IOM committee mentioned earlier in the meeting will provide the foundation for these essential changes. The recommendations the subcommittee is bringing forward are those changes that can be made without changing the text of Subpart C. He also noted that few Federal agencies have adopted Subpart C, and its provisions apply only to studies funded by these agencies. Those that have adopted Subpart C include HHS, the Social Security Administration, and the Central Intelligence Agency (CIA). The Department of Defense (DOD), Ms. Decot interjected, follows Subpart C but takes its guidance from the Secretary of Defense instead of HHS. The vast majority of studies involving prisoners, therefore, are regulated only by Subpart A and by a patchwork of protection afforded by various State standards. However, Mr. Beck pointed out that some IRBs may still use Subpart C guidance to frame their internal policy, even when it is not required.

The subcommittee's recommendations as initially presented were as follows:

- **Recommendation 1: Definition of a Prisoner.**

The Subcommittee suggests that the interpretation of a prisoner in Section 46.303(c) be kept as it is, that is, narrowly defined by the words of the regulations.

OHRP should consider some additional circumstances in which liberty is so restricted that informed consent cannot be said to be voluntary (e.g. community correctional settings and halfway houses, probation and parole). For all subjects for whom there is a "nexus" between their conditions of restricted liberty and the decisions of the civil or criminal justice system, research involving those subjects should be reviewed consistent with Subpart A's protections, including protections under Section 46.111 (b) for subjects "vulnerable to coercion or undue influence."

OHRP should consider issuing guidance on such protocols, suggesting questions IRBs should ask and findings they should record before approving a protocol.

The Subcommittee noted with some alarm that for institutions that have not voluntarily extended their assurances to respect Subpart C for all prisoner protocols, then for protocols not funded by HHS, there may be no additional protections for these prisoner-subjects. The only additional protections would originate from Subpart A's protection of subjects "vulnerable to coercion or undue influence." Subpart A cites "prisoners" as such a group.

The Subcommittee therefore notes that two categories of subjects should be covered under Subpart A: those who do not meet the formal definition of "prisoner" under Subpart C but whose liberty is restricted by the civil or criminal justice system, and those whose institutions, in which the relevant IRB is situated, have chosen not to extend their assurances to include Subpart C to all protocols including prisoners as subjects.

Note that if an institution has a prisoner protocol that is NOT HHS funded, but the institution has extended its assurance so that Subpart C is respected for all protocols involving prisoners as subjects, the IRB must make all the required findings of Subpart C BUT is not required to certify the study to OHRP for approval.

- **Recommendation 2: Subjects who are Incarcerated Subsequent to their Enrollment in a Study.**

At the present time, Subpart C review is required for a study to proceed when any subject is a "prisoner" under the Subpart C definition. This has proved troubling for studies that have no specific connection to correctional settings but in which one or more subjects are incarcerated subsequent to enrollment and participation. In these cases, it cannot be said that initial consent was gained under the duress of any correctional system.

Note that 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."

In October 2004, SACHRP, after discussion of the Subcommittee recommendations, recommended that OHRP guidance on the issue of the "subsequently incarcerated" be changed, so that:

> When any research subject is subsequently incarcerated, and the study has not been reviewed

under Subpart C, Subpart A protections should be deemed to apply, and there must be a focused inquiry by the researcher(s) and the IRB regarding the risks and benefits to that particular subject of continuing in the protocol as a "prisoner."

For clinical intervention protocols there would be no clear rule as to whether the subsequently incarcerated subject should or could continue. That determination requires a focused evaluation of the specific protocol and the specific circumstances of the subject. This analysis is required in any case under Subpart A, which mandates special focus on vulnerable subjects.

- **Recommendation 3: Prisoner Representation in IRB Review in Multi-Site Studies**

(1) Under current Subpart C regulations, although at least one member of an IRB reviewing a protocol must be a prisoner or a "prisoner representative with appropriate background and experience," in protocols subject to review by more than one IRB (e.g., multi-site studies), "only one Board need satisfy this requirement." Subpart C, Section 46.304(b).

(2) The Subcommittee regards this "one IRB" requirement as wholly inadequate under Subpart C (or for that matter, under Subpart A) to protect prisoners in one protocol who may be held in widely dispersed locations, and widely varied circumstances, and whose circumstances of participation may be very dissimilar. For example, having one prisoner representative from a prison system with a good health care system would seem insufficient by itself to allow approval of a study to move forward when the study also involves recruitment and participation of prisoners in state systems whose health care is clearly inadequate.

The Subcommittee therefore recommends that OHRP Guidance should state that even though, formally under Subpart C, one IRB with one prisoner representative would suffice for multi-site study review, the IRB of appropriate jurisdiction is still responsible for exploring and determining what the specific risks are in the local prison or jail before passing on the protocol for the local site.

(3) In the case of central IRB review of a multi-site protocol, this would mean that the central IRB should consider the circumstances of each site, for example by requiring some report from researchers as to the conditions in the varied sites of a study. Only in this way can the IRB consider, under Subpart C and/or Subpart A's protections of "vulnerable populations," the actual circumstances of prospective subjects. Otherwise, it seems to the Subcommittee impossible to have any assurance that consent and participation of subjects in each site are truly voluntary, or have even been gained in a private setting.

- **Recommendation 4**: **The Prisoner Representative.**

(1) OHRP guidance should be provided to assist IRBs searching for a prisoner representative and to suggest the qualifications of persons who may qualify.

(2) The three primary considerations for a prisoner representative should be

1. ***Empathy for prisoners, sharing concerns that prisoners would have about a study***
2. ***Particular knowledge of correctional settings, including some awareness of local conditions in which the study will be conducted, and***
3. ***Independence from the prison administration and other outside influences.***

Mr. Barnes observed that chaplains are often seen as the most appropriate representatives, but many of them are influenced by their affiliation with the prison administration.

(3) Some sources might include:

- ***Family members of prisoners***
- ***Former prisoners***
- ***People in recovery from substance addiction who have had experience as inmates in the correctional settings***
- ***Service providers who assist the correctional population, including in the release process.***

(4) The burden of protecting prisoners in research should rest not only on the IRB, but also on investigators, who because of their presence in the correctional settings will have more awareness of actual circumstances than an IRB.

OHRP guidance should make clear that while IRBs may be a check on the system of research protections, each investigator has a duty to assure that research in correctional settings is done in an ethical manner and that informed consent and participation by prisoners are voluntary.

- **Recommendation 5: Definition of Minimal Risk.**

  a) The subcommittee observed that the definition of minimal risk in Subpart A is different from that in Subpart C because prisons are places of great psychological, physical, emotional and economic risk. ***(The interpretation of this difference should be similar to the special interpretation of Subpart D for chronically ill children– additional risks on top of those already present are not justified.) The existence of greater situational risk for prisoners does not justify a greater tolerance for research risk in the deliberations and judgments of the IRB.***

  In response to a question from Ms. Selwitz, Mr. Barnes clarified that the standard of protection that the subcommittee believes should apply to prisoners is the level of risk considered acceptable and tolerable in the "outside," noncorrectional setting.

  b) OHRP should add a section to its present Subpart C guidance discussing the difference between the Subpart A and Subpart C definitions. Using examples, the new guidance should explain how minimal risk might be viewed for different protocols. OHRP guidance should result in this definition's working to heighten, not undermine, protections for prisoner-subjects.

- **Recommendation 6**: **Expedited Review.** ***The subcommittee supports current OHRP guidance, which prefers review of prison research by a full convened IRB. Expedited review of protocols that fall under Subpart C would not necessarily include the input of the prisoner representative, thus frustrating the purpose of having such a representative in the first place.*** Best practice would therefore indicate a need for review by the prisoner representative.

- **Recommendation 7: Follow-Up Care.**

a) ***The Subcommittee recommends that "follow-up examination and care" be interpreted to include any examination or care that is related to the study's clinical intervention and is medically necessary (1) after the end of a study OR (2) after a subject can no longer participate in a study due to release.***

b) ***New OHRP guidance should suggest that for studies reviewed under Subpart C, when it can reasonably be anticipated that some subjects will be released before the end of the protocol, the protocol should contain an explicit discussion, considered both by the IRB and by the subject during informed consent, that details how early release will affect the subject and what follow-up will occur when this happens, as well as what follow-up will occur in the institution after study is over.***

c) ***When one of the effects of intervention is medical disability, it should be the obligation of the researcher to ensure there is adequate provision for future required examinations and care. If the person is discharged prematurely, the PI should not be required to ensure continuing treatment of the underlying condition being treated in the study, but the researcher and the protocol should take into account any adverse effects of the research itself.***

d) ***If the research identifies a medical problem, it is the obligation of the researcher to make his or her best efforts to assure that a discharge or release plan secures follow-up care.***

- **Recommendation 8: Definition of Control Group.**

(1) In current OHRP guidance, if one arm of a protocol provides "standard of care," that arm is considered to fall under Section 46.306(a)(2)(iv), into the category of "control groups which may not benefit from the research." Thus, any study that provides standard of care is held to trigger the requirement of an HHS Secretary's consultation with experts, causing significant delays in prison-based research and even deterring researchers from proposing such studies in correctional settings.

This definition of "control group" has had the effect of delaying or deterring research that is *not* the category of research intended to be choked off by Subpart C.

(2) The Subcommittee suggests that OHRP guidance be changed to be more in accord with standard views of the research community, under which standard of care would be considered to be an arm providing benefit.

In addition, guidance should specify that a protocol with a placebo arm in a study for which there is standard treatment for the condition, would be considered an arm not "benefit[ting] from the research," thus requiring an expert panel consultation.

(3): The Subcommittee also suggests that OHRP guidance indicate that the following applies under Subpart C:

> Before an investigational medical intervention can be initiated, the IRB should make a finding that treatment offered in prison or jail meets the community standard of care. This standard should apply also to social and behavioral research. According to the Subcommittee's view, if standard of care is provided and if both arms of a protocol must provide at least that standard of care, then the inmate is benefiting from both arms of the protocol, and Secretarial review should

not be triggered.

Mr. Barnes dropped this second section of Recommendation 8 before presenting it formally, since it raises issues that proved controversial in the discussion of Recommendation 7. He noted that this recommendation could be referred to the IOM committee for further deliberation.

KEY DISCUSSION POINTS, SUBPART C

Members raised the following questions and concerns.

Reconsent. In regard to Recommendation 2, Dr. Hauser asked for clarification as to whether reconsent should be required when a subject was subsequently incarcerated, and if so, why. Mr. Barnes responded that reconsent would not always be required, but that in some cases the change in circumstances would indeed require a new consent process in which the prisoner is informed of what is and is not possible in terms of maintaining confidentiality (for example, for an individual enrolled in an HIV/AIDS clinical trial). Mr. Beck added that people in prison have very little, and consequently deprivations and benefits that may seem insignificant "on the outside" may have much more significance on the inside. Therefore, the risk-benefit equation is different. He observed, however, that reconsent would not be needed in all studies; for example, it would not necessary in a study for which only a follow-up interview to look at outcomes is required.

Interruption of therapy. Dr. Hauser was also concerned about the potential for interrupting therapy during the new review of benefits and risks (Recommendation 2). Mr. Barnes noted that current OHRP guidance indicates that the subject can continue in a trial if the researcher deems it critical for the subject's health and wellbeing. Dr. Prentice further clarified that an IRB chair may authorize a subject who becomes incarcerated to continue participating until the IRB meets, if it is in the best medical interest of the subject. Dr. Gyi was concerned, however, that this guidance is not familiar to many IRBs, which might interrupt therapy out of a fear of being out of compliance.

Persons with restricted liberty. Dr. Gyi asked for a clarification of procedures for subsequently persons who are not actually imprisoned but do have restricted liberty (Recommendation 2). Mr. Barnes said the subcommittee would not want therapy to be interrupted if it were in the person's best interest, but would recommend that a new analysis occur for the individual as a member of a vulnerable population.

Requirements for prisoner representatives. Ms. Kornetsky asked whether it was the subcommittee's intent to bar all prison employees from serving as prisoner representatives (Recommendation 3). Mr. Barnes said this was not the intent; for example, a prison employee might serve as a representative on a study carried out at another prison**.** Also, the concern related to chaplains applies only to chaplains who are direct employees of the prison system. Ms. Kornetsky pointed out that IRB members routinely review protocols for their places of employment. Mr. Barnes rejoined, however, that the prison setting is a different category. Dr. Fisher accepted this distinction, but questioned the practicality of ruling out chaplains as potential prisoner representatives.

Dr. Fisher observed that the words "and other outside influences" (Slide 2) would be difficult to operationalize. Mr. Barnes suggested, instead, "*related outside influences,"* such as those from the criminal justice system of the state or locality. However, Dr. Fisher felt this influences were not clearly defined. Mr. Beck then clarified that the subcommittee saw the three considerations as goals, rather than requirements; it recognized that it would be very difficult to find representatives who could satisfy all three criteria.

Dr. Prentice asked whether the subcommittee had considered what individuals might best serve this role in different circumstances, for instance, a maximum security penitentiary as opposed to a city jail. Mr. Beck responded that the prison representative would not necessarily be the source of all knowledge of an institution, and in some cases the IRB might wish to bring in additional advisers. He also suggested that representatives may need training in order to be effective. Mr. Barnes added that researchers also need to shoulder a significant responsibility to understand the correctional setting and be able to explain how subjects will be protected in this context.

Dr. Gyi asked whether the subcommittee would find it acceptable for an IRB to explore these questions without a prisoner representative. Mr. Beck responded that the subcommittee strongly advocates the use of a prisoner representative to advise the IRB. Without such an individual, the IRB might not even know what questions to ask.

Members also asked for clarification of how the IRB would fulfill its responsibilities under Recommendation 3. Mr. Barnes explained that the IRB would be expected to direct probing questions to the investigator at the facility.

Minimal risk. Dr. Fisher suggested that section (b) of Recommendation 5 was premature, in that the subcommittee on Subpart A is just beginning its deliberations. Mr. Barnes agreed to strike (b).

Follow-up care. Dr. Fisher observed that the specific responsibilities of the researcher, community, hospital, and institution under Recommendation 7 were unclear. She wondered how the researcher would be able to assure continuing care, in that aftercare is typically not funded. Noting the qualifying phrase, "where the board finds there may be a need for follow-up," Ms. Selwitz also asked for an explanation of which protocols might be found to have this need. Mr. Beck cited instances in which the effects of abruptly ending an intervention could be toxic. He also stressed the importance of the investigator suggesting to a discharged prisoner with an illness where he or she might seek continuing care in the community setting. Mr. Barnes added that such information should be given to discharge planners.

Dr. Hauser questioned that follow-up care could be ensured in our current system of health care, whether after prisoner discharge or at the completion of study. Mr. Barnes said that some access to a reasonable standard of care does exist in some correctional systems that is comparable to what poor people are able to access through Medicaid. He suggested it was preferable to do research in these settings. He pointed to the early AZT studies in Central Africa, which were roundly criticized because even though AZT may have proved a beneficial intervention, those enrolled had no alternative. He agreed, however, that a decent standard of care is not within the reach of many nonincarcerated persons, such as illegal immigrants or the working poor. It is not possible to change the whole system of care in the country, but reasonable discharge planning is achievable.

Dr. Fisher also questioned the idea that research should not be conducted if there is no standard of care, which appears antithetical to demonstrating the importance of instituting a particular type of care to prison systems. Mr. Barnes said that where there is no standard of care "in the world," the subcommittee would not oppose an experimental intervention in the prison setting. The difficulty is when the prisoner must enroll in a protocol in order to be able to achieve the standard of care available in the community.

Dr. Fisher concurred that the investigator has a responsibility for addressing post-care problems that can be anticipated, such as toxicity resulting from sudden stoppage of medications, but not for assuming the broader responsibility for ensuring ongoing treatment. Dr. Prentice pointed out, however, that if standard

of care is available as recommended, the prisoner should be able to continue to receive some acceptable form of care. He understood the investigator's obligation not as actually providing ongoing care if the prisoner is discharged to a community, but making an appropriate referral to a clinic where care might be available to the subject.

Mr. Barnes pointed out that the subcommittee is seeking to interpret the language of Subpart C, which says that in regard to criterion 7, "adequate provision" for care must be made. He and Mr. Beck observed that not all protocols actually require continuing care; the concern arises primarily in studies that offer medical interventions for chronic conditions.

Dr. Prentice observed that SACHRP would not be able to reach unity on Recommendation 7. He noted that the difficulty of accessing needed health care is a social problem that the IOM committee will need to address.

Standard of care. The Chair asked what community should serve as the referent under Recommendation 8. Mr. Barnes indicated that the standard of care would be a national one, as it is in medical malpractice theory. Sites that have a deficient standard of care would not be approved for participation in the protocol. Mr. Beck explained that the rationale for this position is that the inducement to participate in almost any form of health care offered is so strong in most prison settings because of inadequate care that almost all such research can be viewed as coercive in some respect. The co-chair noted that the subcommittee's approach is a controversial one, in that some would argue strongly for as many health protocols as possible being pursued in prison precisely as a means of providing care that would otherwise be unavailable. On this point, Mr. Barnes said, the subcommittee's position is actually less radical than the position OHRP itself has taken.

Dr. Prentice questioned the consistency of this proposal with the approach taken in Subpart D, which requires that the anticipated ratio of benefit to risk must be at least as favorable to the subject as other available alternative approaches. He noted that his IRB examines alternative approaches available at the medical center and possibly in the city, but not in other areas. Mr. Beck said that in his experience multi-site studies are uncommon; however, a multi-site study of Hepatitis C would find care completely lacking in some States. In those states, offering any form of care would have to be viewed as coercion – in the sense of having "undue influence" – since the prisoners would have no other option. Dr. Fisher challenged this interpretation, however; she pointed to Ruth Macklin's definition of coercion, which is, having to choose to do something that you otherwise would not have wanted to do. Prisoners may want the potential benefits of research. Mr. Beck reiterated his strong belief that research should not be used as a means of addressing the problem of inadequate health care in prison settings.

Dr. Prentice suggested that the recommendation might emphasize the importance of "available care" rather than insisting on "standard of care." Mr. Barnes was concerned that this approach recognizes substandard care and may be seen as implying that it is acceptable. Mr. Barnes suggested the term "acceptable standard of care" might replace "community standard of care" to offer some flexibility. Some members continued to question the feasibility of the approach, while Dr. Weiner found the suggestion of lowering the standard of care required unacceptable. Mr. Barnes suggested that the IOM committee might be the best forum for addressing the thorny issue.

Definition of control group. Ms. Selwitz supported Recommendation 8, but recognized that it provided only a "band-aid fix." In response to members' requests for clarification, Mr. Beck explained that the subcommittee's concern was that the current guidance means that good research, which involves an intervention and a control arm, would require an expert review. Mr. Barnes further clarified that under

current requirements, if one arm of a study has reasonable probability of improving the health and wellbeing of the subject but the other only provides standard of care, the study cannot be approved by an IRB and must go to an expert panel. However, Dr. Prentice offered the interpretation that if the IRB can find the prospect of benefit for two active agents; one in each of the study's arms, the study should *not* trigger Secretarial review. He pointed out that a standard therapy arm does not trigger Secretarial review for children.

At Dr. Fisher's request, Dr. Carome clarified OHRP's rationale for its position. He observed that the statement that a control group may not benefit is a truism. He said it would be a therapeutic misconception to assume the control group would always benefit. Since the IRB is directed not to consider the risks and benefits related to procedures that subjects would get outside the research context, there is no benefit to participation when the group would be able to receive the procedures anyway. In any research, he said, there is a possibility that the subjects either in the experimental group or in the control group may not benefit. It would be problematic from an ethical standpoint to imply that research is always beneficial.

Dr. Gyi pointed to a study in the mid-1980s that compared all currently anti-arrhythmics to a placebo arm and found that the available anti-arrhythmics actually produced a higher mortality rate. Dr. Hauser added that a recent atrial fibrillation trial had shown that patients on suppressive therapy actually experienced more adverse events than those who were simply rate controlled. Many members agreed that there was a problem with the rule itself. Mr. Beck observed that the rule has created an unjustified and artificial barrier to good research. Dr. Prentice pointed out that at the time Subpart C was written, the idea was that participation in research, especially by vulnerable populations, should be discouraged. The advent of AIDS has changed the climate; today, the benefits of research are stressed. Dr. Hauser felt that good research in prison settings should be encouraged.

Dr. Schwetz commented that there is no "quick fix" for the current regulation. He said the subcommittee's thinking would be helpful to others and should be clearly articulated. Mr. Barnes assured him that the subcommittee's final report would clarify the rationale for its approach.

PUBLIC COMMENT, SUBPART C

Members of the public commented as follows:

- Ms. Caroline Minor expressed concern about the portion of Recommendation 5 that reads, "OHRP guidance should result in this definition's working to heighten, not undermine, protections for prisoner-subjects." Her concern is that the subcommittee is offering a "band-aid that turns into another Tourniquet," resulting in the approval of even less prisoner research.

- Dr. David Shore, the NIH liaison to the Subpart C subcommittee, observed that the language related to control groups that do not benefit may reflect the concern at the time Subpart C was being drafted that prisoners would be preferentially assigned to groups that could not benefit from research.

- Mr. Gary Chadwick, University of Rochester, commented positively on a statement contained in the presentation of Recommendation 4 to the effect that "the burden of protecting prisoners in research should rest not only on the IRB, but also on investigators, who because of their presence in the correctional settings will have more awareness of actual circumstances than an IRB." He suggested that if the term "correctional settings" were replaced with "research settings," the result

would be a recommendation that works well across all subparts.

In regard to the two categories of permissible "minimal risk" research (Recommendation 5), Mr. Chadwick commented that he assumes category one relates to minimal risk psychology research and category two to minimal risk sociology research. He suggested that the subcommittee consider the meaning and intent of the two categories.

Mr. Chadwick was also concerned about the provision in Recommendation 6 requiring a "full convened IRB." He said this would remove flexibility, observing that IRBs are frequently criticized for under using the option for expedited review.

In reference to Recommendation 8, Mr. Chadwick observed that the recommendation conflicts with FDA's recent guidance that placebo arms in research should be considered beneficial. It is important to harmonize regulations and guidance.

He added that a major purpose of Subpart C was to stop pharmaceutical companies from doing research in prisons, and it did a good job.

- Mr. John Mather, an independent consultant, suggested that Recommendations 7 and 8 both relate to areas that are "too broke to even do a quick fix." He also questioned the assumption that social and behavioral studies are presumed to be complete when active participation ends, noting that alcoholism, drug abuse, and mental health disorders constitute areas in which post-discharge problems and responsibilities may arise.

MOTIONS AND ACTIONS, SUBPART C

Recommendation 1 was **approved** unanimously.

Recommendation 2 was **approved** unanimously.

Recommendation 3 was **approved** unanimously with **amended language.**

Dr. Fisher questioned the second paragraph of (2), which states that "even though, formally, under Subpart C, one IRB with one prisoner representative would suffice for multi-site study review, the IRB of appropriate jurisdiction is still responsible for exploring and determining what the specific risks are in the local prison or jail before passing on the local site." She was concerned that this was a great deal of responsibility for the IRB. Amended language for this portion of the recommendation, suggested by the Chair, is as follows:

The IRB of appropriate jurisdiction is responsible for determining the specific conditions in the local prison or jail that are pertinent to subject protection before passing on the protocol to the local site.

Dr. Gyi asked that the subcommittee report provide more information on how assessment of local conditions should be done.

Recommendation 4 (The Prisoner Representative) was **approved** unanimously **with amended language.**

- (2) Instead of "the three primary considerations…" the language is now, "Among the primary goals for a prisoner representative should be…" This change was offered by Mr. Barnes.

- (2) consideration 1: This now states, "can adequately represent the rights and interests of prisoners." This change was made in response to a concern about how empathy could be operationalized expressed by Dr. Fisher.

- (2) consideration 3: "Other outside influences" are no longer mentioned. Instead, this consideration reads, "able to express views independent from the prison administration."

Recommendation 5 (Definition of Minimal Risk) was **approved** unanimously **with amended language.**

- The first section of recommendation (b) was removed ("OHRP should add a section to its present Subpart C guidance discussing the difference between Subpart A and Subpart C definitions.")

- At the Chair's suggestion, the standard of protection is understood to be referenced to "healthy persons *in safe environments*."

Recommendation 6 (Expedited Review) was **approved** unanimously **with amended language.**

- New language states that "expedited review would be preferred in Subpart C protocols when the prisoner representative would be at least one of the reviewers."

- Final wording will indicate that expedited review is acceptable if appropriate.

Recommendation 7 was withdrawn and not approved.

Recommendation 8 (Definition of Control Group) was approved in part and with amended language.

- (1) was approved unanimously without change.

- (2), paragraph 1, was approved (1 opposed). The Chair interpreted this approval to mean that if one arm of a study provided standard of care, this would not trigger a Secretarial review because that arm could provide the prospect of therapeutic benefit to the subject.

- (2), paragraph 2, was also approved (5 approved, 3 opposed).

- (3) was dropped and not approved.

TUESDAY, FEBRUARY 1

Overview of Agenda and Additional Business
Ernest Prentice, Ph.D.

The Chair provided an overview of the proposed agenda. He reminded members that the purpose of the discussion of compliance oversight activities is to examine the current state of affairs in compliance following the wave of shutdowns of institutional research programs by the Office for Protection from Research Risks (OPRR), now called OHRP, that began in 1998. In addition to presentations by persons familiar with government oversight programs, several representatives outside of government have been asked to present their views.

Adverse Events Issues: Update and Discussion
Amy Patterson, M.D, NIH; Jean-Louis Saillot, M.D, Schering-Plough Research Institute

Remarks by Amy Patterson, M.D., NIH

Dr. Patterson provided a report on the progress of the Federal Adverse Event Task Force. She began by observing that reports of adverse events (AEs) are intended to signal a need to attend to the safety and well-being of the research participant, to consider protocol changes, or to offer insights related to mechanisms of drug action, new therapeutics, or applications. At present, however, there are serious barriers to achieving these benefits. These include variations in terminology that frustrate attempts to compare data, different reporting requirements for various funding agencies that slow communication, and an excessively large number of AEs reported to IRBs, making it difficult to separate true signals from "noise."

The task force was formed as a result of SACHRP's recommendation, in a July 2004 letter to the HHS Secretary, that "OHRP and FDA should *promptly* issue clear and consistent joint guidance on IRB review of both internal and external adverse event reports (AERs) which will best serve to protect human subjects and effectively reduce regulatory burden." A task force was formed in response to these concerns, as well as to the agency's own recognition that it has an obligation to respond to requests for clarity from the research and IRB communities.

The task force is charged with proposing a specific means for promoting harmonized and streamlined federal requirements for reporting, analyzing, and communicating adverse events in clinical research. Participants include not only OHRP and FDA, but also the Department of Defense, the National Institute of Health (NIH), the Veteran's Administration, the Centers for Disease Control (CDC), and the Agency for Healthcare Research and Quality (AHRQ).

Dr. Patterson described the specific objectives and progress of the task force as follows:

- One of the principle barriers to streamlining or harmonizing adverse event requirements across agencies and clarifying them is that agencies speak different languages. The task force intends to *reduce variability in the terms and definitions used by the various agencies* (such as "unanticipated problem" vs. "unexpected" or "adverse event"), then to analyze and align federal adverse event reporting policies.

It has completed a first draft of a comprehensive mapping of terms used by participating agencies in regard to adverse events. It is also examining where changes in terminology can be made easily and where they would be difficult (for example, when they are rooted in regulatory language). It will look for "low hanging fruit." This task will result in guidance that will clarify the relationship of the various terms.

- The task force will also *develop a best practices blueprint for reporting, analyzing, and applying safety information.* It will seek to minimize inefficiencies in the flow and analysis of safety information, reducing the "signal to noise" ratio for IRBs and clarifying the responsibilities of various parties. Accomplishing this task will require a work flow analysis. To fulfill this task, it is convening a number of focus groups that will include representatives of industry, PIs, and the IRB community to take a fresh look at reporting requirements and try to streamline them. OHRP has already prepared a first draft of new guidance that addresses adverse reporting for multi-center trials, outlining criteria for when adverse reports should be forwarded to other sites.

- The task force is also seeking to *harmonize clinical and scientific information gathered in adverse event reports*. It is considering the feasibility of requiring one core AE report that PIs can send to multiple federal agencies, known as the Basal Adverse Event Report (BAER). This report will provide a baseline set of core medical information that would be accepted by all agencies. It will not "reinvent the wheel," but will incorporate current and evolving HHS standards for data transmission and vocabularies.

- The task force will seek *to improve the analysis, synthesis, and dissemination of information*. This objective is the most difficult and complex of all, but it is also one of the most critically important. As questions have arisen in the public sector about how safety information is communicated during drug development, this objective has become increasingly relevant. The group will explore strategies for promoting transparency in the evaluation and communication of safety information.

The task force began last fall and has begun to convene focus groups to address identified objectives. It has also begun to map out data requirements for the BAER. In the spring it expects to assemble focus groups that will examine the process at the local level. The summer of 2005 is the current target for having draft products and recommendations "vetted" by participating agencies.

Remarks by Jean-Louis Saillot, M.D.

Dr. Saillot represented the preliminary views of the IRB-Sponsor Roundtable, a small group formed in 2004 that is examining the challenge of adverse event (AE) reporting in multi-site clinical studies. He noted that the group's aims dovetail with those of Dr. Patterson's, but the scope of their proposal is much smaller. He explained that the IRB Sponsor Roundtable includes individuals from both the IRB community and sponsors, providing an opportunity for productive dialogue. It is co-chaired by Dan Nelson of the University of North Carolina and by Justin McCarthy from Pfizer.

The mission of the roundtable is to propose practical strategies for improving processes that enhance subject protection. The group also intends to engage other stakeholders in the clinical research community to facilitate a broader dialogue and build consensus.

Dr. Saillot pointed out that the sheer number and disaggregated nature of AE reports make it difficult, particularly for IRBs, to effectively evaluate their significance and implications for study subjects. Highlighting *relevant* data, as opposed to reported all data, leads to transparency. A particular concern relates to IRBs participating in multi-site trials, which may be overwhelmed by receiving AE reports from all the sites involved in the study. (An increasing number of clinical studies are sponsored by the pharmaceutical industry, and many Phase II and III studies are multi-site; they are governed by Investigational New Drug [IND] regulations.) The current function and infrastructure of IRBs does not allow them to function as safety oversight committees for such trials. They do not have access to the type of information they would need to evaluate the large volume of disaggregated AERs and put them in proper context.

The roundtable sees the need for a new adverse event reporting model that would ensure that medically relevant data on adverse events is communicated to IRBs in a meaningful way so that they can fulfill their role in protecting human subjects. In the new model, medically relevant events and those that are more likely to change the risk/benefit equation would be highlighted. Appropriate checks and balances would be maintained thought a multi-party process involving IRBs, principal investigators, and sponsors.

Preliminary recommendations from the roundtable included:

- Existing guidance predates multi-site trials; new guidance that addresses the unique challenges of multi-site studies would be helpful.

- The roundtable suggests that external reporting by the investigator be limited to "relevant" reports – those that might lead to modification of the study protocol or revisions of the informed consent form, or those that reflect major concerns that could impact the study.

- PIs would identify "relevant" external AE reports that require notification to IRBs (their obligation to submit all appropriate internal AEs would be unchanged). Sponsors should clearly identify to PI those external AE reports that meet criteria for reporting. Both sponsors and PIs would be required to document their analysis of external AEs.

- The roundtable suggests that a "safety communication plan" (SCP) be developed as part of the study protocol. Elements of the SCP could include the proposed frequency for submission of aggregate safety information and the proposed format for the submission of periodic qualitative assessment reports. If a Data and Safety Monitoring Board (DSMB) is used, the SCP would include a description of how it functions and specify both the method and frequency with which DSMB reviews will be communicated to Investigators and IRBs.

The roundtable expects to continue to meet to refine its proposal. It will also conduct outreach to interested stakeholders to get their feedback.

DISCUSSION

Timelines. Noting that Dr. Patterson envisions a draft product by June of 2005, Dr. Prentice asked how long it would take to move through the necessary levels of review and implement recommendations. Dr. Patterson responded that there are multiple efforts underway, some of which are short-term and some of which will require "patience and considerable input and dialogue with the research and IRB community to make sure we end up in the right place."

SACHRP members were eager to be informed of the Task Force's progress. Dr. Patterson agreed to provide a brief interim report at SACHRP's April meeting and a more substantive report in August. She said she was optimistic about the prospects for success, given that "we are in a different culture now from five years ago."

Relationship of Initiatives. Dr. Prentice also asked Dr. Patterson how the model Dr. Saillot presented fits in with the task force's discussions to date. She responded that the roundtable's efforts are viewed as complementary and will inform the task force's efforts. Dr. Cates agreed that the two efforts will "dovetail beautifully"; he particularly welcomed the roundtable's input on workflow issues related to the reporting and analysis of adverse events.

Revisions of regulations. Noting that Dr. Saillot had indicated that regulations would not have to be revised to accommodate the roundtable's proposed model, Dr. Prentice asked Dr. Patterson whether she agreed. Dr. Patterson said she could not speak definitively in respect to FDA regulations, but found the proposals consistent with extant regulations that empower IRBs to request aggregated information and analysis. Dr. Carome agreed that what has been presented is consonant with how OHRP believes AEs should be handled under the regulations.

AE reporting to OHRP. Dr. Prentice asked Dr. Carome how many AEs are actually reported to OHRP. Dr. Carome indicated that not all AEs in all trials must be reported – only those related to the research over which OHRP has purview. For this research, it receives a few hundred reports annually. He noted that many things that go wrong (such as infections and death) are expected under the protocol and do not have to be reported. Dr. Prentice further clarified that not only HHS-funded studies, but also those sponsored by institutions that have a Federal-Wide Assurance (FWA) that voluntarily agree to comply with §45 CFR 46 must report all unanticipated problems involving risk promptly to OHRP.

Role of DSMBs and DMCs. Ms. Kornetsky noted the important role that will be played by data safety monitoring boards (DSMBs). Dr. Patterson responded that the task force would look at these issues, noting that NIH is holding a conference on best practices for data safety monitoring boards and data monitoring committees (DMCs). In response to a question from Mr. Barnes, she explained that FDA has published draft guidance on the independence of DSMBs and DMCs (2002); a new iteration is expected shortly.

Documentation of analysis of AEs. Ms. Kornetsky reported that IRBs often have difficulty getting analysis of AEs, which is often withheld as proprietary information. Dr. Saillot stated that FDA has issued important guidance on what data it sees as independent from sponsors. He also observed that DSMBs will not be required for every study. However, training may be needed for both sponsors and investigators to help them identify when AEs are reportable. In regard to the difficulty accessing proprietary information, Dr. Saillot and Dr. Prentice believed that sponsors could not withhold safety-related information from IRBs as proprietary. However, Mr. Barnes reported that he had also had difficulty getting access to the analysis of AEs. Dr. Saillot then observed that methodological barriers do exist; the statistical analysis and safety analysis needs to be shielded from the people actually involved in conducting the trial.

Participation in task force. In response to a question from Dr. Hauser, Dr. Patterson assured him that the Center for Devices is represented. The task force is trying to be cognizant of the broad scope of research with human subjects. Dr. Gyi expressed particular concern that FDA-regulated products are represented, noting that regulatory change might be needed in this area. Mr. Adams added that input from attorney groups and other members of the public is important.

Climate for interagency harmonization. Dr. Jones asked whether the situation has changed to the point that harmonization is possible. Dr. Patterson said that a different culture exists at present. There are more multi-center, collaborative trials and a greater perceived need for streamlining and harmonization.

Measurement of progress. Dr. Polan asked what metrics may be used to measure progress and success in the harmonization effort. Dr. Saillot agreed to give this further thought.

Global reporting of AEs. Dr. Prentice asked Dr. Saillot how global reporting of AEs would be affected by actions taken in the U.S. He also inquired about the differences between IND definitions and those used by the International Conference on Harmonization (ICH). Dr. Saillot responded that ICH and IND definitions are conceptually the same, though the terms differ. He did not think U.S. efforts were likely to impact multinational research significantly.

Subpart A Presentation; Future Plans
Felix Gyi, Pharm.D, M.B.A., CIP, Co-Chair; Daniel Nelson, M.S., CIP, Co-Chair

Mr. Nelson reported on the formation, charge, and future plans of the recently formed subcommittee focusing on Subpart A. He reminded those present that Subpart A regulations were promulgated in an era when protections of human research subjects were nominal and oversight mechanisms were nonexistent or inconsistent. In the changed modern environment, application of Subpart A has resulted in conflicting interpretations of what constitutes appropriate oversight, sometimes adding to regulatory burden without additional meaningful protection of human research subjects.

Mr. Nelson introduced the subcommittee's members, noting that six out of the thirteen are investigators (a SACHRP stipulation). Community representation is also included. There is strong interest in the subcommittee's work, and many groups will be contributing *ex officio* members.

The subcommittee has two primary goals:

- To enhance the protection of human subjects, and
- To reduce the regulatory burdens that do not contribute to the protection of human subjects.

To accomplish these goals, the subcommittee will review and assess all provisions of Subpart A of §45 CFR 46 and relevant OHRP guidance documents. Based on this review and assessment, it will develop recommendations for consideration by SACHRP in three categories:

(1) Recommendations on the interpretation of specific Subpart A provisions.

The subcommittee has been asked to consider specific terms and provisions in §45 CFR 46 in the context of the contemporary biomedical and behavioral research environment. Examples include the definitions of research, human subjects, minimal risk, minor changes, and unanticipated problems.

(2) Recommendations for the development of new, or modification of existing, OHRP guidance.

The subcommittee is asked to consider current OHRP guidance as well as areas in which guidance is needed in order to enhance human subject protection, achieve greater consistency across sites, and reduce regulatory burdens. An example would be types of social and behavioral studies that are not considered human subjects research under the regulatory definition, such as oral histories and quality improvement projects. The subcommittee will also try to clarify the dividing line between minor contingencies and substantive issues that might lead to a deferral and return to the full IRB. It will address issues related to the level of detail required in IRB minutes with a view to reducing regulatory burden.

(3) Recommendations regarding possible revisions to Subpart A.

Examples of possible revisions include the categories of exemptions, assurance requirements, the definitions of research and minimal risk, requirements related to continuing review and expedited reviews, and IRB membership requirements.

The inaugural meeting of the subcommittee was held by teleconference on January 18, 2005. A first meeting of members in person is slated for February 14. The subcommittee plans to determine the concerns of groups such as OHRP, other agencies, and accreditation bodies and use their input to help prioritize tasks.

DISCUSSION

Members made the following key points:

- Ms. Selwitz noted that an NIH committee has addressed the issue of "regulatory burden" related to Subpart A and issued a report. She recommended that its work be reviewed.

- Dr. Weiner hoped that members of the Subpart A subcommittee would consider the work of other subcommittees in their deliberations so that definitions and approach are consistent.

- Noting that some of the definition issues cited could easily be subcommittees of their own, Mr. Barnes counseled Co-Chairs to give priority to the areas where they believe they can make a difference relatively quickly and avoid becoming bogged down. Dr. Prentice concurred with the suggestion that short-term and long-term issues be differentiated in the interests of progress.

- Dr. Gyi indicated that the subcommittee intended to review that was done on Subpart A by other groups and agencies. Ms. Selwitz requested that materials related to Subpart A be highlighted, since these groups often addressed many other areas.

- Dr. Schwetz asked whether other subcommittees have found it useful to divide work among smaller subgroups. Ms. Kornetsky said it is helpful to task a smaller number of people to address certain difficult or controversial things and return to the group with recommendation. Mr. Barnes said that individual group members on the Subpart C subcommittee were asked to develop a position paper and report back to the group on certain issues.

- Dr. Schwetz stressed that Subpart A is important to everyone, and the subcommittee's work will require time. He highlighted the need to keep concerned parties aware of what is occurring. Ms. Selwitz suggested that subcommittee members be encouraged to use existing communication networks, such as the ListServe of the Applied Research Ethics National Association (ARENA). Members should be encouraged to report back to stakeholders they represent through newsletters or other appropriate means. Dr. Weiner added that the lay public should also be informed through disease-specific groups involved in research, many of which have their own newsletters. Dr. Jones observed that many agencies have existing lines of communication to reach investigators.

  Dr. Schwetz further clarified that it was not his intention to burden the subcommittee with the responsibility for such communications.

Public Comment

The Chairman invited members of the public to comment.

- Dr. Paul Goebel of the Chesapeake Research Review commented that he would be interested in knowing how often IRBs stop studies on the basis of outside AEs. He considers this an important metric. He added that IRBs are blunt instruments that can start or stop studies, but are not intended to manage them or to guarantee the safety of study subjects. He suggested that outside AEs should not go to IRBs, but rather to the sponsors, who can analyze the data and convey it to investigators for action as needed.

- Dr. Goebel also observed that informed consent forms are too lengthy and not appropriate for a public that is increasingly composed of nonreaders. He suggested that revisions allow the presentation of information in a video format.

- Dr. Goebel noted that guidance is needed related to the categories of research that can be expedited; he said that categories (3) and (4) were intended to be examples and not an all-inclusive list, but IRBs have been faulted for expediting unlisted research.

- Dr. Goebel asked the subcommittee to consider expanding exempt programs – for example under 101(a) (5) – to include programs that are conducted for public benefit but are not official government programs.

- Dr. Goebel also asked the subcommittee to consider ways to simplify the progress for multi-institutional research in order to lessen or eliminate the duplicative IRB reviews that must be done at all institutions involved in a project. He recommended that IRB review be done only by the institution where research is conducted, not the home institutions of each investigator.

- Ms. Caroline Miner expressed concern that the subcommittee's work would increase the difficulties for those doing sociobehavioral research. Mr. Nelson responded that subcommittee members include persons with this expertise.

- Ms. Marjory Speers, Executive Director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), reported that she had served as staff of the National Bioethics Advisory Commission (NBAC) when it had a project that looked at Subpart A and the oversight system. She urged the subcommittee to review NBAC's work. She also cautioned members, based on the group's experience, to steer clear of the issue of how to define research and spend their efforts on areas that will be more productive.

- Ms. Speers highlighted concerns from the behavioral and social science areas related to the elements of disclosure and documentation of consent. She said we are moving away from a consent process that is easily understood by research subjects.

- Ms. Speers advised the subcommittee not to forget institutional officials, who are key decision makers. They should be brought into the process.

- Ms. Speers advised the subcommittee to address a third goal, which is to promote research. She stressed that the regulations should further the research agenda.

- Dr. John Mather highlighted issues related to regulatory burden. He suggested that thought be given to education and training for the investigator. Secondly, he requested that the subcommittee address the ways in which information systems can help or impede progress.

- Mr. Gary Chadwick saw the responsibilities of investigators as a "missing piece" in Subpart A. FDA has a series of regulations on the responsibilities for investigators, but many investigators are still unaware of requirements applicable to their work. He also asked whether the subcommittee would be allowed to rewrite the regulations. Dr. Prentice responded that it is not clear whether agreement on revisions is likely to be achieved, but it was left on the table. Finally, Mr. Chadwick noted that education is a poor way to change behavior.

- Pat Scannel, Washington University School of Medicine, reinforced the importance of the investigator receiving information on AEs.

- Ms. Susan Poland, Georgetown University, suggested expanding education to programs for teachers being recertified. She stressed the importance of being able to explain ethical obligations to children who are becoming excited about science and may be interested in pursuing it as a career. Dr. Prentice observed that the Northwest Biomedical Research Association has introduced education on the value of animal research into the secondary school curriculum and is now addressing the ethics of human subject research.

MOTIONS AND ACTIONS, SUBPART A

Responding to Ms. Speers' suggestion, Dr. Prentice suggested a third goal. Mr. Barnes made a motion to this effect and Dr. Hauser seconded it.

The subcommittee on Subpart A will address a third goal in addition to the two already identified, which is to promote scientifically and ethically valid research.

This motion was unanimously approved.

Discussion of Compliance Oversight Activities

Remarks by Kristina Borror, Ph.D., Director, Compliance Division, OHRP; Joanne Rhoads, M.D, M.P.H., FDA; Michael Klag, M.D, Johns Hopkins University; Thomas Puglisi, Ph.D., CIP, PriceWaterhouse Coopers; Chris Pascal, J.D., Director, Office of Research Integrity, HHS

Remarks by Kristina Borror, Ph.D., Director, Compliance Division, OHRP

Dr. Borror provided information about the activities of OHRP's compliance oversight activities. Key points included:

- OHRP has conducted over 800 for-cause investigations since January, 1990. It is reducing its backlog and now has 21 open cases.

- The number of new cases initiated annually rose in the 1990s and are now going down; it may be that institutions are "getting the message," but it is also true that OHRP now defers more frequently to the FDA or to other departments when appropriate.

- OHRP has never debarred an agency, but has used suspension or restriction. The numbers of suspensions or restrictions annually rose in the mid 1990s but are now quite low (at most one institution per year).

- OHRP has conducted 12 not-for-cause investigations since 9/01, targeting only those agencies with OHRP-approved assurances. Agencies who are in infrequent communication with OHRP are the most likely targets, or those for which complaints have been received that are too vague to investigate. The process of review in such cases is generally similar to for-cause investigations (described below), but are shorter and involve fewer people.

- Between October of 1998 and June of 2002, OHRP issued 269 determination letters to 155 institutions. It did 18 site visits and issued a total of 1,120 citations of noncompliance or findings of deficiencies.

Dr. Borror explained that a for-cause investigation is often triggered by charges made by subjects or their family members. Other sources are internal whistle blowers, IRB members, consumer advocacy groups, the press, and rarely, representatives of Federal agencies or funding agencies. When the allegation is received, OHRP determines whether it has jurisdiction: that is, whether the problems reported relate to its regulations and the institution involved has an applicable assurance. If it does have jurisdiction, it writes a letter of inquiry to the appropriate institutional official (usually the person who signed the assurance), with a copy to the IRB chair, the IRB administrator, and the investigator who is the subject of the complaint. The inquiry letter informs them of the complaints and asks for related records, such as information on policies and procedures or on educational programs, as well as pertinent minutes. These documents are reviewed and there is usually an exchange of correspondence.

Rarely, there is also a site visit; in the few cases in which they are needed to get to the bottom of what is occurring, they last two to three days and involve a team composed of three-four OHRP staff and the same number of expert consultants. The team reviews 50 to 75 protocols to determine how the system is functioning and also conducts interviews with IRB chairs, members, and administrators, and staff, as well as investigators. On the last day, the team does an exit interview and presents oral findings. The most common outcome is an identification of areas of noncompliance and required corrective actions. In

extremely serious cases, the assurance may be restricted pending corrective action. Other possible outcomes are a finding that there is not a problem of noncompliance; a withdrawal of the assurance so that single-project assurances must be used instead; a recommendation that a particular institution or department be temporarily suspended or permanently withdrawn from participation in a particular project or that peer review groups be notified of the compliance problems; or debarment of institutions or investigators from HHS-supported research (an option OHRP has never used).

The most common problems cited are related to the criteria required for IRB approval. Problems with informed consent are also common, with a high percentage of issues related to overly complex language. Problems with the IRB are even more common than problems related to the investigator; rarely, senior institutional officials are involved in problems of noncompliance. OHRP is taking a proactive stance to try to prevent such problems.

Remarks by Joanne Rhoads, M.D, M.P.H., FDA

Dr. Rhoads explained that FDA oversight comprises the Center for Drugs, the Center for Biologics, and the Center for Devices. The Review Divisions within each Center are responsible for evaluating key elements and determining whether it is safe to administer the product to humans or safe to proceed with the submitted protocol. The Divisions must consider:

- The scientific quality of the investigation
- Preclinical considerations (Chemistry, Toxicology and Pharmacology, Pharmacokinetics in animals)
- Previous experience in humans, and
- The sufficiency of the protocol and investigational plan.

Regulatory oversight for FDA is accomplished through the Bioresearch Monitoring Program (BIMO), which involves all the Centers.

Dr. Rhoads then offered a specific description of how her organizational unit, the Division of Scientific Investigations within the Center for Drug Evaluation and Research, performs its BIMO responsibilities. It must ensure good laboratory practice, *in vivo* bioequivalence, human subject protection, and good clinical practice. To accomplish this, the Division does not work on its own, but develops assignments for a field cadre in consultation with the Office of Regulatory Affairs. It also participates in inspections and offers expertise as needed, evaluates exhibits and findings, makes a determination, and recommends scientific follow-up.

Dr. Rhoads stressed the relationship between the good laboratory practices (GLP) inspection program and human subject protection. She noted that the goal of GLP is to ensure that the data quality from preclinical testing is adequate, because this data determines whether or not it is safe to administer a product to humans. Data that is of poor quality or is unreliable translates into more risk for human subjects. Dr. Rhoads's division does 60 to 70 inspections annually as part of a surveillance program to ensure the preclinical data on which protocols are based are sound.

Inspections are also carried out by the Bioequivalence Inspection Program of the Center for Drugs. This crucial program is designed to ensure the safety and quality of generic drugs. Recently, for example, a clinical investigator was disqualified after it was found that although a subject's death was attributed to a heart attack, he had been dosed with a drug for 22 days despite showing classic signs of a known toxicity.

The Good Clinical Practice Program focuses on clinical investigators, sponsors, and monitors to determine whether they are adhering to applicable guidelines, whether subjects' rights and safety are protected, and whether the studies supporting the marketing application are valid. Program staff may perform site inspections, investigate complaints, and complete data audits. For-cause investigations may be conducted in response to specific complaints (usually from sponsors and monitors). The number of complaints received has been increasing annually; 200 were received in 2004.

These detailed inspections last a week to two weeks. Problems are usually found, often involving Medicaid and Medicare fraud. At the end of the inspection, the field inspector submits exhibits collected to support his or her observations, and reviewers determine whether the field inspector's conclusions are supported. Based on this review, the agency either takes no action, requests voluntary action, or takes official action such as sending a warning letter or initiating disqualification proceedings. Sometimes an investigator is referred for criminal prosecution.

FDA's Center for Drugs currently conducts about 400 clinical investigator investigations annually. The number of international inspections required is increasing; this year, over 80 were conducted.

More complaints are received every year, with over 200 submitted in 2004. FDA allows complaints to be submitted anonymously using a form available on its Web site. Of investigations that begin with complaints, about 25 percent have serious outcomes. Common deficiencies relate to protocol violations, adverse event reporting, informed consent, drug accountability issues, and failure to follow written procedures.

FDA also has an IRB inspection program that does about 150 on-site inspections annually. These inspections typically last about a week. Common deficiencies include failure of the IRB to follow its own written procedures, failure to review research as required, misunderstanding of expedited review, recordkeeping problems, and issues related to informed consent. In working with IRBs, the agency recognizes the huge differences that distinguish IRBs from each other. It focuses most of its resources on IRBs that are doing high-risk research. The agency is trying to complete more of these inspections as the study is progressing rather than after its completion.

Remarks by Michael Klag, M.D, Johns Hopkins University (JHU)

Dr. Klag is the Vice Dean for Clinical Investigation at the Johns Hopkins University School of Medicine, which has over 3200 active protocols. About 70 percent of funded research (equivalent to $400 million) has IRB review or exemption, indicating involvement of human materials or subjects.

After the death of a research participant in June of 2001, the University was investigated and briefly suspended. Multiple concerns were found related to the literature review, use of a non-FDA approved product, failure to discuss protocol at full meeting, and changes in the protocol, as well as other aspects of IRB process. The suspension was terminated after only three days, when the University filed a Corrective Action Plan that included:

- Re-reviewing all IRB protocols
- Reporting monthly to OHRP
- Developing new standard operating procedures (SOPs)
- Increasing the diversity of IRB members, and
- Educating IRB members.

As a result of this experience, JHU made a number of changes. The institution:

- Restated its commitment to the principles of the Belmont Report and best practices in clinical research
- Doubled the number of IRBs (from 3 to 6), increased FTEs from 4 to 28, and gave salary support for IRB members
- Had all IRB members retrained by OHRP
- Contracted with Western IRB to review new proposals
- Created new position of Vice-Dean for Clinical Investigation (in November 2001), and
- Initiated a review of IRB processes and the IRB function by an independent consultant, resulting in a comprehensive reorganization.

Without the shutdown, Dr. Klag told the group, changes would not have occurred, or would have occurred over a longer period of time. However, given the circumstances, the change process was far from ideal. Initially, following the shutdown, the University operated in a "culture of fear." Guidance became law, and strict policies and procedures were imposed. JHU's attempts to find direction were impeded by the different languages that seemed to spoken by regulatory agencies. From the speaker's perspective, suggestions for improvement from these agencies were often unclear or unhelpful. Although receiving a suspension definitely constitutes a "teachable moment," regulatory agencies did not seem prepared to use it to the fullest.

The speaker suggested these communication difficulties could be attributed, in part, to the different backgrounds and experiences of the regulatory staff as compared to researchers and IRB members. While dedicated and committed, few have research experience or training. Many do not understand the processes that are integral parts of research, such as subject recruitment and data collection. Differences in culture and style further impeded communication. From a process perspective, he found the regulatory agencies unprepared to suggest a close-out strategy for protocols, especially those involving experimental treatments for fatal diseases.

In his closing reflections, Dr. Klag suggested that Federal regulatory agencies develop a better understanding of the culture and practice of IRBs, researchers, and academic health centers. He saw a need for translators and educators who can help effect communication between the regulatory and research worlds. Likewise, he recommended a clearer distinction between guidance and regulation.

Finally, the speaker pointed to an urgent need to simplify and harmonize Federal regulations. HHS, FDA, and Health Insurance Portability and Accountability (HIPAA) regulations are often inconsistent (an example being AE reporting). Certain agencies (NIH, the National Center for Research Resources [NCRR], the Department of Defense, and the Centers for Disease Control [CDC]) are enacting additional policies and procedures which go beyond HHS regulations. This creates confusion that can lead to noncompliance.

Remarks by Thomas Puglisi, Ph.D., CIP, PriceWaterhouse Coopers

Dr. Puglisi focused his presentation on the regulatory climate for research and sources of noncompliance. He pointed to a public perception of serious and repeated deficiencies in protecting human subjects, leading to avoidable injuries and death. Members of the public hear of conflicts of interest, misleading or deficient informed consent, unreported adverse events, and unapproved research or unapproved changes, leading to a perception of inadequate IRB oversight.

FDA and OHRP identify the same kinds of deficiencies in their research communities, although they take different approaches. FDA focuses on the IRB and the Clinical Investigator, while OHRP focuses on the institution through the assurance process. The FDA conducts 200 – 300 inspections annually, while OHRP conducts only 4-6 for-cause and 5-6 not-for-cause visits annually, but has a strong educational outreach.

There are significant barriers to agencies recognizing and reporting their own deficiencies. These include a lack of institutional monitoring programs, which may relate either to a genuine lack of resources or to the institutional culture and investigator resistance. There is also an understandable fear of the consequences: sanctions, penalties, and the suspension of research may cause significant losses in research dollars, negative publicity with resultant damage to the institution's reputation, and possible litigation.

Dr. Puglisi identified specific sources of noncompliance:

- *Lack of education.* Those involved in noncompliance – whether they are investigators, IRB members, or IRB staff – may simply be unaware of a specific requirement. Lack of institutional "will" makes exposure to education less likely.

- *Multiple and complex regulations.* These make education increasingly essential, but can nevertheless be overwhelming.

- *Lack of resources.* Some agencies are unable to address increasing responsibility for scientific review, volume of studies, documentation requirements, complex regulations, competing institutional priorities, and generally scarce resources for health care and related research. He also held that the continued emphasis on local review leads to duplication of effort and conflicting determinations. He also pointed to the problem of increasing amounts of research being carried out in non-research organizations that lack the necessary infrastructure and training.

- *Lack of institutional "will."* Institutions may fail to recognize the failure to recognize importance of compliance and the magnitude of risk they face if charged with noncompliance. Institutions may fail to appreciate the need for professionalism on the part of IRB staff. Since the Johns Hopkins shutdown, however, more IRBs have recognized they had been overtrusting of the investigators and needed to do more rigorous reviews.

The speaker made several specific recommendations he believed would enhance compliance:

- The most beneficial change would be a single authoritative source of regulatory interpretation, guidance, and enforcement, with an advisory body composed of stakeholders and an interagency coordinating committee.

- Education for research investigators should be required, but many options should be given.
- Certification of investigators should be encouraged and recognized.
- Greater use should be made of expedited review processes.
- Regulatory options for layered review and oversight of multi-site research should be developed.
- Regulatory simplification and harmonization are essential.

Finally, he elaborated on the need for more effective and meaningful "carrots and sticks" to motivate compliance. His suggestions included:

- Increase random inspections of IRBs.
- Immediately fine and/or suspend enrollments pending corrective action for individual or systemic noncompliance identified during random inspections.
- Encourage self-reporting by not requiring fines or suspensions where the institutional corrective action plan reasonably protects subjects.
- Exempt accredited Human Research Protections Programs (HRPPs) from random inspections

Remarks by Chris Pascal, J.D., Director, Office of Research Integrity (ORI), HHS

Mr. Pascal explained that ORI is responsible for ensuring compliance with the HHS research misconduct regulation, which applies to roughly 4,000 institutions funded by the Public Health Service (PHS). The regulations require institutions to develop internal standards of integrity for the institution, its employees, and its students; to investigate and report misconduct; and to comply with other aspects of the regulation. ORI conducts compliance reviews of the required policies to ensure that regulatory requirements are addressed.

The office's programs include prevention, education, and technical assistance. ORI is often in a position to address problems in which the accused individual's rights are not respected by the institution. It also protects the rights of the complainant, recognizing that whistleblowers may be vulnerable to retaliation.

Findings of research misconduct are based in large part on written policies. ORI has done over 1400 such reviews over the last 10 years. Compliance issues may include:

- Failure to sequester evidence in a timely fashion or to retain the evidence
- Lack of appropriate expertise on the investigation committee
- Failure to pursue the allegations to completion
- Conducting the investigation at the inquiry stage, and
- Problems with admission or settlement.

While ORI has no direct responsibility for OHRP or FDA compliance issues, it can have overlapping jurisdiction in clinical research areas; in such cases, information is shared as cases are investigated.

DISCUSSION

Key points raised by members included the following:

- The Chair asked Dr. Klag whether a threat of a shutdown, as opposed to an actual shutdown, would have had the same result. Dr. Klag said the needed resources might not have been made available without the actual shutdown. However, the institution had already begun to realize that it had a cultural problem it needed to fix.

- Dr. Prentice asked Dr. Puglisi for his estimate of the magnitude of the problem that many institutions have provided inadequate resources for their human protection programs. Dr. Puglisi assessed the problem as "huge" for community hospitals and health systems.

- Ms. Selwitz asked whether it was true that when an IRB suspends or terminates an FDA protocol, an FDA investigation is likely to follow. While Dr. Rhoads assured members that this was not FDA policy, members agreed that it was a common perception and experience. Dr. Rhoads noted that when investigations do follow, they are not intended to be punitive, but simply to gather more information. Dr. Gyi noted that in some cases, however, a "483" can result in a loss of business opportunity because of the way it is viewed by the industry. It might be wise, he suggested, to educate industry on the purpose of the inspection process.

- Dr. Gyi asked whether institutional accreditation might result in a reduced need for inspections. Dr. Borror responded that accredited institutions are much less likely to be chosen for not-for-cause visits.

- Mr. Adams wondered how many of the complaints received by FDA are found to be bogus. Dr. Rhoads responded that inspections result for about half the complaints received, and about 25 to 30 percent of such inspections find substantive problems.

- Dr. Prentice asked Dr. Borror whether an institution that reports noncompliance frequently to OHRP, with identified corrective action, is likely to receive a site visit. She responded that this is possible, though this scenario is uncommon.

- Dr. Klag observed that the FDA letter received by the university was written in regulatory language and it was not clear what the university was being required to do or not do. He urged regulatory agencies to take advantage of the "teachable moment" when the institution is being informed that regulations are not being followed to communicate their expectations as clearly as possible.

- Noting that the field of human subject protection took a "gigantic leap" between 1998 and 2001, Dr. Prentice asked whether there is a current drift back to the days in which institutions were less proactive and more reactive. Dr. Puglisi responded that there are three kinds of institutions: those that have a strong conviction that human subject protection is the right thing to do, many of which are actively pursuing accreditation; those that are strapped, relatively unfamiliar with regulatory requirements, and plodding along as best they can with limited resources; and those that invest their resources using a risk-management approach. These institutions are beginning to show some retrenchment in terms of resources allocated to human research protections. Some highly entrepreneurial institutions are beginning to place increased priority on getting protocols through quickly and making investigators happy – a source of concern.

- Ms. Selwitz stressed the importance of making research ethics and regulatory issues an integral part of the academic curriculum, as well as the credentialing of clinical investigators. She asked speakers what can be done to make these issues an "integral part of the fabric" for PIs, as well as subjects. Dr. Puglisi stressed the importance of making research ethics part of the curriculum, both in biomedical sciences and in social and behavioral sciences. He said he believed that a different credentialing process would be required for social and behavioral education. While some educations strongly encourage credentialing of study coordinators and clinical research investigators, funding is a problem.

Discussion of Committee Business

Dr. Prentice highlighted the need for improved education for investigators. At the invitation of the Chair, Mr. Adams commented on the progress with certification of investigators by the Association of Clinical Research Professionals (ACRP). He said that about 14,000 have received ACRP certification since 1991 and approximately 10,000 have been recertified.

In addition to ACRP, two other organizations offer certification for clinical investigators. The American Association of Pharmaceutical Physicians (AAPP) has recently inaugurated a program and has certified about 20 PIs. The Drug Information Association has certified about the same number. Some investigators see a commercial advantage in going through the certification process; others are motivated by self-improvement, a fear of being audited, or a "push" from their study coordinators or research assistants. An increasing number of employers are requiring certification for coordinators and assistants, but not yet for investigators. ACRP believes that the entire team should be certified, from the PI to the coordinator.

Dr. Prentice reviewed the developing agenda for SACHRP's next meeting. By the April meeting, Subpart C will no longer be active. There will be reports from the subcommittees on Subpart A and D, and Dr. Patterson will provide a very brief update on the task force's progress. The Chair also suggested developing a program that would address issues related to investigator certification and education. He said he would welcome e-mails on possible topics for the April meeting.

Mr. Barnes suggested it would be helpful to hear from an investigator who was able to report on what is needed to bring his or her peers "into the fold." Ms. Kornetsky added that it would be useful to hear from an investigator who could help the committee explore why there is resistance among investigators. Dr. Jones suggested that MD physician researchers, Ph.D.s, and biomedical researchers all have different barriers and can be reached through different education strategies.

At 4:01 pm, a motion to adjourn was unanimously accepted.

Secretary's Advisory Committee on Human Research Protections
January 31 – February 1, 2005
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 April 18, 2005

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