Secretary's Advisory Committee on Human Research Protections (SACHRP)

April 18 and 19, 2005
Alexandria, VA

Minutes

MONDAY, APRIL 18

Welcome and Opening Remarks

Ernest Prentice, Ph.D.

The Chairman welcomed everyone to the meeting and thanked members of the public for attending. He reminded attendees of SACHRP's Charter, renewed in September of 2004, which comprises protection of vulnerable populations. He noted that SACHRP has "accomplished quite a bit" in its last 2 years. SACHRP works closely with staff members of the Office of Human Research Protection (OHPR) and Dr. Bernard Schwetz, Director. Dr. Prentice particularly recognized the contributions of Cathy Slatinshek, Executive Director of SACHRP, and of Kelley Booher. OHRP staff members also serve as liaisons on SACHRP subcommittees. Finally, Dr. Prentice recognized the contributions of *ex officio* members of SACHRP, who are intimately involved in SACHRP deliberations and provide advice related to their priorities and concerns.

Report on Issues

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

Dr. Schwetz informed SACHRP of developments in several diverse areas as follows.

The Department of Homeland Security is in the process of determining how to implement its Common Rule and setting up an Institutional Review Board (IRB). Mark Rosen will be the *ex officio* representative for the new Department.

The Equivalent Protections Document was published in the *Federal Register* on March 24 in order to seek public comment over a period of 60 days. A summary of the working group's report and key questions raised were included in the notice.

The Food and Drug Administration (FDA) published its central IRB document for Multi-Site Studies on March 28; the agency is seeking public comment over a 60-day period.

The comment period on the Joint FDA/OHRP Activity for Mandatory IRB Registration is closed; FDA and OHRP are collaborating on the final rule, which will be issued later this year.

The IOM committee on ethical considerations in prisoner research met on March 16-17, 2005. Nancy Dubler, Co-Chair of the SACHRP subcommittee that examined these prisoner research issues, is an expert advisor to the committee as well as a liaison for the Board on Health Sciences Policy. Dr. Schwetz attended the inaugural meeting and was impressed by the Committee; members understood what they were and were not there to do, and they made good progress. OHRP staff member Julia Gorey is the OHRP liaison to the IOM committee and will be involved as needed.

OHRP has had a series of meeting s to plan an invitation-only Workshop on Central IRBs, as recommended by SACHRP. It has modified its planning process to work with some sponsors. The workshop is now envisioned as reviewing alternatives to local IRBs, including Central IRBs, and is expected to occur in September or October of 2005. Workshop attendees will develop recommendations that will come back to SACHRP for consideration and provide a basis for further discussion at a larger conference on the same theme.

In regard to Adverse Event Reporting, the FDA held a Part 15 hearing on March 21st where 19 speakers contributed comments and information. The docket remained open until April 21. The comments received were diverse and impressive. The next step is for FDA to review comments and develop plans for guidance and/or a rule. Also, OHRP has written draft guidance on the subject, which is under review internally and among other agencies. The Adverse Event Task Force continues to meet and make progress.

To celebrate the 25th anniversary of the Belmont Report, OHRP has interviewed members of the National Commission and their staff. OHRP has created a Belmont Historical Archive; materials are posted on its Web site (***http://www.hhs.gov/ohrp/belmontArchive.html***).

Overview of Charges to Subcommittees; Approval of Minutes

Ernest Prentice, Ph.D.

The Chair provided an overview of charges to existing SACHRP committees and complimented the subcommittees on their work. He pointed out that SACHRP's recommendations in regard to the 407 Review Process have been accepted by the Secretary and implemented by OHRP. The Chair said he was impressed with the significant contribution of members of the Subpart D committee. He highlighted the new committee on Subpart A, which will review and assess all provisions of Subpart A. The work of the Subpart C committee is essentially over; Dr. Prentice complimented the Co-Chairs of this subcommittee and all its members on their fine work.

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

Susan Kornetsky, M.P.H.

Ms. Kornetsky reported that the subcommittee on Subpart D has met and sought to address SACHRP's concerns related to its recommendations on §45 CFR 46.404, 405, and 406. She stressed that the

subcommittee has done as much work as it can on these issues and said she did not feel that re-examination of the issues already identified would be fruitful. Subcommittee members have challenged themselves as they gave thought to each issue, showing a willingness to re-examine their stance when appropriate. The Co-Chair also reported that she had had an opportunity to do a presentation to seventeen different institutions on some of the concepts the subcommittee has put forward and that the feedback was positive.

Ms Kornetsky emphasized that the work to be presented will be the "floor" for further work by the subcommittee. The recommendations have received conditional approval in prior meetings by SACHRP, which recognized that the recommendations build on each other and therefore wanted to review them as a group before giving them final approval.

KEY PRESENTATION POINTS, §45 CFR 46.404

Ms. Kornetsky presented the subcommittee's sixth report to SACHRP. She explained that the goals for this meeting were to clarify and reach consensus on recommendations, including terminology and procedures, related to the following Subpart D Regulations: §45 CFR 46.404, "research not involving greater than minimal risk"; §45 CFR 46.405, "research involving greater than miminal risk but presenting the prospect of direct benefit to the individual subjects"; and §45 CFR 46.406, "research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition."

Ms. Kornetsky reviewed the recommendations related to §45 CFR 46.404 (research not involving greater than minimal risk) that have already received conditional approval from SACHRP. These included:

- **Proposal 1: Uniform Standard.** The definition of "minimal risk" at §45 CFR 46.102 (i) when applied to Subpart D should be interpreted as those risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests. This is consistent with reports from the National Human Research Protections Advisory Committee (NHRPAC) and the Institute of Medicine (IOM).

- **Proposal 2: Minimal Risk Should be Age Indexed**. Evaluation of minimal risk under Subpart D should be indexed to the risk in daily life and the routine medical and psychological exams experienced by children of the same age as the subject population.

- **Proposal 3: 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 4: Equivalence Criteria.** Research procedures involving children can be approved as "minimal risk" if the probability and magnitude of harm are equivalent to risks of daily life or routine examinations with respect to duration, cumulative characteristics, and reversibility of harm. The terms "probability" and "magnitude" are contained in the regulations. This proposal means that the procedures do not have to be the exact ones performed in the routine examinations, but do need to be equivalent to the types of things that are done in such examinations. This approach is also consistent with reports by IOM and NHRPAC.

- **Proposal 5: Well-Child Visit: Referent for Routine *Medical* Examinations or Tests.** 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. The well-child visit encompasses both routine medical examinations and routine psychological examinations or tests. This proposed approach, based on the IOM's recommendations, is an attempt to "ground" the meaning of "daily lives of children" with appropriate reference points. Examples of well-child visit procedures that might be considered as equivalent include:

- Physical examinations
- Measurement of height, weight, head circumference
- Assessment of obesity with skin-fold calipers
- Collection of blood or voided urine
- Measurement of heart rate and blood pressure
- Hearing and vision tests
- Modest changes in diet or schedule
- Testing of fine and gross motor development
- Noninvasive physiological monitoring
- Medical and social history
- Psychological examinations or tests, and
- Guidance and education (for the child, the parents, or both).

- **Proposal 6. 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 7: The Uniform Standard Must Apply Internationally.** Research which is conducted under Subpart D outside of the United States must utilize the same uniform standard of minimal risk that is applied in the United States.

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.404

Members raised the following discussion points and concerns.

Proposal 1. Uniform Standard. Mr. Adams asked whether the committee had considered developing suggested guidance on the meaning of "safe environment." He was concerned about how the concept would be interpreted across cultures. Ms. Kornetsky emphasized that whether in the U.S. or in other countries, children living in less safe environments should not be submitted to greater risks on that account.

Dr. Prentice suggested the definition of "minimal risk" be reworded slightly to enhance clarity: "…those risks encountered *in daily life* by normal, average, healthy children living in safe environments or during the performance…."

Proposal 2. Minimal Risk should be Age Indexed. Dr. Weiner proposed that minimal risk should be indexed to developmental status as well as age. Ms. Kornetsky agreed.

Proposal 4. Equivalence Criteria. Mr. Barnes suggested that Proposal 4 should be revised to indicate that acceptable levels of risk should be equivalent to *or less than* the risks of daily life.

Proposal 5. Well-Child Visit as Referent. Dr. Prentice asked for clarification of the meaning of "guidance and education…" in the context of a research procedure. Ms. Kornetsky clarified that the subcommittee was thinking of the type of guidance a provider may give a family or child in the context of a well-child exam, such as advice on smoking cessation or avoiding certain sexual practices. Dr. Prentice suggested that "guidance and education interventions," or a similar rewording, would be clearer. Co-Chairs will consult on the best rewording to clarify the meaning.

Proposal 6. Index Routine Psychological Tests to Standardized Screening or Assessment Measures. Dr. Prentice proposed language to make the all referents parallel and specific. The latter measures will now be described as follows: neurological or motor disorders *screening*; social development *assessment*, family and peer relationships *assessment;* emotional regulation *scales;* and *scales for* feelings of sadness or hopelessness.

Ms. Kornetsky emphasized the need for flexibility in using these measures, since any of them as applied to a specific population could conceivably exceed minimal risk.

Proposal 7. The Uniform Standard Must Apply Internationally. Dr. Prentice noted that it would be almost impossible to come up with a culturally specific, country-specific relevant definition of "minimal risk" tied to daily life; he emphasized the importance of ensuring that the same standards that apply in the U.S. apply to other countries as well. It is possible that protocols reviewed internationally might be approved under different sections (e.g., a protocol might be approved here under §404, but approved under §406 in another country); this affords a measure of flexibility.

Ms. Selwitz asked whether the subcommittee had received input from individuals that work in the international community in the development of this proposal. Ms. Kornetsky said that researchers who do international research were not specifically represented. However, she pointed out, these are recommendations of the U.S. Department of Health and Human Services (HHS). Dr. Gyi said he was concerned about the perception that HHS is imposing a level of "cultural, as well as regulatory, imperialism." Mr. Barnes, however, observed that the intent of the regulations is to establish levels of risk that are appropriate when U.S. Government funds are used for research, and it would be wrong to allow children in other countries to be exposed to higher levels of risk than would be acceptable in the U.S. He added that local IRBs will often be unfamiliar with what would be considered a "safe environment" in the U.S.

Dr. Weiner felt that the determination of acceptable level of risk is ultimately up to the parents, regardless of their external environment. However, Ms. Kornetsky noted that a "culture of respect" exists in some countries that might lead parents to cooperate with an authority figure without question. She added that varying cultural perceptions also exist within the U.S.

MOTIONS AND ACTIONS, SUBPART D, §45 CFR 46.404

Recommendations related to §45 CFR 46.404 were unanimously approved with the following changes:

- Proposal 1 will be reworded as follows: The definition of "minimal risk" at §45 CFR 46.102 (i) when applied to Subpart D should be interpreted as those risks encountered in daily life or during the performance of routine physical or psychological examinations or tests by normal, average,

healthy children living in safe environments.

- Proposal 2 will reference *developmental status* as well as age.

- Proposal 4 will read, "equivalent to *or less than.…*"

- Some of the procedures listed in Proposal 6 will have additional wording as follows: neurological or motor disorders *screening;* social development *assessment;* family and peer relationship *assessment;* emotional regulation *scales*; *scales for* feelings of sadness or hopelessness.

- The word "must" will be changed to "should" to make the language consistent (Proposal 7).

KEY PRESENTATION POINTS, §45 CFR 46.406

Ms. Kornetsky reviewed recommendations related to §45 CFR 46.406 that have already received conditional approval from SACHRP. She reminded the committee that SACHRP had asked for examples to illustrate how an IRB would work through the decision-making process, and the subcommittee has provided several. She also stressed that the subcommittee had sought to simplify the recommendations as much as possible to avoid adding to the regulatory burdens on IRBs.

- **Proposal 1: Criteria for "Minor Increase over Minimal Risk."**

  1. The procedure does not meet minimal risk criteria.

  2. The investigator has presented *sufficient evidence* about *the procedures, population*, and the *qualifications of research personnel* to assure the IRB that

     a) the increase in the probability and magnitude of harm is *only slightly more* than minimal risk;

     b) any potential harms associated with the procedure will be *transient and reversible* (restricted to the time of the procedure or a short post-experimental period); and

     c) there is no or an extremely small probability that participants will experience pain, discomfort, stress, or harm associated with the procedure that is severe.

  Ms. Kornetsky explained that the subcommittee has reversed itself on the issue of whether a "minor increase" could be better defined than simply saying it means a "little bit more." It now believes the best that can be done is to say such a risk is "only slightly more." She also emphasized that the qualifications of the researcher and the setting in which the research will be done are extremely important, as well as the perspective of the participants. The investigator must be able to present evidence to support his or her contention that the risk is only slightly more.

- **Proposal 2: Definition of Condition**. The term condition should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristics that an *established body of scientific or clinical evidence* has shown to negatively affect children's health and wellbeing or to increase their risk of developing a health problem in the future.

A condition may be something that would affect a child currently or, potentially, in the future. A "fishing expedition" should be ruled out; the researcher must have acceptable evidence to show that a condition exists. An example would be a predisposition to diabetes or to a genetic disorder. Also, living in an "unsafe environment" can be considered a condition. For instance, children living in countries with high incidence of malaria have a condition for the purpose of a study testing would have a condition for a study presenting a minor increase over minimal risk which tests immunogenicity for a potential vaccine for malaria.

Healthy preschool children may have a "condition" for a study designed to test immunogenicity of a potential vaccine for a common childhood disease, but they *would not* have a "condition" for a study testing the pharmacokinetics of a drug for potential treatment of childhood Leukemia.

- **Proposal 3: Vital Importance.** For interventions to be considered of "vital importance," there must be clear and significant scientific evidence that their use is likely to yield generalizable knowledge that would contribute to the understanding of the etiology, prevention, diagnosis, pathophysiology, amelioration, or treatment of a condition or disorder. Ms. Kornetsky observed that every researcher considers his or her own research to be of "vital importance"; a higher threshold must be used to convince an IRB that this is so.

  Under this proposal, a healthy comparison group may be approved if data are vital to understanding the comparison group's condition. An example of an approvable study would be a comparison of biological markers in HIV + and HIV – newborns whose mother is HIV positive if the research is also designed to further understand factors contributing to neonates' natural immune response against maternal HIV. However, research designed only to answer a question of vital importance to a population with a disorder or condition that requires a healthy comparison group for scientific validity would *not* be approvable under this section. An example of a proposed study that would *not* be approvable would be a comparison of brain activity responses to Ritalin in children with and without ADHD. However, if considered worthwhile, an IRB could submit this research for review under §46.407.

- **Proposal 4: Definition of Commensurate.** In applying the criteria for "commensurate" risk, IRBs should determine that the research interventions or procedures *are reasonably similar* to those procedures and interventions that *children with the condition or disorder as a class* have experienced or are expected to experience.

  - Under §406, the level of acceptable risk is determined by the definition of "minor increase over minimal risk."

  - The "commensurate" criterion means that some children may not be permitted under §406 to experience even a minor increase over minimal risk because of their own or their parents'/guardians' unfamiliarity with the procedure, or because the research imposes an unfair burden on the subjects.

  The commensurability requirement refers to ways for individuals to think about whether parents or children can consent or assent; it is not intended to suggest a relative standard.

Ms. Kornetsky presented several different examples as illustrations, applying the proposed criteria presented to each one. In the first example, the researcher proposes to examine the time course and

mechanism of insulin resistance in children who are obese and therefore predisposed to diabetes. The researcher proposes to use an insulin clamp procedure, introducing glucose in one arm and insulin in the other through an IV. In this instance, the proposed insertion of two IV lines for 4 hours and the injection of insulin would make the research more than minimal risk. The research could be approvable if the appropriate evidence is presented by the researcher. If the researcher proposed to add a group of normal weight children as a control, however, the research would no longer be approvable because those children would not have a "condition." However, the study could be submitted for review under §46.407.

Another hypothetical example presented by the subcommittee is that clinicians have reported that autistic children with diabetes have mood swings that may be associated with blood sugar levels that are more variable than observed in normal children. They propose similar procedures to those used in the previous example. In this instance, even though the effect of the measures proposed is still transient and reversible, there is empirical evidence to suggest some probability that children who are autistic would find restraints and invasive procedures highly stressful. Consequently, the study could not be completed under §46.406.

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.406

Members raised the following questions and concerns.

Proposal 1: Criteria for "Minor Increase over Minimal Risk." Ms. Selwitz wanted the opportunity to review examples of how criteria would apply to social science research where, for example, "reversibility" is not an option. An example of a nonreversible occurrence would be a breach of confidentiality. Dr. Prentice suggested that the subcommittee may need to find language that allows more flexibility in considering the nature of the "harm." He provided language for consideration: "…any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm and restricted to the time of the procedure or short post-experimental procedure."

Proposal 2: Definition of Condition. Dr. Jones pointed to the difficulty of assessing when a body of evidence was sufficient to define whether or not a condition exists.

Proposal 3: Vital Importance. Dr. Jones questioned whether the words "clear and significant" were sufficient. Mr. Cortesi added that there can be strong differences of opinion as to what is said by the scientific record.

Proposal 4: Definition of Commensurate. Mr. Barnes argued that while the history of legislative interpretation supports the subcommittee's proposed meaning for the term "commensurate," the language of the statute does not support it. The use of the term "expected" undercuts the idea that the intent is to point to familiar risks. He felt that the regulation could have referenced assent and consent if that had been the intention in including this language.

Dr. Weiner observed that the examples discussed do not sufficiently clarify the intended interpretation of "commensurate." She also pointed to the importance of the definition of the class of subjects, underlining her opposition to anything implying a relative standard for a particular subject population. She was concerned that the proposed guidance could be ignorantly interpreted as allowing for a sliding scale that would decrease protection. Ms. Flanzer stressed that the interpretation of "commensurate" should not be used to imply a "sliding scale." She cited the principle of distributive justice. Mr. Barnes observed, however, that if the uniform standard of "minor increase over minimal risk" is met, the interpretation of "commensurability" in light of the child's particular circumstances can only heighten protection.

Dr. Prentice said the intent of the framers was to be sure that there was some flexibility in regard to procedures approvable under §406; they did not want to restrict the meaning to only those procedures a child would have already experienced, but did want to restrict the level of risk by providing some referent for what would be acceptable. He believed that the language cannot be interpreted as applying only to assent and consent since it references "expected" procedures the child has not experienced.

After a break during which a new version of the proposal was drafted, Committee members had further discussions on the new language. Dr. Weiner continued to be concerned that IRBs would fail to understand the intent and would justify certain procedures for children with health impairments on the grounds that they were "commensurate with their experience." Dr. Prentice reiterated that the intent is to add protection by requiring that the child or parent have sufficient familiarity with the procedure. He noted that the recommendations issued will be associated by an appropriately detailed rationale. Ms. Kornetsky added that IRBs are eager to receive clear guidance on this issue.

Mr. Barnes said he still did not see "familiarity" or "unfamiliarity" with the procedure as the issue in this section of the regulations. The motion cited in the next section incorporates new wording designed to satisfy his and others' specific concerns.

Application of Criteria. Dr. Weiner asked whether the criteria were intended to be sequential. Ms. Kornetsky said they were not necessarily sequential; what mattered was the fact they were considered independently. Mr. Barnes advised that the subcommittee's final report stress that the criteria are independent variables and one cannot be read as modifying another.

Dr. Jones stressed the importance of showing there are no other alternative procedures that are less risky than those proposed. Dr. Prentice said this requirement was not specifically stated in Subpart D, but was inherent in Subpart A.

Ms. Selwitz wondered how the criteria would work as applied to a social science study. She suggested that the final report contain an example illustrating their use in such a case. Dr. Prentice agreed this was important, particularly in regard to the definition of what constitutes a "condition."

MOTIONS AND ACTIONS, SUBPART D, §45 CFR 46.406

Recommendations related to §45 CFR 46.406 were unanimously approved with the exception of the proposed definition of "commensurate" and the following change in language:

- In proposal 1, the meaning of "reversibility" will be qualified by language such as "reversible in respect to the harm."

Revised language for Proposal 4, the Definition of Commensurate, was presented and carried with 4 yes votes, 0 no votes, and 3 abstentions.

- *[The stem part remains the same:]* In applying the commensurate criteria, IRBs should determine that the research interventions or procedures are reasonably similar to those procedures and interventions that children with the condition or disorder as a class have or are expected to experience.

    - Under §406, the level of acceptable risk is determined by the definition of "minor increase

over minimal risk."

- The "commensurate" criterion means that some children may not be permitted under §406 to experience even a minor increase over minimal risk, either because of their or their parents/guardians' unfamiliarity with the procedure or because the research imposes an unfair burden on the subjects.

OTHER DECISIONS

The final report regarding §45 CFR 46.406 will stress that conditions must be satisfied independently.

The subcommittee was asked to provide examples of applications of the criteria to social science studies.

KEY PRESENTATION POINTS, §45 CFR 46.405

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." Ms. Kornetsky noted that IRBs sometimes "stretch" to try to make a case for "direct benefit." Under this section, more than minimal levels of risk are considered justified by anticipated benefits. Alternative approaches must be considered in determining the benefits; the anticipated benefit must be at least as beneficial as the available alternatives.

- **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 appropriately proportional to the probability and magnitude of benefit. In other words, as the risks to which subjects are exposed go up, so must the anticipated benefits.

- **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. This requirement means that in some instances, a proposal cannot be approved even when it has potential to provide a direct benefit. These occur infrequently, but they can occur.

- **Proposal 3: Evidentiary Basis for Risk-Benefit Decision.** 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."

  One example would be a phase 1 pediatric cancer protocol presenting greater than a minor increase over minimal risk (based on toxicity estimated in preclinical and adult studies) that presents a very small probability of direct benefit (a 6 percent to 10 percent probability of tumor shrinkage associated with longer survival). This study could be approved under §46.405 for children with cancer who are non-responders to currently available treatments. For these children, for whom there is no available alternative procedure, the benefit is appropriately proportional to the probability and magnitude of risk.

  A second example cited by Ms. Kornetsky is a phase 1 pediatric cancer protocol presenting more than a minor increase over minimal risk of toxicity (as estimated from preclinical and adult

studies) that will give a level of dosage with no probability of ameliorating the subject's disease or disease management. This research would *not be approvable under §405*. However, it could be approvable under §406 if it met the §406 criteria (minor increase over minimal risk, of vital importance to the subjects' disease, commensurate with their actual or expected experience, and appropriate parental permission and assent obtained).

- **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 if the procedures' efficacy is not a focus of the research.

  A research study uses *conscious sedation and magnetic resonance imaging (MRI)* to study basic brain activity in children with ADHD. The investigator states that the MRI has direct benefit because in some children he/she may discover *a nascent silent tumor*. This monitoring procedure would not be approvable under §46.405 because evaluating a technique to detect tumors is not an intent of the research, MRI is not used in standard practice to detect nascent tumors, and there is no evidence that children with ADHD are more prone to such tumors.

  Ms. Kornetsky noted that errors are being made in this area, and guidance is critical.

- **Proposal 5: Component Analysis.** Each procedure in a treatment study must be evaluated independently in terms of potential benefits and risks to subjects. Different procedures in a single trial may be approved or disapproved under different Subpart D standards.

  Ms. Kornetsky illustrated the import of this proposal through the following example. In a clinical trial of brain tumor therapy, one of the procedures to determine the extent to which the dose actually affected the target tumor presents more than minimal risk. The investigators have not provided sufficient evidence that knowing the extent to which the dose affected the tumor target would provide information directly related to decisions regarding the individual subjects' treatment. Although this procedure may be important to the research design, since it will not have direct subject benefits, it must be evaluated under §406.

- **Proposal 6. Reduced Regulatory Burden of Component Analysis.** The responsibility to demonstrate to the IRB which procedures do or do not have the prospect for direct benefit is the responsibility of the investigator.

- **Proposal 7. Opt-Out Provision.** If procedures without the prospect of direct benefit are included in a treatment trial, investigators and IRBs should consider an opt-out provision for those procedures.

  - If the research cannot be reasonably conducted without procedures that have no clinical relevance for the child's treatment, and the procedures represent no more than a minor increase over minimal risk, the *informed consent* must clearly explain the nature and rationale for such procedures.

- To avoid family exploitation, IRBs should require strong evidence that the study cannot be conducted without each of the nonbeneficial procedures.

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.405

Proposal 4: Monitoring Procedure. In reference to Proposal 4, Dr. Weiner wanted to be sure that "the child" is intended to mean "the individual child," not the class of subjects. The word "individual" will be inserted to ensure this interpretation is clear.

Proposal 5: Component Analysis. Dr. Gyi expressed a concern that an IRB might approve an invalid design as a consequence of approving some sections and not others. He believed IRBs would need some education on the implications of component analysis.

Dr. Prentice stressed the value of component analysis in ensuring a higher level of protection for children. He noted that procedures might be approvable under different categories. Dr. Weiner added that this is also an advantage to research; it puts the burden on the investigator community to be creative and identify less invasive procedures where possible. Ms. Kornetsky pointed out that if these questions are not asked, the responses will not be known and cannot be considered in the IRB's deliberations.

Proposal 6. Reduced Regulatory Burden of Component Analysis. Ms. Selwitz observed that as an investigator, she would perceive this aspect of the guidance as a regulatory burden. In communicating to investigators, the emphasis should be on how this will improve protection.

Proposal 7. Opt-Out Provision. Dr .Weiner advised clarifying that the "opt out" provision could apply to any category, including the future use of tissue.

Terminology. Dr. Weiner cautioned that the terms "study," "procedure," and "protocol" should not be used interchangeably.

Implementation. Dr. Jones asked Ms. Kornetsky to comment on how investigators are doing now and what support they will need to apply these proposals. She responded that education will be needed, and she believes the guidance will be welcome. Dr. Gyi added that IRBs will also need education, particularly in regard to the application of component analysis. He also wanted to be sure the final report illustrated the application of these proposals to social science.

Additional §407 Reviews. Mr. Adams how many additional §407 reviews might be required as a result of this proposal. Ms. Selwitz said many more such reviews were likely to be required. Dr. Prentice clarified, however, that if one component is referred to review, the minutes of the application would identify that component as the reason for the review.

Ms. Selwitz raised the question of how to provide the equivalent of a §407 review for a study that is not funded by HHS. Dr. Prentice responded that some universities do convene equivalent panels in this circumstance; he and Ms. Kornetsky have both been asked to serve on them.

MOTIONS AND ACTIONS, SUBPART D, §45 CFR 46.405

Recommendations related to §45 CFR 46.405 were unanimously approved with the following changes:

- Language will be revised to ensure that study, procedure, and protocol are not used interchangeably.

- Regarding proposal 6, new language will make it clear that the "opt out" provision applies to every category.

- Language in Proposal 4 will now reference the *individual* child.

CLOSING DISCUSSION AND DECISIONS, SUBPART D

Next Steps. Dr. Prentice explained that next steps in regard to Subpart D will be to draft a letter for Dr. Mike Leavitt, Secretary of HHS, containing SACHRP's recommendations. An accompanying set of appendices will explain the rationale for these recommendations. The approach will be similar to that illustrated by the letter sent previously in regard to §45 CFR 46.407. Members will be given an opportunity to review the letter before it is sent.

Feasibility Study. Dr. Jones asked the subcommittee to consider the possibility of a feasibility study to see how IRBs apply the new guidance. This could yield insight into the kinds of education needed and the types of issues that arise. It would be interesting to see whether different IRBs come to the same conclusions in the same or similar situations, particularly in using component analysis. Ms. Selwitz supported this idea and suggested that an IRB *without* a pediatric hospital be included in order to provide insight on the IRB population as a whole. Dr. Prentice referred this proposal to the subcommittee for discussion.

Future Directions. Ms. Kornetsky identified future directions for the subcommittee. It will consider how guidance applies to two controversial areas: the classification of housing hazards studies and placebo controls. Mr. Barnes pointed out that both of these will be controversial. Ms. Kornetsky noted that an Institute of Medicine (IOM) panel is examining some related issues.

The subcommittee will then begin examination of §408: Parental Permission and Child Assent, which is one of the "cornerstones" of additional protections for children.

Application to FDA's Subpart D. At the invitation of the Chair, Dr. Lepay commented on the implications of SACHRP's recommendations for FDA's Subpart D. Dr. Lepay said that FDA was following the discussion closely, and Sara Goldkind from the Office of Pediatric Therapeutics, the agency's ethicist, has participated in the subcommittee's discussions as an *ex officio* member. FDA is operating under an interim final rule and awaits SACHRP's final recommendations, which will be a basis for discussion as the agency develops its final rule and preamble.

PUBLIC COMMENT (PERIOD 1): SUBPART D

Members of the public were invited to comment before SACHRP members voted on final recommendations for Subpart D. (Here, for clarity, these recommendations immediately follow the relevant section.)

Dr. David Morasky of Family Home International commented on the proposal for a Uniform International Standard (§404, Proposal 7). Noting that we do insist on a uniform standard across multiple culturally

diverse domestic sites in the U.S., he supported the use of such a standard internationally. He noted that IRBs do have some leeway to interpret regulations as they apply them to their sites.

Ms. Vera Sharaz, President of the Alliance for Human Research Protection (AHRP), commented that IRBs' failure to protect subjects is the reason for this panel. She questioned to what extent "tinkering with the regulations" would improve the problem, which she saw as the poor track record of IRBs. She gave several examples of cases in which IRBs have approved experiments that should not have been permissible, placing subjects at risk. She said she feared that the kinds of inappropriate decision-making by IRBs that led to an IRB-approved experiment that exposed toddlers to possible lead poisoning might be "endemic to the entire research community." She gave the examples of an experiment called CHEERS that would have exposed toddlers to pesticides and one experiment at Yale University that exposes healthy adolescents to the an antipsychotic drug, Zyprexa. She stressed that information presented by investigators is not likely to be reliable.

Mr. John Noble, Treasurer of the Alliance for Human Research Protection and a Professor of Social Justice at Catholic University, said he found the discussion encouraging. AHRP believes that the Children's Protection Committee proposed for inclusion in the original 1973 regulations is a good idea that should be revisited. He recommends a research ombudsman system under court oversight that could provide parents with impartial information on proposed research would be preferable to having a briefing from a "self-interested" researcher.

PUBLIC COMMENT (PERIOD 2)

A second public comment period was opened after all motions on Subpart D had been finalized.

Michael Susko, president of Citizens for Responsible Care and Research (CIRCARE), the oldest nonprofit advocacy organization dedicated to the protection of human subjects in research, expressed his appreciation for the committee's work. However, he called attention to what he called "important gaps" in their deliberation. He urged the committee to include the perspectives of research subjects, their families, and their advocates. He pointed out that Subpart A, now to be addressed by a subcommittee, is the "heart and soul" of Federal protections and he stressed the importance of the recommendations on this subpart to human subjects. He urged SACHRP to establish a subcommittee composed of human subjects, families, and advocates and invite them to participate in the deliberations of this committee and its subcommittees. CIRCARE believes it is critical for people who have been research subjects or their advocates to be involved in the decision-making process. In addition, CIRCARE supports the National Human Subject Protection Act, which he said would offer humans the same protections now afforded animals, and a National Federal Registry of comprehensive and mandatory adverse event reporting..

Dr. Prentice said the committee shares many of these concerns. He said the committee plans to ask various patient advocacy group representatives to voice their concerns at the committee's next meeting (August 1-2). He emphasized that human subjects are the most important consideration for SACHRP, followed by their families. The committee's work is designed to enhance protection of these subjects.

Ms. Vera Sharaz of AHRP spoke a second time. She observed that each change contemplated by the committee comes "at the heels of another research scandal." The major issue, she said, is lack of accountability when something goes wrong. She did not believe that relying on the same IRBs to do better will be sufficient unless there are enforced penalties for violations that harm human subjects. She urged greater attention to enforcement of the standards that exist and pointed to the need for greater transparency – including disclosure of risks, adverse events, and findings. So far, she said, "the system is

protecting the system."

Dr. Prentice rejoined that he has seen dramatic improvements in human subject protections since the research shutdowns by the then-Office for Protection from Research Risks (OPRR) in 1998. Accreditation has also led to some improvement. He pointed out that the regulations were written in the 1970s, and guidance is not as extensive as it should be. Also, IRBs have been under-resourced.

Dr. Weiner asked whether this Committee and each of its subcommittees have a public member who is a past or present patient, a patient advocate, or family member of a research participant. Dr. Prentice said that Isaac Hopkins and Gigi McMillan provide public input on the Subpart A Subcommittee. The Subpart C subcommittee benefited from input from an ex-offender and a prisoner advocate.

Report of the Subcommittee on Subpart A

Felix Gyi, Pharm.D., M.B.A., CIP; Daniel Nelson, M.S., CIP

KEY POINTS, PRESENTATION ON SUBPART A

Mr. Nelson reviewed the charge to the subcommittee. It has three primary goals:

- To enhance the protection of human subjects,
- To reduce the regulatory burdens that do not contribute to the protection of human subjects, and
- To promote scientifically and ethically valid research.

Mr. Nelson stressed that he did not see these goals as incompatible, but rather as complimentary and intertwined, such that improvement in one area will lead to improvement in the others as well. 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;

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

(3) Recommendations regarding possible revisions to Subpart A.

Mr. Nelson reported that the subcommittee held a teleconference on January 18, 2005 and had its first face-to-face meeting on February 14, 2005 in Alexandria, Virginia. After reviewing the charge to the subcommittee, members reviewed the regulations section by section and identified related issues.

The subcommittee also invited certain groups of stakeholders to give testimony. These include the accrediting bodies, represented by the Partnership for Human Research Protections and the Association for the Accreditation of Human Research Protection Programs. The purpose of this input was to identify the types of issues they have seen arise that should be addressed. Representatives of Federal agencies (FDA, the Veterans Administration [VA] and OHRP) were also invited to provide perspectives on problem areas.

Based on this input and additional insights from subcommittee members, the subcommittee identified several issues for further examination. These included the following:

- ***Continuing review.*** Attention to this area was seen as a priority**.** Major questions are cited below.

- ***Expedited review.*** This is also a priority area. Again, major questions are cited below.

- ***Assurances.*** How do people understand and apply the provision related to being "engaged in research"? What issues arise in regard to offsite research in nontraditional settings?

- ***Multi-site research.*** The system has developed based on a local review mechanism that does not work as well in modern times. A new look at cooperative review mechanisms is needed.

- ***Recordkeeping and reporting***.

- ***Investigator responsibilities***. These are not adequately addressed.

- ***Informed consent.*** A host of issues must be addressed, including the application of waivers and issues related to practicability. Related problems are now surfacing in the context of litigation and liability.

- ***Exemptions.*** These create problems because the IRB sometimes loses sight of the study; there may be a need for some form of continuing review in these cases.

- ***IRB review of exceptions and deviations.*** Single subject exemptions or deviations from study criteria are handled in a variety of ways.

- ***Vulnerable populations.*** Who is included? What is meant by "additional safeguards"? How are legally authorized representatives defined, and what roles do they play?

- ***Definitions.*** All these categories hinge on definitions, which the subcommittee must address as it proceeds.

Mr. Nelson noted that adverse event reporting not on the initial list of issues, since a national process is already underway to explore related concerns and options.

The members then proceeded to establish priorities among the issues. In prioritizing them to be addressed, they considered the importance of problem, the ease of fixing the problem, the effect of problem on human research protections, and the contribution of issue to regulatory and nonregulatory burden. The subcommittee then divided into two working groups, one focusing on continuing review and another on expedited review. Dr. Gary Chadwick and Dr. David Strauss are Co-Chairs for the Continuing Review Working Group; Ms. Moira Keane and Dr. Tom Puglisi are Co-Chairs for the Expedited Review Working Group. Each working group has already produced a thoughtful working paper.

Questions to be explored related to *continuing review* include:

- When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB and PI can close the file?

- Are there circumstances where continuing review can appropriately be conducted less often than once per year?

- Should categories 8 and 9 from the expedited review list (November 1998) be expanded or clarified?

- What is the role of the IRB in literature searches at continuing review?

- How should exempt research be handled at continuing review?

- What is the role of review for "unanticipated problems" and "adverse event reports?"

- What is the proper interface between data monitoring committees (DMCs) and the IRB when performing continuing review?

- In light of accreditation standards, what types of study monitoring are appropriate and reasonable in the guise of IRB continuing review? What data/information improves human subject protection?

- Some IRBs have established as institutional policy a "five-year" review, i.e., a resubmission and "initial" review after a set time. Is this a best practices model for the protection of human subjects, or even an appropriate model?

- Does the current HHS guidance regarding setting the date of continuing review need to be changed to allow more flexibility in the review timing? How should temporary lapses in approval be handled?

- What does the phrase "verification from sources other than the investigators that no material changes have occurred since previous IRB review" [§46.103(b)(4)] mean for continuing review?

- For research sites with more than one IRB, does the continuing review need to be performed by the same board that made the initial approval? How do special IRBs that only conduct continuing review impact the process? Is this a best practices model for the protection of human subjects, or even an appropriate model?

- What documents does the IRB need to be given to conduct a continuing review?

- Can existing guidance on continuing review be consolidated and integrated?

Questions in regard to expedited review include:

- Regarding the "Conditional Approval" mechanism: Do "minor changes" identified as contingencies for approval by the convened IRB, but not explicated for simple concurrence, really need to return to a convened meeting? Can the IRB Chair or primary reviewer be given the authority to make discretionary judgments on behalf of the IRB?

- Is there a need for additional categories, or more examples in existing categories, on the November 1998 expedited review list?

- Is additional guidance needed concerning the interpretation of "minimal risk" in the context of expedited review?

- Is additional guidance needed concerning the interpretation of "minor changes" in the context of expedited review? Should examples be provided similar to those provided in some of the "minimal risk" categories?

- Is there a need to define "administrative changes" to research that do not warrant even expedited review and approval.

- Could IRBs be permitted to define their own "minimal risk" categories based on the nature and experience of the investigators or institutions for which they are responsible?

- Is there need for guidance on the appropriate use of expedited procedures for review of adverse events (AEs), serious adverse events (SAEs), safety reports, and reports of unanticipated problems involving risks to subjects or others?

- Is there a need to clarify use of expedited review for minimal risk activities in research involving children or prisoners, or will this be addressed by Subpart C and D Subcommittees?

- Can existing guidance on expedited review be consolidated and integrated?

Next steps for the subcommittee include finalizing recommendations within the two working groups, reviewing them as a full subcommittee, and submitting them for review by SACHRP. A two-day meeting of the subcommittee is planned in the summer.

The Co-Chair observed that there is considerable interest in the Subcommittee's deliberations. Members are open to input as the subcommittee proceeds with its work.

KEY POINTS, DISCUSSION OF SUBPART A

Dr. Prentice observed that the subcommittee has made remarkable progress, and the working papers produced are very detailed. He asked whether the considerations cited would be likely to require an amendment of the Common Rule. Mr. Nelson responded that this would clearly be a last resort. Dr. Gyi agreed.

NOMINATION TO ACCEPT SUBPART C FINAL REPORT

The final report of the Subcommittee on Subpart C was unanimously approved with the following changes:

- p. 3 and throughout: use the term "recommends" instead of "suggests."

- p. 5, 3rd bullet point: use the term "prisoner representative" instead of "prisoner member."

- p. 5, 3rd line from bottom: Use the following new language: "…..treated appropriately as *inclusion of a vulnerable subject* in the study."

- P. 5 and throughout: Use the term "his/her" instead of alternating "his" and "her."

- P. 7, second bullet point. Replace "Federal government IRBs" with "FWA IRBs that are considering research with prisoners as subjects."

- P.9. item 2: Add the qualification, "additional risks on top of those already present *because of a chronic illness*…"

- P. 9, item 6: Instead of "risk/benefit ration" use the language, "contemplate the risks and benefits."

ACTION ITEM:

- A thank-you letter will be sent to each member.

Closing Discussion and Adjournment

Dr. Schwetz encouraged the Subcommittee on Subpart A to seek input from the community of IRBs on their priorities. Mr. Nelson agreed that this was important. However, he said the group has been seeking input and getting little response to its questions. It is also interested in reaching out to social and behavioral research organizations to request their input. Dr. Prentice suggested a Workshop on Subpart A as it applies to behavioral social science research at the Annual meeting of Public Responsibility in Medicine and Research (PRIM&R), at which concerns would be invited. Ms. Kornetsky agreed to relay this suggestion to the Program Planning Committee, which she chairs.

Dr. Schwetz asked SACHRP how to address the recurring allegation that the IRB system is broken. How can this be evaluated? To the extent that the system is broken, what exactly is broken and how can it be fixed? Dr. Prentice responded that he did not believe the IRB system is broken. However, he believed there were inconsistent levels of protection due to varying resources and education. SACHRP is trying to reduce inconsistency through appropriate guidance and education. The issue, he said, does need further dialogue.

Dr. Weiner suggested a needs analysis to provide data on key issues. Dr. Schwetz pointed to a recent report from the Academy of Engineering on accident prevention He said the airline and railroad industries have ways of tracking "near misses" that the health care community, with the exception of the Veterans Administration, generally does not. OHRP is exploring this area with *ex officios*. If such information could be captured, it would provide input that would make it possible to upgrade the quality of protections.

Mr. Barnes agreed with Dr. Prentice that most IRBs do the best they can. However, for the five percent that create problems, these entities will modify their behavior only through enforcement. Some investigators feel they can do whatever they want as long as the IRB does not find out about it. Historically, the burden of human resource protection rests on the investigators' shoulders, and IRBs are there only to try to limit their excesses. More should be done to educate them on their obligations.

TUESDAY, APRIL 19

Welcome and Opening Remarks
Ernest Prentice, Ph.D.

The Chairman welcomed everyone and presented an overview of the agenda for the day.

Perspectives on the Role of the Institutional Official
Remarks by Judith Brookshire, M.S., Director, Office for Protection of Human Research Subjects, UCLA; Richard Bianco, Assistant Vice President of the Academic Health Center, University of Minnesota

The Chairman commented on the key role of the Institutional Official (IO), since the IO provides the assurance of compliance with Federal regulations. This is a position of leadership that also has implications for the creation of an organizational culture that supports compliance.

Remarks by Judith Brookshire

Ms. Brookshire pointed out that the regulations do not specify the necessary qualifications of an institutional official, the person responsible for ensuring the independence of the IRB, as well as its support and its standing within the institution. They say only that the IO must have legal authority to act and speak for the institution and should be someone able to ensure that the institution will effectively fulfill its oversight function. She stressed that the IO can be part of the foundation for a successful IRB program.

She reviewed the IO's responsibilities, which include the following:

- Overseeing all research involving human subjects performed under the auspices of the institution;
- Creating a campus culture that promotes and upholds the highest ethical and scientific principles in the review and conduct of human research;
- Committing the institution to compliance with HHS & FDA regulations and local law for the protection of human subjects;
- Designating one or more IRBs to fulfill the requirements of the Federal regulations;
- Ensuring that the IRB is properly constituted and functions in accordance with the regulations;
- Ensuring the IRB receives appropriate institutional support and adequate staffing to support the IRB review function and record keeping duties – a key requirement, without which the IRB cannot adequately fulfill its duties;
- Ensuring that the investigators meet their obligations to the IRB;
- Ensuring that the IRB has the authority to approve, require modifications, or disapprove all human research activities, including proposed changes in ongoing, previously approved, human subjects research;

- Ensuring the IRB receives appropriate institutional support and adequate staffing to support the IRB review and record keeping duties;

- Ensuring that investigators meet their obligations to the IRB;

- Ensuring that the IRB has the authority to approve, require modifications, or disapprove all human research activities, including proposed changes in ongoing, previously approved, human subjects research;

- Ensuring the IRB has the authority to suspend or terminate the approval of ongoing, previously approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected, serious harm to subjects; and

- Making sure that there is sufficient communication, training; and education of the research community, the IRB, and the IRB administrative staff.

Ms. Brookstone highlighted a review by a task force of the Association of American Universities (AAU) in 2000 that assessed the challenges faced by university research management in protecting human subjects. The task force stressed that active institutional support is the foundation for a successful, ethical human subjects research program. It recommended strengthening training and support for IRB operations and that senior university management stress the importance of conducting human subjects research in accordance with the highest standards of ethical conduct to their entire campus communities. The report also highlighted the importance of ongoing communications between senior management and the IRB. By "senior university management," Ms. Brookstone suggested, they were pointing to a responsibility of the IO.

The speaker then turned her attention to the issue of where the IO should be placed within the university hierarchy. She pointed out that a person who is directly involved in research funding may not be sufficiently immunized against financial and other pressures. She suggested that IOs should be at the highest level in the institution in order to have the authority needed to make decisions on behalf of the institution and command the respect of the research community. She stressed that the IO must seek to foster "a culture of conscience" in the research enterprise; otherwise, investigators may be given the message that it is acceptable to skirt the IRB and go directly to the IO for approval. An effective and conscientious IO will instead encourage investigators to engage and negotiate with the IRB throughout the review process.

The consequences of a lack of sufficient IO support and infrastructure for the IRB are dire and directly affect the ability of the IRB to fulfill its basic functions. Without the resources needed to promote accountability, the IRB becomes isolated and faculty members to not want to serve as IRB members; it can become difficult to retain appropriate staff, placing the institution at risk of serious mistakes. The IO must strive to prevent this by helping create a culture in which all stakeholders work together in an environment of support, trust, and respect.

Remarks by Richard W. Bianco

Mr. Bianco, who is the IO for the University of Minnesota, referred to the IO as the institution's "Go to Jail Guy" – the one who can be held accountable to the Federal Government for the university's pledge to fulfill its responsibilities.

Mr. Bianco recalled that in the early 1990s, the university's research programs were almost shut down. The institution had a decentralized, weak oversight system and a superstar researcher who was essentially "beyond oversight." Grant and clinical income were at all-time highs. After a whistleblower involved the Federal Government, serious violations were uncovered, and the institution had to pay millions of dollars in sanctions. As a result, education and training programs were set up institution-wide for all levels of investigators, faculty, staff, and students. Also, its compliance program was integrated: IRBs, the Animal Care Committee, biosafety, conflict of interest, and post-approval monitoring were all moved under one umbrella, regulatory affairs. As a result, faculty learned that conducting research was not a right but a privilege, and a new culture emerged. However, he said, senior faculty remain a problem.

Ms. Bianco described the key elements of an effective compliance program. He stressed the importance of a policy based on the principle, "trust but verify." Post-approval monitoring, he said, is key to maintaining compliance. He also stressed the importance of integrated compliance in preventing system breakdowns – though he added that the primary risk always remains at the PI level. For this reason, he believes, PIs should be trained and certified. In addition, he said, compliance staff should be certified professionals able to gain and keep faculty respect.

The speaker differed strongly with the idea that the IO should be placed high within the administrative structure. He said an IO who is too highly placed will not have enough detailed knowledge to understand the meaning of the assurance he or she is signing and will not know the pertinent rules and regulations. Also, it is very difficult, if not impossible, for an official such as the Vice President of Research (VPR) to recognize other roles with the role of IO. The VPR, for example, is responsible for the funding of research programs and must serve as a faculty advocate.

In the Minnesota model, the IO is the Assistant Vice President; his main focus is compliance. He is an active researcher who has credibility with both faculty and administration. As such, he can appreciate both sides of the issues that arise. He reports to the President of the University, while ensuring that the Vice President of the Academic Health Center and the Vice President for Research are "in the loop." Minnesota's integrated approach allows the institution to oversee all its research programs, including veterinary compliance and animal research, are in compliance. IRB members can serve on each other's committees, while IRB administrators serve as *ex officios* in conflict situations. He argued that this strategy helps ensures that all programs are in compliance – not just segments of them.

Finally, the speaker suggested that there was a need for a national organization or event at which IOs could assemble to discuss these issues. One possibility would be a meeting through PRIM&R.

DISCUSSION

Following these presentations, SACHRP members asked several questions.

IO Qualifications. Dr. Prentice asked speakers whether they felt that, in general, that IOs understand regulations and support IRBs in achieving compliance. Ms. Brookshire observed that IOs want to be responsible and supportive, but lack an understanding of their responsibilities to ensure IRB autonomy and pursue an integrated approach to ensuring compliance. Dr. Prentice observed that he himself has a supportive IO, but is totally dependent on the Chancellor for resources, which are often inadequate. Mr. Bianco, in contrast, does have a definitive budget he feels is "pretty good."

Ms. Selwitz commented that her experience was one of having an IO who is able to control resources; she differed with Ms. Brookshire's contention that a vice president of research would be a poor choice for an

IO. Ms. Brookshire responded that conflicts of interest were indeed possible if the IO is also the one responsible for bringing in research money, and if the IRB appears to be standing in the way of fulfilling this responsibility. However, she held that it was possible to put safeguards in place to avoid such conflicts. Mr. Bianco continued to feel that there would be at least a perception of conflict of interest in the mind of the public if the IO is the Vice President for Research. In addition, faculty members may appeal to a VPR who is not the IO if they are having trouble with the IRB or the IO; this organizational "venting" can be healthy.

Ms. Kornetsky cautioned against being too prescriptive about the best location of the IO. A variety of models exist, and it is the end result that matters in assessing the workability of any approach.

Ms. Selwitz observed that there are also inherent conflicts of interest in a situation in which an investigator (or the investigator's sponsor) is paying an IRB to do a review of the proposed research. In a sense, she said, an independent IRB is an equivalent of an IO in some respects.

Motivation to Comply. The Chair also asked whether, as the memory of the institutional shutdowns of the 1990s fades, motivation to comply is also fading. Ms. Brookshire responded by quoting an unnamed institutional official as remarking that "OHRP is not the last word." Financial pressures lead to a tendency to cut corners, and there is clearly some slippage. Mr. Bianco suggested that strengthening the IO function would be helpful.

IO Conference. Mr. Bianco reiterated his offer to host a conference in Minnesota for the purpose of engaging IOs in compliance issues. Having knowledgeable IOs, he said, might lead to more applications for accreditation. Ms. Selwitz supported the value of this strategy and said she thought that PRIM&R would be very interested in cosponsoring such an event. Other possible cosponsors mentioned by SACHRP members were the National Institute of Health (NIH), The Association of American Medical Colleges (AAMC), the American Hospital Association, and the Association of Community Hospitals (ACH).

Dr. Prentice suggested that IOs would be most likely to attend such a conference if it were sponsored by OHRP and if IOs received direct invitations from the OHRP Director. Dr. Schwetz , however, said that IOs and investigators seldom attend OHRP's regional conferences. He agreed that direct targeting might improve attendance. He also shared that he had had an opportunity to speak to research deans about compliance issues at a recent AAMC meeting, which was quite welcome. OHRP could host a conference like the one proposed with a partner, such as FDA.

Mr. Bianco encouraged this approach; he said that if an IO received a call from OHRP or SACHRP to come to a conference, he or she would clear the schedule and come. The IOs might then form an organization of their own as a next step.

Changing Organizational Culture. Dr. Prentice asked what the IRB administrator and Chair could do to rectify a problem in the organizational culture at their institutions. Ms. Brookshire responded that the best chance of change lies in the negotiation that occurs between the IRB and investigators. If treated with respect, many investigators will "come on board."

Mr. Bianco added that it was important to give those who serve on IRBs academic credit for service that is considered in promotions and tenure.

Dr. Schwetz highlighted the "culture of indifference" at some institutions as dangerous and upsetting. Institutional commitment is key in ensuring compliance: it is unlikely investigators will be concerned about such issues if their dean is not concerned about them.

Bypassing Institutional Authority. Mr. Barnes asked the speakers to react to his assertion that Federal agencies "do nobody any favors" when they allow principal investigators to bypass institutional officials on compliance issues and go directly to a Federal grant official on issues related to accountability. Ms. Brookshire and Mr. Bianco both agreed. Mr. Bianco added that it was "incomprehensible" to him that other entities would "handcuff" the institution in this way.

Pressures to Waive Regulations. Dr. Polan asked how common it was that "superstar" researchers demand changes in regulations. Ms. Brookshire said it was "fairly common." Mr. Bianco added that pressure on the IRB to approve research most frequently comes from the office of a Senator or Congressman. Mr. Barnes observed that the tradition of the institution is important; if there is a tendency to "cry academic freedom" when issues arise regarding research practices, meaningful oversight can be frustrated.

Private Institutions. Dr. Gyi expressed concern about ensuring adequate oversight in private research settings. Dr. Gyi raised the specific concern that an IRB in a decentralized model may not have the linear relationship within the organization needed to hold investigators accountable. Ms. Brookshire responded that investigators working with private IRBs and in all clinical research settings are likely to have certification and training. Mr. Bianco added that all researchers with Minnesota faculty appointments are required to use the University IRB; post-approval monitoring is used to help maintain a culture of compliance.

Mr. Barnes observed that the vast majority of research is done in the community hospital setting by private physicians who are using the community hospital IRB as their IRB of record for studies done in their private offices. In this setting, he has seen little institutional recognition of the role of the IO.

Promoting Certification. Mr. Adams asked what could be done to encourage investigator certification. Ms. Brookshire said that at her institution, UCLA, it is not possible to be an investigator without certification and training, using a "home-grown" process. This process includes both biomedical and sociobehavioral components. Mr. Bianco, however, felt that research certification is unlikely to encourage responsible conduct in a faculty member. Rather, he held out more hope for progress by concentrating on education and training for the nurse coordinator position. Dr. Prentice agreed, adding that it is difficult to get investigators to come to training; instead, his institution focuses its efforts on the protocol coordinators.

Dr. Jones agreed that nurse coordinators are essential for addressing issues that arise in daily functioning, but the researchers need help as well. Mr. Barnes agreed, wondering about the best approach to reaching doctors with essential information. Mr. Bianco noted that while first year medical students are overwhelmed by a packed curriculum, the residency period may be an appropriate time for this training. Ms. Brookshire said she has done over 60 presentations to residents last year.

HRPP Accreditation Standards for Investigator Education

Remarks by Jessica Briefer-French, Vice President, Human Research Protection Accreditation, Partnership for Human Research Protections (PHRP); Marjorie Speers, Ph.D., Executive Director, Association for the Accreditation of Human Research Protection Programs (AAHRPP)

The Chair introduced representatives from the two accrediting bodies of the Human Research Protections Program (HRPP), AAHRPP and PHRP. Both consider investigator training and education as they perform their HRPP assignments.

Remarks by Jessica Briefer-French

Ms. Briefer-French began by introducing PHRP and the National Committee for Quality Assurance (NCQA). She explained that PHRP is a new organization with the mission of promoting and enhancing the safety of people involved in human subjects research through accreditation. It was born in 2001 as a partnership of NCQA and the Joint Commission for Accreditation of Healthcare Organizations (JCAHO). It accredits a wide organizations involved in human research, including medical centers, hospitals, and independent review boards. NCQS is an older accrediting organization that has evaluated over half of the VA medical centers currently conducting research.

She noted that accredited organizations are still a small percentage of organizations in which research occurs, and they generally represent those that have the best infrastructure to support human research programs. Also, she observed that research is increasingly being conducted in settings that are not subject to direct accreditation, such as private medical practices and community settings.

Since the accreditation process is intended to apply to a broad range of organizations, standards for training are purposefully broad. Organizational training requirements for a setting that does Phase I or II research or device trials will differ from settings in which research is primarily in the fields of epidemiology of health services, using strategies such as chart reviews. In each instance, risks are different and the approaches to mitigating them through training will also differ.

Investigator training is intended to convey organizational values and procedures, ensure a common understanding of key principles, facilitate autonomous decision-making, and ensure – ultimately -- ethical and compliant research. PHRP's standards require the organization to specify requirements for training and education that include the type and scope of required human subject protection education and training. They must also be able to identify individuals for whom education and training are required and methods for assuring that these individuals have met education and training requirements. However, training alone is not enough: systematic and integrated institutional support is essential as well. The speaker compared this support to systems that support pilots and help ensure they perform effectively. For example, they have co-pilots and automated navigation systems.

PHRP also checks whether the organization has at least one measure that it tracks regularly to determine how well investigators are performing. PHRP wants to see that the organization is monitoring and measuring investigator performance within a continuous quality improvement cycle. It is important that the organization is measuring something relevant to what investigators do that can serve as a benchmark for that performance area. The measurement should also be a current one (taken within the last 12 months) in order to be meaningful. PHRP also assesses the organization's response to performance shortfalls and whether they have remeasured to determine the effectiveness of the organization's intervention.

PHRP also considers whether the organization it is assessing has clear and explicit expectations for investigators, specifically with respect to the informed consent process (an area in which there are frequent compliance issues). The organization should outline all the aspects of the consent process and also have guidance for investigators on how to construct effective consent forms.

PHRP evaluates the organization's compliance with its standards by reviewing its policies, procedures, and communication with investigators. It reviews standard operating procedures (SOPs), investigator guidance, and training logs. It verifies training certificates of investigators involved in sample protocols, reviews quality measurement or compliance audits, and reviews measurements taken to assess investigator performance.

Ms. Briefer-French felt that additional measures were needed to promote compliance. Possible strategies include government licensure of researchers, an expanded medical curriculum that has a greater focus on research ethics and methods, establishment of clinical research as a board-certified specialty, and promoting investigator training and demonstration of competence through a variety of means, possibly including certification.

Remarks by Marjorie Speers

Dr. Speers focused her remarks on AAHRPP's investigator domain. She stressed the integral role of investigator in protecting research participants. She noted that the oversight system has evolved to one of moderate protectionism; she suggested that this state of affairs was not a positive one if it means the investigator's role is not respected and that investigators are not held accountable for their own responsibilities. She reminded SACHRP that the IO report recognizes the role of the investigator and sees the responsibility for protecting human subjects as shared among IRBs, investigators, and organizations

AAHRPP assesses investigators' knowledge and behavior, as well their compliance. In determining whether they are aware of and follow ethics principles and standards, it assesses whether or not investigators

- consider conflicts of interest,
- employ sound study design,
- understand risk, including how to minimize risk and detect harm,
- recruit participants fairly and equitably,
- determine what resources are needed to protect participants,
- develop informed consent processes appropriate to the type of research and study populations, and
- respond to participants' complaints or requests for information.

To determine investigator compliance, evaluators assess whether they are qualified for their research role by training and experience, assess and report unanticipated problems, maintain oversight of protocols and research staff, and carry out research with adequate data and safety monitoring.

Dr. Spears stressed that training alone cannot guarantee that an individual is competent and knowledgeable, since knowledge does not necessarily translate to behavior. She also pointed out that practitioners in scientific and scholarly disciples need different kinds of training to address different issues. Preparation should include both training (skills) and education (concepts and theories). The speaker proposed integrating research concepts and practices into both the undergraduate and post-

graduate curricula. Key topics include scientific methodology, design and analysis of research, recruitment methods, informed consent procedures, ethical principles, and regulations. By starting early to influence and train future scientists, she suggested, we may have greater impact on the value placed on ethics. A wide variety of strategies should be considered, including Web sites, brown bag lunches, and mentoring programs.

DISCUSSION

Dr. Prentice observed that apparently many investigators have little if any training in research ethics and human subject protection; in addition, training requirements are inconsistent across institutions. The speakers agreed.

Investigator Training. Dr. Gyi asked for comments on how it might be possible to reach out to groups that do investigator training and try to encourage an integrated approach that would raise the level of competency. Dr. Spears suggested integrating education and training into the curriculums of medical, social science, pharmacy, dental, and other programs. Mr. Adams, however, pointed to the problem of what can be taken out of the curriculum in order to accommodate additional material (particularly for medical students). He suggested, as a practical matter, the education would have to occur at the point that people become engaged in research.

Promoting Competence. Dr. Prentice wondered how a significant number of investigators could be persuaded to avail themselves of an opportunity for certification. He was particularly concerned about reaching physician researchers in the private sector. Mr. Adams noted that the majority of people taking the certification exam at present are from independent cites rather than medical centers, so there is some movement in this direction. He suggested the use of incentives, such as not having to fill out all the personal information on the 1571 form, as recognition of demonstrated competence.

Dr. Polan noted that academic health centers have more leverage on this issue; at her institution, a researcher cannot submit a grant application unless he or she has certification. She also observed that most physicians have hospital privileges and these hospitals must be accredited; it might be possible to require hospitals to train physicians that practice there and establish a means of assuring the training occurred (perhaps through an interactive Web site.)

Mr. Barnes suggested a closer look at ways of enforcing standards and at penalties for professionals who violate them. IRBs can revoke the right of individuals to conduct research; faculty members can lose tenured jobs or be discharged; state medical boards can withdraw licenses. Currently, he said, even in cases of egregious research misconduct, such as falsifying results or failing to obtain patient consent, state medical societies fail to take significant disciplinary actions. He suggested that Dr. Schwetz engage in dialogue with the national organization of state medical boards and provide education on medical ethics. Mr. Adams suggested engaging the state licensure boards rather than medical societies, since this is the real source of regulatory power. He also proposed a blind study of data in the national practitioner data bank to identify problems institutions have experienced.

Dr. Jones pointed to research that suggests that behavior change is best accomplished through interactive means and tools, including case studies. She also suggested peer review as an effective means of promoting change. Through professional organizations, it may be possible to change what it means to be a professional. By engaging these organizations actively, it may be possible to reach key people who are highly respected in their field and can sway the entire culture and climate.

Assessing Competence. The Chair asked speakers to explain how they assess investigators' knowledge and behavior. Dr. Spears said that AAHRPP's approach is to break into site teams and interview randomly select investigators. The interviews explore how they apply the principles related to areas such as research design, safety monitoring, and informed consent. They are able to get a sense of what they do and do not know. Ms. Briefer-French reported that PHRP primarily examines protocol files, asking such questions as whether safety monitoring plans exist, whether there is an appropriate process for informed consent, and how risks are minimized. She also stressed the role of the organization in measuring and monitoring the investigator's performance over time.

The Role of DHHS. Ms. Selwitz asked speakers to identify the most appropriate roles for HHS in promoting curricula for students. Ms. Briefer-French repeated that licensing investigators would be a way of ensuring some basic requirements are met. An individual could qualify for a license at various points in time. Dr. Spears suggested that entities such as NIH could build training into on research ethics into its educational grant programs for new investigators and students, as well as fellowship and stipend programs. It could also offer grants to universities to develop curricula. In addition, HHS could work with the AAMC to influence medical schools to build education on research ethics into curricula or into residency programs.

Issues Involving Investigator Education

David Korn, M.D., Senior Vice President, Division of Biomedical and Health Sciences Research, Association of American Medical Colleges (AAMC); Charles Flexner, M.D., Associate Professor, Johns Hopkins University; Paul Braunschweiger, Ph.D., Department of Radiation Oncology, University of Miami School of Medicine and the Collaborative IRB Training Initiative (CITI)

Remarks by David Korn

Dr. Korn explained that the AAMC data base on curriculum does not provide information on how medical schools are addressing the ethics of clinical research. However, he is able to review some of guidance given to medical schools and teaching hospitals on this subject.

The speaker highlighted several initiatives that have strengthened training of clinical investigators. These include:

- NIH requirements that key personnel involved in the design and conduct of clinical research studies involving human research participants must be educated and this education must be described (though no specific requirements were given),
- Training award programs given to support high-quality multi-disciplinary training in clinical research,
- Financial incentives from INH institutes to support the career development of patient-oriented clinical researchers,
- Peer-reviewed NIH awards for activities that enhance the protection of human research subjects,
- The Patient Advocates (or Research Subject Advocates) program, and
- The availability of Web-based training developed by the Collaborative Institutional Training Initiative (CITI).

The AAMC, Dr. Korn explained, does not have regulatory authority; its specialty is "exhortation." In the late 1990s, it established a task force on clinical research that urged medical schools and teaching hospitals to develop a culture supportive of clinical research and to transmit excitement about this to a new generation of students, residents, and fellows. It also recommended that training programs define a

rigorous set of competencies, including ensuring an understanding of the ethics related to good clinical practices in human subjects research.

Dr. Korn informed SACHRP that a Medical School Objectives Program laid out knowledge, skills, attributes, and objectives for medical students in a 1999 report. Since then, special panels have been convened to address specific topics, including one that explored the question of how clinical research can be incorporated in undergraduate medical education. Understanding the ethics related to subscribing to good clinical practice in human subjects research was the first knowledge objective identified by the special panel. The panel's report also identifies the need for ethical sensitivity and awareness of potential conflicts of interest. The report concludes, however, that "clinical research…is ultimately learned by example." Consequently, the special panel recommended that medical students be exposed to clinical investigators and have the opportunity to participate in clinical research. The report urges medical schools to "cultivate the development of a clinical research community that would engage medical students and actually expose them to the excitement of clinical research throughout the curriculum." Currently, few residents receive this exposure.

Remarks by Charles Flexner

Dr. Flexner described a Johns Hopkins program that provides graduate training for clinical and translational researchers that is as rigorous as the curriculum required for graduate students in the basic sciences. The program defines clinical investigation as scientific experimentation in which the patient is the principle unit of activity (human subjects research). The program is founded on the belief that the principles that govern clinical research are not different from the scientific principles that govern science research. However, the biological variability inherent in human subjects leads to major scientific differences in experimental design. In addition, there are substantial ethical and regulatory differences.

The program's students have finished medical school, and in most cases have finished at least 2 years of residency or clinical fellowships. Master's students begin with a year of didactic coursework, then spend most of their time on research, working with an academic adviser. Johns Hopkins offers a Master's of Science degree, a Ph.D. in Clinical Investigation, and a one-year program of coursework leading to a Master's of Health Science degree for people who are employed and cannot take time off to do research. The institution also offers a course on "The Science of Clinical Investigation" for faculty members, study coordinators, clinical fellows, and others who want more exposure to clinical research skills but are unable to become full-time students.

The 70 core credit hours include training on ethical and regulatory issues in clinical research, a survey on clinical investigation, biomedical measurement, and sources of variability in measurement of human subjects. To date, about half of 122 students enrolled have graduated. The 25 students entering next years program represent the entire spectrum of specialties within the School of Medicine.

The program has several sources of funding, including NIH awards, training grants, private foundation awards, and some pharmaceutical company scholarships.

Dr. Flexner added that a one-and-a-half day research ethics course is now required of all clinical fellows at Johns Hopkins, regardless of whether or not they intend to do human subjects research. Also, he noted that all investigators engaged in such research must take mandatory training consisting of a minimum of four separate Web-based courses.

The speaker closed by raising a variety of questions, including the following:

- If shorter courses of training are desired, how can they be tailored to the needs of investigators?
- Who should set the standards?
  Who should certify the training has been adequate?
- Do all investigators need to be formally trained and/or certified?
- Should there be exemptions for those with graduate degrees in clinical investigation or those doing only minimal risk research?
- Should there be grandfather clauses?
- Should people like the speaker have to take tests before participating in some else's research project?
- How often should a certified investigator be recertified?
- Should nonphysician investigators (such as Ph.D. scientists) be subject to the same kinds of oversight as physicians?

Remarks by Paul Braunschweiger

Dr. Braunschweiger discussed the Collaborative Institutional Training Initiative (CITI), which has developed an IRB training program. The initiative began as a collaborative between the University of Miami and the Fred Hutchinson Cancer Center. The CITI organization is now comprised of about 470 institutions worldwide. CITI maintains a Web-based training program that is updated twice a year, with an editorial board to peer review new and existing content.

The current content consists of a basic course and a refresher course available to all participating members. Components are as follows:

- CITI Basic Course www.citiprogram.org

  - 12 Biomedical Modules
  - 11 Social / Behavioral Research Modules
  - 5 General Interest Modules
  - Quizzes

- CITI Refresher Course www.citiprogram.org

  - Case studies and scenarios
  - Biomed Refresher I
  - Biomed Refresher II (available June, 2005)
  - SBR Refresher I (available June, 2005)

An international research course is expected to be available in May, 2005. Initially, it will be available in Chinese and Spanish; it will then be translated into Russian and French. (The CITI International Research Course will be available at www.irbtraining.org.) A program on Good Clinical Practice (GCP) is being developed for Fall 2005, and a Responsible Conduct of Research (RCR) program is planned for spring of 2006.

Member organizations use the CITI Program in a variety of ways. These include:

- Investigator certification,

- IRB member training,
- IRB coordinator training,
- As a refresher course,
- For re-certification or continuing education,
- As a Web-based alternative to seminars or lectures, and
- As a component of undergraduate or graduate bioethics courses.

Learner demographics for 1,100 respondents show that approximately 30 percent are students, 20 percent are PIs, 15 to 17 percent are clinical investigators, and 4 to 5 percent are IRB members or coordinators. So far, nearly a quarter of a million people have been registered to use the program's proprietary software, which became available in May of 2004. Surveys of these learners find that most of them accept the mandate that key personnel engaged in human subjects research should participate in training on the subject and report that the time spent taking the course was worthwhile.

Dr. Braunschweiger said that CITI developers are considering developing education and training initiatives for IRB members and coordinators, including modules on IRB functions and process and continuing education materials with case studies and scenarios.

DISCUSSION

Basic Education. Dr. Prentice asked Dr. Braunsweiger whether the CITI program provides sufficient education in research ethics and human subjects protection. Dr. Braunschweiger responded that the CITI course works best as a component of an institutional program which might, for example, include brown-bag lunch sessions, seminars, and institutional ethics programs.

Program Impact. Dr. Gyi expressed alarm that even with a robust program in place at Johns Hopkins since 1993 to promote sound practices in human subjects research, subject Ellen Roche died in 2000 (after inhaling hexamethonium, a drug found by the FDA to have "substantial potential toxicity," in a research study). Dr. Flexner responded that the investigator in the Ellen Roche affair was not a graduate of his program. He added, however, that even if people are well trained and supervised, he does not believe that research risks drop to zero. It is important to use cases like that of Ellen Roche to analyze systems and determine what more could have been done to prevent harm to subjects.

Promoting Mentoring. Ms. Kornetsky said that young investigators often seek help from her, and she believes that mentoring programs are an effective way of communicating knowledge. She asked for ideas of how the number of senior clinical investigators willing to serve as mentors could be increased. Dr. Korn re-emphasized the importance of instilling passion for basic research in medical students by including it in the curriculum.

Residency and Fellowship Training. Dr. Polan suggested that since it is when medical students become residents and fellows that they actually begin to do research, this is the best time for education on human subjects protection. She asked how training on the conduct of research might be integrated. Dr. Korn responded that the American Board of Internal Medicine has created a Research Track. Also, the American Board of Pathology has always been generous in giving formal credit for research training. These instances illustrate the importance of board receptivity in integrating the subject into the curriculum. Dr. Flexner cautioned, however, that today's interns and residents must fulfill twice as many requirements from the American Board of Internal Medicine as were required 15 years ago; they have a limited number of hours available for professional activities, and very few have time to engage in

research. The more hurdles and regulations are associated with clinical research, he said, the fewer physicians will want to pursue it.

Educating Private Sector Physicians. Dr. Prentice asked panelists to comment on how best to reach physicians in the private sector with education. Dr. Flexner responded by asking who is responsible for overseeing the conduct of their research. He noted that some individuals enroll their patients in protocols to give them access to investigational therapies, while others do so because it is profitable. Currently, it is the sponsor who assumes the larger part of the burden of ensuring that subjects not exposed to undue harm, reflecting poorly on them. Those who enroll patients in protocols that will be subject to FDA review are monitored on a regular basis and may be dropped by the sponsor if they do not know what they are doing.

Dr. Korn added that the fact that so many trials are being conducted outside of academic centers is a compelling reason for incorporating material on the ethical foundations of clinical research into undergraduate medical education.

An FDA Perspective. Dr. Lepay commented that FDA relies on the sponsor to be able to select investigators and ensure investigator education. He doubted that certification alone would ensure compliance but would like to see more information on how existing programs have impacted performance. He agreed with Dr. Korn that education should begin at an early stage. He stressed that FDA is interested in promoting high-level academic and ethical science; he believes doing this will require broader conversations to determine where leverage can be found to achieve this aim.

PUBLIC COMMENT (PERIOD 3)

Dr. Gary Chadwick expressed concern that the committee's vote on the important issue of commensurability had been split, even after months of expert input. He argued that the best solution on this issue would be to recommend to the Secretary that OHRP continue the discussion in this area because no consensus was reached.

He also cautioned that SACHRP avoid making recommendations that stifle new researchers and drive experienced ones from the field. He is concerned that component analysis, for example, may not work in "real life." Regulations should be easy to understand and obey.

Dr. Prentice responded that while he prefers unanimous votes, he believes that the Committee's decision on commensurability reflects the recommendations and spirit of the National Commission; he does not believe it will inhibit the conduct of research. In regard to component analysis, he argued that this is an important way to examine the risk-benefit relationship. He pointed out that nontherapeutic components are too often added to therapeutic trials. He added that SACHRP's goal is not more or less regulation, but better guidance and better regulation. Ultimately, whatever guidance OHRP develops based on SACHRP's recommendations will be submitted for public comment. He feels the guidance under consideration will help investigators, if they are educated properly to understand its implications.

Dr. Weiner stated her belief that the protections discussed in relation to Subpart D will add to protection for children. Ms. Kornetsky emphasized, as Co-Chair of the subcommittee on Subpart D, that the subcommittee itself had full consensus on all its recommendations. She added that research has not come to a halt at institutions that currently use component analysis, including her own.

Ms. Barbara Lidico with the University of Medicine and Dentistry of New Jersey highlighted the absence of regulations to govern the increasing percentage of research carried on in private institutions and doctor's offices. She said many investigators associated with the university indicate they can easily open up their own private practices and conduct their studies as they wish. While her institution holds major national conferences and does thorough investigator training, "it just doesn't seem to be enough without a fully integrated national standard that is one standard for all." Dr. Prentice commented that many people share this concern.

Incentives and Disincentives for IRB Monitoring/Audit Programs

Dennis Swanson, M.A., Director, Research Conduct and Compliance Office, University of Pittsburgh; Ada Sue Selwitz, M.A., Director, Office of Research Integrity, University of Kentucky

Remarks by Dennis Swanson

Mr. Swanson said that the University of Pittsburgh implemented its auditing program in 1997, employing four full-time equivalent auditors to audit human subject research protocols approved by the University of Pittsburgh IRB. All auditors are themselves former research coordinators. The University has about 3,500 to 4,000 active IRB-approved research protocols in progress at any one time, with 550 to 600 new full-board submissions annually.

The auditing program is part of the Education and Compliance Office. It seeks to function as an educational rather than a "policing" program. Auditors conduct both random and for-cause audits. Ast the request of any IRB committee, they may monitor the informed consent process (a more common request on high-risk or complex protocols. They can produce quality assurance audits for the IRB committee, such as checking to see that 100 randomly selected informed consent forms had all the required elements.

Random audits are held for the following reasons:

- To assess adherence to:
  - Federal regulations and standards,
  - IRB policies, and
  - IRB-approved research protocols;
- To ensure that the rights and welfare of research subjects are properly protected; and
- To provide education to HSR investigators.

The highest priority is given to federally or internally funded studies that are of high to moderate risk to research subjects. Subjects that are receiving increased Federal or public scrutiny, such as gene transfer studies, are also given priority. In addition, abbreviated audits are done on protocols for which the IRB approval has expired, but for which the investigator has not officially submitted a termination notice. Clinical trials or studies sponsored by industry or by pharmaceutical companies do not receive priority because an FDA requirement for such studies is an active monitoring program. Also, FDA conducts random audits of the respective clinical trials. The university requires the investigator to provide copies of monitoring results so they can be relayed to the IRB, thus extending the auditing program without using additional resources.

Audits typically last three to four days. Findings are generally presented to the principal investigator first for review and response (though a major problem would immediately be reported to the IRB Chair). The investigator has an opportunity to respond to the findings. Copies are then given to the responsible

administrator (who is more likely to become upset if sanctions are imposed and he or she was not informed of a problem) and to the IRB Executive Committee, which determines whether additional actions or sanctions are needed. Throughout the process, confidentiality must be maintained.

The experience of the program has been that problems at the "noise level" are found routinely – for example, problems with documentation and recordkeeping. Such problems can be dealt with through education. More serious problems must be dealt with more seriously, including reporting to the Federal agencies funding the research. Policies and procedures must clearly distinguish the reportable problems from others that can be addressed through education. Over-reporting of problems that are not serious can change investigators' perceptions of the program and impair cooperation. Consequently, it is advisable to include an internal "stick" short of such reports. An example would be placing a hold on additional enrollment until the issues are addressed. Mr. Swanson recommended that institutions collaborate with OHRP as these policies and procedures are developed.

At the University of Pittsburgh, examples of serious noncompliance reportable to Federal agencies include:

- Performance of non-exempt human subject research without obtaining IRB approval,
- Failure to obtain IRB approval of implemented substantial modifications to an IRB-approved research study,
- Failure to systematically obtain the required informed consent of research participants, and
- Material failure of IRB to comply with Federal regulations governing human subject protections.

Continuing non-compliance that is reportable includes noncompliance that results in

- suspension or termination of IRB approval, or
- replacement of the principal investigator.

The institution's Executive Committee is composed of the IRB Chair, the six IRB Vice-Chairs, university legal counsel, the medical center's legal counsel, and the Director of the IRB Office. Establishing a committee such as this to review audit reports is important to maintain confidentiality and ensure consistency, especially in regard to when sanctions are opposed.

Future directions for the auditing problem will address the need to expand the program's impact, perhaps by auditing departments and reporting issues back to the department. Also, to prevent noncompliance, program staff are considering holding pre-enrollment audits to work with the investigators before problems develop.

Remarks by Ada Sue Selwitz

Ms. Selwitz explained that the auditing program at the University of Kentucky began in 1996 by performing random audits performed by staff members and IRB members. However, audits intended to be educational were not perceived as such by investigators, and the audits also required more time and resources than were available. As a result, the program was scaled down to one dedicated FTE pursuing more limited goals and objectives. The IRB loved this program, but unfortunately it was still not perceived by investigators as a welcome opportunity for quality improvement.

An enhancement award from the National Institute of Health (NIH) provided an opportunity to reassess the program and improve it. Ms. Selwitz reviewed some of the important decision points that such programs must make:

- Who oversees the program? Is it internal or external to the IRB/IRB office, or a combination?
- What are your objectives? Are you primarily interested in compliance, quality improvement, or a combination? (Her program now pursues a combination of these objectives.)
- Who assesses the findings? If findings go back to the IRB, the program will be perceived as compliance-oriented. Now, Ms. Selwitz explained, her program sends only some findings back to the IRB.
- What standard will you use? There are many to choose from, and what you choose dictates what you do.
- What actions should be taken, when, and by whom? What is reportable?

Turning to lessons learned, Ms. Selwitz stressed the importance of not "setting policy through noncompliance." If the institution never properly articulated a policy, it should not punish an individual for noncompliance. She also stressed that the process of quality assurance is labor intensive for all concerned and requires expertise in many areas.

Ms. Selwitz's program currently pursues three objectives:

1. To assess individual protocol or PI compliance as directed by the IRB,
2. To evaluate Office of Research Integrity (ORI) and IRB procedures for compliance and efficiency, and
3. To assist the investigator and staff in complying, monitoring, and responding to external reviews.

The program achieves these objectives through:

- Directed on-site reviews (Objective 1),
- Administrative assessment reviews (Objective 2),
- Routine on-site reviews, as the workload permits (Objective 3), and
- Self-Assessment reviews (Objective 3).

Currently, Ms. Selwitz's program is not able to perform random on-site reviews because the quality improvement person is working on accreditation. However, it has developed a self-assessment form for PI use. The form will be reviewed and staff will work with the PI on areas in which improvement is needed; however, it will not be sent to the IRB unless there is an egregious violation.

Incentives to establish a program like this include the following:

- To ensure compliance,
- To strengthen protections (though it is an unproven assumption that compliance translates into protection),
- To improve efficiency and consistency,
- To demonstrate institutional commitment,
- To strengthen education efforts, or
- To achieve accreditation.

Disincentives may also exist. These could include:

- An existing human research protection culture that is not ready for change,
- Lack of adequate resources/staff and concerns about the impact on staff workload,
- The Impact on researchers and/or IRB workload,
- A lack of QA/QI expertise to carry out the program,
- Institutional concern about reporting to regulatory agencies and regulatory responses,
- Concerns about generating data that could be used in litigation, and
- Lack of regulatory requirements to do this, coupled with lack of resources to address existing regulatory requirements.

DISCUSSION

Response to Reportable Violations. Dr. Prentice observed that while there are no regulatory requirements for any institution to have an auditing program or a means of improving quality, such programs are appearing, possibly in part as a result of accreditation. He noted that there is a concern that if serious or continuing noncompliance is reported to OHRP or to FDA, regulators may respond with audits, creating a problem for the institution. This is a serious disincentive.

Mr. Swanson responded that his approach to concerns about Federal regulators is to "co-opt them" by thoroughly reporting all steps being taken so there is no need for them to come and investigate further. Ms. Selwitz commented that the nature of the violation and concern appear to be factors in the Federal response. She noted that when she did a quality assurance check to find out whether protocols were in compliance with particular guidance, she found that in 3 protocols out of 2,700 a required report had not been done. OHRP's first response was to say the PIs should be shut down. This did not happen, but it was difficult to work through the issues. She stressed the importance of approaching the Federal agencies with a plan for dealing with any identified problems and of the agencies taking the plan fully into account.

Dr. Prentice said that more investigators or coordinators are reporting noncompliance issues at his institution, and he believes it is important to respond to self-initiated reports in a proactive, education, and nonpunitive way, taking corrective action. Dr. Lepay explained that when FDA receives information on noncompliance, the agency considers the nature of the violation, how longstanding it is, how quickly it was recognized, and the nature of the corrective plan in forming its response. Sometimes a situation is a recurrent one that indicates something is wrong at a fundamental level and must be responded to accordingly. Other times the agency does choose to work with the institution to help it enforce its own sanctions. The aim is to work reasonably to improve the system. Speaking for OHRP, Dr. Schwetz stressed that the agency must respond to the problems of which it becomes aware.

Ms. Selwitz invited Ms. Shirley Hicks, who directs OHRP's Division of Education and Development, to comment from her experience with the Quality Improvement Program initiated in 2002. She wondered how OHRP handled egregious violations discovered in the course of a voluntary review performed at the request of an institution for the purpose of quality improvement. Ms. Hicks explained that program staff routinely identify "noise level" compliance issues that are addressed through education and guidance. Fortunately, staff members have not yet encountered serious or continuing noncompliance. If this is found, the IO will be informed, corrective actions will be identified, and the institution will be advised to self-report. Dr. Schwetz will also be informed of the findings, and the IO will be made aware that this step will be taken.

Investigator Response. Ms. Kornetsky asked speakers to comment on the feedback received from the investigator community on their programs. Ms. Selwitz said she is getting good feedback on the new self-

assessment form. However, only a handful of people have availed themselves of this service. Few people express appreciation for the reviews, however, since they are (correctly) perceived as, at least in part, compliance oriented. Ms. Hicks said OHRP's program gets mixed feedback from investigators, depending on how the program is set up and the attitudes of people involved; however, some do find it educational and helpful.

Liability Concerns. The Chair highlighted the reported concerns about the use of data in litigation as a serious disincentive to quality improvement initiatives; if a plaintiff files a lawsuit and the lawyer learns of the auditing program, he said, the lawyer will definitely request the results of any audit of the profile in question.

In regard to such liability issues, Mr. Swanson suggested that people with such concerns should perhaps not be doing human subject research. Ms. Selwitz added that after consulting with her legal counsel, she avoids keeping a paper trail that would benefit an investigator suing the institution. The legal counsel also advised her that having such a program demonstrates the institution's commitment to meet or exceed standards.

Detecting Precursor Events. Dr. Schwetz suggested that audit programs such as those described might eventually become "smart" enough to be able to detect accident precursors rather than noncompliance and teachable moments; this would be a significant system advance. Dr. Weiner invited speakers to comment on precursor events they can identify through available data. Mr. Swanson responded that sloppy submissions and data keeping are a common cause for concern. Sponsors of device trials, he said, do not do a good job of monitoring and advising investigators such as surgeons, who are often unfamiliar with requirements of research.

Wrap-up and Adjournment

The Chair expressed gratitude to SACHRP's subcommittees, noting that those who have not attended their meetings cannot possibly appreciate how hard they are working. Looking ahead, Dr. Prentice recalled that SACHRP's August meeting will have a major focus on public advocacy groups, which will be invited to express their concerns. SACHRP is expecting an eventual report on the Central IRB initiative, on which OHRP is moving ahead. He is also pleased with the progress of Federal efforts to address issues related to adverse event reporting. A report from the IOM committee exploring ethical foundations for prisoner subjects will also eventually come to SACHRP for review and consideration.

Noting that the IO is the weakest link at some institutions, he suggested that OHRP consider organizing a conference specifically designed to attract these individuals and educate them on their roles.

He noted that SACHRP has been invited to write the AAMC and encourage them to address issues related to investigator education and certification. Further discussion is needed about this possibility.

Secretary's Advisory Committee on Human Research Protections
April 18-19, 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 by _____ August 1, 2005
Ernest D. Prentice, Ph.D., Chair Date