Secretary's Advisory Committee on Human Research Protections
March 13 and 14, 2006 – Alexandria, VA

Minutes

MONDAY, MARCH 13

Welcome and Opening Remarks
Ernest Prentice, Ph.D.

The Chairman welcomed everyone to the meeting and introduced a new member of the Secretary's Advisory Committee on Human Research Protections (SACHRP), Dr. Neil Powe. He reminded attendees of SACHRP's Charter, issued on September 8 of 2004, which comprises protection of human research populations, especially vulnerable populations such as children and prisoners.

SACHRP works closely with staff members of the Office of Human Resource Protections (OHRP), who act as liaisons on SACHRP subcommittees. Dr. Prentice thanked *ex-officio* members of SACHRP. He also expressed appreciation to all OHRP staff who work in partnership with SACHRP.

The Chairman provided an overview of charges to existing SACHRP committees. He noted that the subcommittee on Subpart D has been very active and observed that the new subcommittee on Subpart A is likely to have a long tenure.

Minutes for the previous meeting (November 1-2, 2005) were approved unanimously. Dr. Prentice then reviewed the agenda for the day.

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

Status of SACHRP Recommendations. Dr. Schwetz summarized the status of SACHRP's recommendations to the Secretary of the Department of Health and Human Services (HHS) as well as the status of activities of concern to SACHRP. He reminded SACHRP that three sets of recommendations have gone to the Secretary (Secretary Thompson, then Secretary Levitt).

The first set of recommendations went to Secretary Thompson in July of 2004. These related to research involving children, the §407 process, accreditation, and the recommendation for an Institute of Medicine (IOM) panel in regard to Subpart C. Dr. Schwetz reported that a new §407 process is in place, with new guidelines. There is a good working relationship between OHRP and FDA when a joint process is required. In regard to accreditation, SACHRP suggested a conference to address key issues such as self-regulation. Dr. Schwetz noted that accreditation has been a dynamic and rapidly evolving process, and it did not seem to be the right time for a conference; the idea is therefore on hold. The Subpart C committee reported that Subpart C might be "broken" and in need of major changes that could not be accomplished through guidance alone. OHRP is therefore funding a committee through the Institute of Medicine to review the ethics of conducting research in prisoners. A report is expected later this year.

The second set of SACHRP recommendations related to the need to harmonize the Common Rule with the Health Insurance Portability and Accountability Act (HIPAA) in regard to research. This recommendation has been sent to the Office of Civil Rights, which is still working on the issue.

The third set of recommendations, which originated in July of 2005, has just been returned to OHRP for action by the Office of the Secretary. A number of issues were to be addressed, including the wider range of jurisdiction within Subpart C and the consideration of the standard of care for protocols involving prisoners. The recommendations also included a number of recommendations related to research involving children and the recommendation to form a Subpart A Subcommittee (now at work.).

OHRP has also acted on SACHRP's recommendation that a workshop be held on IRB review strategies. Also, the FDA has been working on draft guidance relative to central IRBs and on the use of central IRBs relative to FDA regulator products. FDA has finalized the document and it will soon be printed in the *Federal Register*. On international issues, OHRP has arranged two sessions for SACHRP to air and explore related issues. OHRP has also followed through on SACHRP's recommendation to issue guidance on adverse events. Draft guidance was issued, and the agency is currently assessing the comments received. FDA is at work on its guidance on the same subject and has held a Part 15 hearing to get advice from the community on this key topic. In addition, Amy Patterson of the National Institute of Health (NIH) and others have formed a Federal Adverse Events Task Force to try to coordinate the handling of adverse event reports and related activities among agencies. The group is finalizing a document for discussion and the activity continues to move forward. OHRP also coordinated presentations for SACHRP on patient advocacy and litigation, which were informative but did not result in any specific, defined action.

Status of SACHRP Nominees. Five new members will be invited to replace SACHRP members who are now leaving. OHRP expects these members to be confirmed by the mid-year meeting of SACHRP in August. Four additional new members will be needed in 2007, which means that there will be considerable turnover on a committee that has been working well. A *Federal Register* notice will be issued this month inviting either self-nominations or nominations of others. Recommendations from SACHRP and audience members are welcome and can be accepted either through or independent of the *Federal Register* process.

Status of the SACHRP Charter. The charter for SACHRP is set to expire on October 2nd of this coming fall. OHRP is awaiting action by the Department on its recommendations for revisions to the charter. Dr. Schwetz has heard nothing to indicate that SACHRP would not be reauthorized.

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

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

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

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

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

Showing a picture of an angel crouched uneasily on a bowling pin, Ms. Nelson observed that IRBs are spending less time protecting human subjects and more time trying, in effect, to balance on the head of a pin. He also commented that while IRB audiences generally appreciate SACHRP's work, he finds glazed eyes among investigators and academicians when he addresses the same subjects. He stressed the importance of keeping the "big picture" in focus as SACHRP proceeds with its deliberations.

Continuing Review (CR)

Mr. Nelson reminded SACHRP that of the 16 recommendations brought forward by the subcommittee at the meeting in November of 2005, 9 have been approved and 7 tabled. Only items that have not been approved were presented for further consideration in this presentation. He also reminded SACHRP that the requirement for CR is a legacy of the infamous Syphilis Study; lack of CR allowed it to go on for decades, long after effective treatment for the disease was available. The provision for CR was intended to prevent research continuing in the face of unacceptable harm, futility, or scientific or ethical obsolescence. The Co-Chair observed that CR plays a central but often undervalued role in the IRB process.

Regulations related to how CR should be conducted are "rather sparse," and there is considerable uncertainty and variability in how IRBs should interpret and apply them. The only section of the Common Rule that addresses the continuing review process with any detail says in its entirety: "An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research" (§46.109[e]). The most recent guidance on CR from HHS was issued in July 11, 2002 and includes no specific instructions to IRBs on how to establish rules and policies to address the CR requirement. In comparison to HHS guidance, FDA guidance is relatively permissive. Mr. Nelson found considerable uncertainty and variability in how IRBs interpret and apply the "rather sparse" regulations pertaining to CR.

When can Continuing Review Stop? The Co-Chair posed the question of whether CR must continue as long as identifying data exist or whether there is a prior point at which the IRB and investigator can close the study file. He observed that HHS regulations do not address this issue and that HHS and FDA have different operational definitions for what constitutes human subjects research – a difference that complicates not only CR, but the oversight of research in general.

Several examples of instances in which "interminable" CR is not valuable include minimal risk social science surveys; individual sites in multicenter trials after activity ceases at the site, though it continues elsewhere; and cooperative group studies that remain open solely to collect survival data. In fact, he held that every study reaches a point at which CR ceases to add value and contribute to the protection of human subjects. Mr. Nelson observed that many investigators remain in possession of

identifiable data long after the study is closed. IRBs currently follow different practices on when to declare a study complete. The subcommittee brought forward the following recommendation:

> **Recommendation 1.1.** *OHRP should clarify its guidance on the required duration of CR. CR may end when all research interventions and interactions with subjects are over and data collection for research purposes is complete, as described in the approved study plan/protocol, at the research site for which the IRB has oversight. The IRB must have reviewed and approved the investigator's plan for data analysis and the safeguards in place for confidentiality protections. The investigator still retains the responsibility to notify former subjects and the IRB if subsequent analyses and/or new information raises concerns about rights, safety, and welfare of human subjects.*

DISCUSSION

SACHRP members discussed the recommendation and raised the following questions.

The Chairman asked why the IRB should continue to be in the loop when a study has been closed for a decade, given that the IRB may in fact have destroyed relevant records. Dr. Gyi responded that the subcommittee did not consider logistics, but asserted that it would still be incumbent on the IRB to determine how an issue that arises after records have been destroyed should be addressed.

Dr. Fisher understood that as long as the researcher has the records of individuals' identities, the research would remain under the IRB's review. She asked for clarification of what is actually required and to what extent the regulations create an obstacle to stopping CR. Mr. Nelson explained that a person becomes a human subject whenever data is collected, regardless of whether the individual knows that data are being collected. This triggers the need for protection. At some point, however, he suggested that active oversight ceases to add value. Dr. Prentice further explained that even though data may be retained, when analysis described in the protocol stops, research may also be considered to have stopped. Dr. Fisher agreed but asked whether the recommendation is really different from existing guidance. Dr. Carome affirmed that the guidance would be a new direction, since OHRP has long stated that the use and analysis of identifiable private information from living subjects constitutes research. Mr. Nelson clarified that the intent of the recommendation is that data analysis might in fact continue for years, and CR would not be triggered unless subjects are re-engaged in the process.

Balancing the concern about protection of human subjects when identifiable information is used and the desire to reduce the administrative burden, Dr. Fisher asked whether there might be a way to streamline CR. Ms. Selwitz said that in fact IRBs do expedite review under such circumstances, but a substantive review is still required, albeit by fewer people. She also pointed out that most IRBs have an electronic record that is maintained for a long time; therefore, it would be possible to manage issues that arise after CR has ceased.

Dr. Fisher expressed concern that the recommendation does not allow for oversight of a sloppy investigator who may fail to report an emerging problem. Dr. Gyi observed that oversight of an investigator-initiated study might be different than oversight of a multi-center study in which the investigator holds data, but may not play a part in data analysis. Mr. Nelson added that the qualitative assessment that an ethnographer performs might also go on for years.

Dr. Powe asked what would happen if a colleague wishes to use identifiable data that have already been collected. Dr. Prentice responded that such use would require a new proposal that would have to be reviewed by the IRB. Dr. Powe wondered whether the recommendation might have the unintended consequence of increasing burden on IRBs if there were new investigators.

Ms. Kornestsky said she felt comfortable with the recommendation, since identifiers would typically be removed from the primary data. However, if the investigator forgot a data point, the IRB would need to become involved. Dr. Fisher agreed with Ms. Kornetsky and wanted to see more explicit language specifying this assumption. She said it was important that the situation covered be one in which, while the link might exist between the data being used and a code book, the current researcher does not use that link.

Dr. Prentice suggested amending the recommendation to encompass situations when "data collection and analysis for research purposes are complete as described in the approved protocol." Dr. Gyi said such an amendment would mean that IRBs overseeing FDA-regulated products would have to continue to provide oversight until the sponsors have completed that analysis. Dr. Prentice held that such analysis would not be described in the protocol since the site investigator is not doing it, but Dr. Gyi said data analysis in commercially sponsored protocols often would be described in the protocol and might take years to accomplish.

Dr. Prentice asked how OHRP guidance justified the apparent inconsistency of saying that research is continuing when the IRB is out of the loop but that it is not continuing when "because of a technicality" the investigator does not have the data for analysis. Dr. Carome said he saw no inconsistency; sites that are not engaged in analysis of identifiable information would not be considered to be engaged in research. However, he said OHRP was not *a priori* rejecting the recommendation.

Dr. Powell asked how the recommendation would apply to an industry trial in which samples are being collected periodically for biomarker analysis. Dr. Prentice said this would constitute further collection of research data, so the recommendation would not apply. However, routine follow-up with patients that does not involve the collection of data for research purposes could continue.

Dr. Fisher suggested adding a provision that analyses for research purposes must also be complete. Ms. Selwitz said that would mean that the status quo would continue and the recommendation would be unnecessary.

ACTION

Recommendation 1.1 was approved without changes.

Circumstances when CR can be Conducted less often than Once per Year. Mr. Nelson raised the question of whether circumstances exist under which continuing review could appropriately be conducted less often than once per year. He commented that the preamble to the original regulations stated that "the precise procedure adopted by the IRB for continuing review without unnecessarily hindering research should be left to the discretion of the IRB." The preamble also stated that appropriate reporting would vary depending on risk from a "simple annual notification" to "more frequent reporting" or, for clinical trials, a "special mechanism to carry out data and safety monitoring functions." Regulations require that continuing review should occur "not less than once per year," but the content of the process is not specified.

The subcommittee felt that the requirement for an annual review limits IRB flexibility to employ appropriate procedures and criteria. It therefore proposed the following recommendation:

> **Recommendation 2.1**. *OHRP should issue an Advance Notice of Proposed Rule Making (ANPRM) to seek comments regarding changing section 46.109(e) to allow IRBs latitude in setting review dates beyond one year (but not more than two years) for minimal risk studies, but potentially for other studies as well.*

Mr. Nelson explained that this recommendation is the only one that would require a regulatory change. He suggested that OHRP issue an advanced notice of proposed rule making to seek comments on the issue. The same notice would also seek comments on the following:

> **Recommendation 2.2.** *In the interim, OHRP should also seek comments on the regulatory application of §46.111 to CR and/or adding a new section that would define simplified criteria and the expectations for the content of CR being based upon current risk level.*

> **Recommendation 2.3.** *In the interim, OHRP should revise its interpretation and develop new guidance to permit IRBs to develop, within their written procedures, policies and procedures for the selective application of section 46.111 to CR. FDA guidance should likewise be updated.*

DISCUSSION

Dr. Prentice pointed to an apparent contradiction between the subcommittee's recommendation that OHRP seek comments on the issue and the recommendation that, in the interim, IRBs be permitted to develop their own procedures. Mr. Nelson and Dr. Gyi explained that it was the committee's wish to do something in the interim to provide flexibility. Dr. Prentice questioned the need for OHRP to go through the advanced notice of proposed rule in regard to Recommendations 2.2 and 2.3; instead, he suggested, the recommendations could focus exclusively on the need for guidance that is relevant to the nature and risk level of the project.

Ms. Kornetsy agreed with the Chairman's suggestion. However, she was concerned that if IRBs were given the latitude to begin developing their own procedures and then comments result in tightening, it would appear that OHRP is being restrictive and over-regulating. She felt that OHRP probably has the authority to issue guidance about what elements should be applied. Ms. Selwitz agreed.

ACTION

SACHRP approved Recommendation 2.1 without changes.

Recommendation 2.2 and 2.3 were approved, with the understanding that they would be rewritten to eliminate the need for an advanced notice of rulemaking and proceed directly to the development of recommended guidance based on the nature of the research, risk level, and other considerations.

An approximate rewording follows:

> *OHRP should revise its interpretation and develop new guidance to (1) define simplified criteria and the expectations for the content of CR based upon current risk level and (2) to permit IRBs to*

develop, within their written procedures, policies and procedures for the selective application of section 46.111 to CR.. FDA guidance should likewise be updated in regard to (2).

Can Existing Guidance be Consolidated? The subcommittee addressed the question, "can existing guidance on continuing review be consolidated and integrated?" While OHRP has come a long way in this regard, the subcommittee feels that the absence of consolidated guidance makes regulatory compliance more difficult than necessary, sometimes requiring IRBs to explore extensive case law. When the recommendation was previously presented to SACHRP, the subcommittee was asked to consider removing any reference to common practice or best practice. This has been done, yielding the following recommendation:

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

Mr. Nelson stressed the need for "simplified, unified, and practical guidance for CR."

DISCUSSION

Dr. Prentice clarified that the recommendation means that current OHRP guidance should incorporate guidance that has been issued in the form of OHRP determination letters. He asked the Co-Chair to clarify whether Recommendation 2.2 and 6.1 are viewed as distinct or as two related points that should be integrated. Mr. Nelson saw the two as separate; Dr. Gyi indicated that the two could be blended, but felt there was merit in separating them.

Dr. Prentice also asked for the subcommittee's perception of the difficulty of accomplishing this goal. The Chairman observed that he did not know the status of the revisions to FDA's information sheets. Mr. Nelson replied that the recommendation as it stands is focused only on OHRP guidance.

Dr. Fisher understood the advantage of consolidating available guidance but was not sure whether the distinction between "case law" and actual guidance could be made. Mr. Nelson stressed that the elevation of single cases to "*de facto* guidance" is a difficulty; what was intended as example sometimes becomes a requirement, whether or not this was intended. Ms. Kornetsky suggested that this concern would seem to apply to all guidance rather than the specific issue of continuing review. Dr. Prentice concurred and saw this as a potential problem. Ms. Selwitz also saw this as a universally applicable concern. Dr. Gyi and Mr. Nelson conferred and removed the recommendation from consideration.

Flexibility in the Timing of CR. Mr. Nelson addressed two questions:

- Does current HHS guidance on setting the date of continuing review (the "30-day rule") need to be changed to allow more flexibility in the timing of review?
- How should temporary lapses in approval be handled?

Under guidance issued in 2002, "OHRP recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project when continual review occurs annually and the IRB performs continual review. Within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur." In practice, he argued, the so-called "30-day rule" has proved logistically problematic. A substantive and

meaningful review requires time for the IRB to ask questions, for investigators to respond, and for the IRB to seek further clarification if need be. The 30-day window may result in lapsed approval. Also, many IRBs send reminder notices before approval period expires; if an investigator responds promptly, information may become stale. The subcommittee felt that a 60-day rule would be more likely to avoid automatic lapses and enable IRBs to be more responsive to prompt submissions by investigators. Accordingly, the following recommendation was brought forward:

> **Recommendation 10.2.** *OHRP should revise its "30-day rule" to remove unnecessary restrictions on IRBs in scheduling continuing reviews. If a defined time window is deemed necessary, 60 days would be more appropriate.*

DISCUSSION

Dr. Prentice observed that the 30-day rule appears inconsistent with the regulatory language; if the period is extended to 60 days, then the next year might conceivably have a 14-month approval period. The Chair asked OHRP to clarify how the 30-day rule fits in with regulatory requirements in scenarios in which an investigator submits early in one year but not the next. Dr. Carome responded that the 30-day rule goes back at least 10 years. OHRP staff felt that over the life of a multi-year project, on average the protocol would be reviewed at least annually. Dr. Carome believed the same rationale would likely apply for a 60-day period.

The Chairman also questioned how many IRBs actually use the 30-day rule; his, he said, does not. Ms. Selwitz believed that most high-volume IRBs do not use the rule, and even moderate-volume IRBs may not do so. It is an important rule for low-volume IRBs that are not likely to meet every month. Ms. Kornetsky added that when a substantial review is done and concerns are raised, 30 days is not a long period of time to address issues that may arise thoughtfully. It takes time to generate letters and assess the response. She felt the 60-day period would be more reasonable. Dr. Gyi commented that larger-volume IRBs that get information ahead of time simply recalibrate the approval date to the date of the meeting. He added that although research must be suspended when time frames are violated, guidance does not require a report to OHRP; the matter is handled locally.

The Chair suggested that when a CR process is already in place and the application for CR is under review, requests for clarifications or modifications should not result in a suspension. He said it should not be necessary to suspend a project simply because it is "two days out of sync." Mr. Nelson responded that Recommendation 10.3, which stated that automatic study suspension was not required when the process was underway, had been withdrawn by the committee as "effectively obsolete" in view of other recommendations; however, it could be reintroduced if it appeared necessary. While the subcommittee felt the 60-day period would supply the leeway necessary to avoid lapses, the Chair felt that the withdrawn recommendation was important for the institutions that do not follow the 30-day rule at present. Recommendation 10.3 was therefore reintroduced.

ACTION

Recommendation 10.2 was approved.

> **Recommendation 10.3.** *OHRP should modify guidance so that when continuing review is underway, automatic study suspension is not required when the expiration date passes before review and approval are complete. Guidance should specify strategies to prevent routine delays*

and open-ended review, and specify conditions and activities that will be permitted in such circumstances.

DISCUSSION

Dr. Prentice placed on the table an additional concept called the "post-30 day rule" which would allow an extension of IRB approval before mandatory expiration, providing that the IRB is already engaged in a substantive process of continuing review. This would apply if the application is legitimate but there are a few questions or issues to address.

Mr. Kornetsky was in favor of the concept, but felt the meaning of continuing review being "underway" should be pinned down. Does it mean, for example, that the investigator got the documents to the office but too late for the next agenda? Dr. Prentice said he believed the review process should have begun so the application is actually under review, whether by the full committee or select reviewers for expedited review.

Dr. Fisher stressed the importance of articulating the reason for the recommendation, particularly in regard to the potential benefits to human subjects. She would be concerned to see the recommendation used to benefit an investigator who simply did not respond on time, but she saw the benefit of avoiding a study suspension that might harm participants. Dr. Prentice responded that whenever the IRB reviews an application and finds significant problems, it is obligated to suspend approval until problems are corrected. He added that the current position of OHRP is that all activities must cease when IRB approval expires. However, the IRB can approve the continuing participation of human subjects if it is in their best interest. The Chair felt the leeway offered by a 30-day extension might especially be helpful for behavioral science studies where it is not possible to prove that participation is clinically in the subjects' best interest, but the risk-benefit ratio would be affected negatively. Ms. Selwitz observed, however, that even low-risk research may still have potential benefits. Sometimes delays occur because of very minor changes, and the leeway would help. It would still be up to the IRB to act in the best interest of the subjects.

Dr. Jones added the subcommittee believed a benefit of the recommendation would be that it would allow time for "substantive reflection" when needed. Dr. Fisher agreed that the recommendation might improve human subject protections by allowing time for a more informed dialogue between the investigator and the IRB. However, she wanted to be sure that investigators who simply get their material in too late are not rewarded, and she felt existing language was too open-ended.

Members felt the recommendation was not ready for a vote and should be reconsidered by the subcommittee. It was therefore tabled. If need be, previously approved recommendations might be reconsidered.

Expedited Review

Mr. Nelson reminded members that HHS and FDA regulations provide for an expedited review procedure under which the IRB Chairperson (or one or more experienced IRB members designated by the Chairperson) may approve research in categories appearing on a list published in the *Federal Register* and found by the reviewer to involve no more than minimal risk. The same process may be used for minor changes in previously approved research that arise during the period for which approval is authorized (one year or less). Expedited review should be as rigorous as full review, but with fewer reviewers; it is *not* "review lite." Reviewers may exercise all the authorities of the IRB

except disapproval, which requires action by the full IRB. All of the applicable requirements for approval must still be met.

The subcommittee felt that expedited review is a valuable mechanism; using this process for minimal risk research frees the time and resources of IRBs and allows them to be concentrated on protecting subjects facing the greatest levels of risk. However, sometimes changes are received that are purely administrative, such as correction of typographical errors or updated contact information for investigators. Currently, low-impact changes in previously approved research must be handled by expedited review or full convened review, which does not contribute meaningfully to the protection of human subjects and may actually reduce such protections by diverting IRB time and effort from more substantive considerations. Accordingly, the following recommendations were presented.

> **Recommendation.** ***Processing of Administrative Changes (1).*** *Implementation of changes to approved research that are solely clerical or administrative should not require convened or expedited IRB review. OHRP and FDA should issue guidance permitting IRBs to define in their written policies and procedures changes to approved research that can be processed by qualified IRB staff.*
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> *Such changes should be limited to those that are entirely clerical or administrative in nature and have no effect on the conduct of the research, its underlying science or methodology, associated risks and benefits, or the potential willingness of subjects to continue participation (e.g., correction of clerical or typographical errors; changes to telephone numbers, addresses, and other contact information; renumbering of pages or sections without changes in content; other changes, as defined in written IRB policies and procedures, that clearly have no effect on the conduct of the research, its underlying science or methodology, associated risks and benefits, or the potential willingness of subjects to continue participation).*
>
> **Recommendation.** ***Processing of Administrative Changes (2).*** *IRBs should be encouraged to give appropriately qualified staff authority for clerical and administrative functions.*

DISCUSSION:

Both recommendations were readily approved with the following "friendly amendment": Recommendation 2 will be reworded to state that "IRBs may give…" rather than "should be encouraged to give…". Dr. Fisher felt that IRBs should be able to make a decision about whether or not they want their own members to carry out such functions.

New Term for Expedited Review. The subcommittee explored the question of whether the term "Expedited Review" should be revised to better reflect intent and process. The term "expedited review" is widely misunderstood to imply increased speed and decreased thoroughness of review. Nevertheless, the spirit and letter of the regulations requires that expedited review be as substantive and meaningful as convened meeting review. Criteria for approval and the requirements for informed consent are identical. The only difference is that one or more experienced IRB members are delegated to perform the review on behalf of the entire membership. Analogous oversight bodies for animal research (Institutional Animal Care and Use Committees [IACUCs]) use the term "designated review" instead. Mr. Nelson argued that a term other than "expedited review" would remove misconceptions about the supposed expedience if this type of review, while emphasizing that it is based on the delegation of authority by the full IRB to the chairperson or other member.

Recommendation. ***New Term for Expedited Review.*** *OHRP and FDA should initiate the process of modifying HHS and FDA regulations to replace the term "expedited review" with the term "delegated review," which more accurately describes the process and regulatory intent.*

Recommendation. ***Harmonization.*** *SACHRP is requested to encourage all agencies under the Common Rule to harmonize this and other changes.*

DISCUSSION

The Chair questioned whether the second recommendation's reference to "other changes" was appropriate in this context because of its broad scope.

Dr. Fisher saw the recommendation to change the term as a "trivial" one that does not increase human subject protections. Dr. Prentice, however, commented that investigators often do have the misapprehension that an "expedited" review must be briefer, simpler, or less detailed. It therefore may give them the wrong impression about human subject protection and their obligations. Ms. Kornetsky pointed out, however, that numerous documents would have to be changed at considerable cost. The Chair directed, however, that SACHRP should make the recommendations it believes make sense without considering the regulatory impediments. Dr. Gyi added that this recommendation would be packaged with others; it would be up to OHRP to react to the recommendations, including deciding on the most efficient and best use of its own resources.

The recommendation regarding the new term was approved with four persons in favor and three abstentions. The recommendation regarding harmonization was approved with rewording similar to the following: *SACHRP encourages all agencies under the Common Rule to harmonize with the new terminology (i.e., delegated rather than expedited review).*

"Not Exactly" Expedited Review: The subcommittee explored the following questions:

- Do minor stipulations 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 other primary reviewer be given the authority to make discretionary judgments on behalf of the IRB?
- Should such mechanisms be considered a form of expedited review and, if so, how should the expedited review procedures be applied in this context?

Mr. Nelson explained that a common outcome of convened IRB review is a list of minor stipulations or contingencies that must be resolved before the IRB grants final approval. Guidance on how to handle such issues with confidence is difficult to find and appears to exist only in determination letters where it is not readily accessible. An OHRP determination letter stipulates that "only when the convened IRB stipulates specific revisions requiring *simple concurrence* by the investigator may the IRB chair or another IRB member designated by the chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure." OHRP has also cautioned against approving research contingent upon "*substantive modifications or clarifications*" that are directly relevant to the determinations required by the IRB without requiring additional review by the convened IRB. It remains unclear, however, what qualifies as "simple concurrence" as opposed to a "substantive" modification or clarification. Another source of potential confusion is the use of the term "expedited review" to refer to "contingent approval."

The subcommittee concluded that current OHRP policy is overly restrictive; the IRB should have the discretion to rely on qualified staff under appropriate circumstances rather than require full board review. The subcommittee therefore recommended the following:

> **Recommendation. Final Approval of Stipulations from Convened IRB Review.** *OHRP and FDA should issue expanded guidance*
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> > *(a) clarifying that final approval of stipulations from convened meeting review (i.e., "contingent approval") is not a form of expedited review, and*
> >
> > *(b) permitting IRBs to describe in their written policies and procedures "stipulation mechanisms" for verifying changes required for approval of proposed research under which mechanisms under which (i) the IRB Chairperson, or designated member-reviewer, may exercise reasonable judgment in verifying that the stipulations of the convened IRB have been satisfied; and (ii) a qualified IRB administrator may verify that the investigator has implemented specific language (e.g., in the protocol, informed consent document, or advertisements) dictated by the convened IRB (and requiring no subjective judgment on the part of the administrator.*

ACTION

The motion was unanimously approved without discussion.

Subcommittee Considerations on Investigator Responsibilities

The Co-Chairs then turned to additional issues under concern by the Subpart A Subcommittee (SAS), the first of which is investigator responsibilities. The subcommittee endorsed the principle that investigators have the primary responsibility for protecting the rights and welfare of their subjects, but there was no consensus on a proposal that would define areas of specific responsibility and insert them in the regulations. Some members felt that while investigators are key protectors in the protection of human subjects, the regulations may send a message that primary responsibility for protecting subjects lies with institutions and IRBs. While HHS regulations implicitly refer to investigators throughout, they explicitly identify them only in the section that deals with informed consent. FDA regulations, on the other hand, include sections that address investigator conduct and responsibility.

SAS considered a proposal that would insert new regulations aimed specifically at investigators into 45 CFR 46. The proposal would state that they have specific areas of responsibility, including qualifications and resources, medical care of subjects, communication with the IRB, compliance with applicable regulations, research products and procedures, assuring informed consent, and reporting. However, after considerable discussion and debate, SAS found no consensus on the need for or advisability of additional regulations. The principle that investigators do have primary responsibility for protecting the rights and welfare of their subjects was endorsed, but many subcommittee members felt that investigator training was a sufficient alternative to new regulations.

Dr. Jones added that the subcommittee agreed that investigators need to be at the table and offer their viewpoint. She did not feel that training in itself was likely to have a strong impact on the culture, but she was also concerned that regulations would be seen as externally imposed. She felt the question should be recast to encompass a variety of possible ways of achieving the goal of increased social

responsibility on the part of investigators. The Co-Chairs explained that it was their intent to continue to discuss the issue and to engage in conversations with investigators, as with other stakeholders, as recommendations are developed.

Subcommittee Considerations on Minimal Risk

Mr. Nelson reported that the subcommittee continues to address the complex topic of minimal risk. . In order to address a wide range of key concerns, the subcommittee plans to prepare a short guidance document that will set forth for SACHRP consideration the most problematic elements in the regulatory definition and the most difficult elements for IRBs and investigators to handle. This will include such issues as whose daily life is referenced as a standard in the definition, the choice of an absolute or uniform vs. relative standard for assessing risks, and the concept of risk equivalence. The document will include examples of common research scenarios. The subcommittee does not envision rewriting the current definition but does see a need to clarify how it should be applied.

Expedited Review of Social and Behavioral Research Activities

The subcommittee endorsed a recent report, "Expedited Review of Social and Behavioral Research Activities," which was prepared by the Social and Behavioral Working Group of the Human Subjects Research Subcommittee and approved in November 2005. The subcommittee is impressed with the report and grateful for its contribution.

Dr. Barratt and Dr. Schwetz are co-chairs of the Human Subjects Research Subcommittee. Dr. Barratt noted that the document will need a further review by the Committee on Science before it becomes a public document.

The document will be made available for review by SACHRP members for the next meeting with a view to possible endorsement by the committee as a whole.

Harmonization of Guidance

Mr. Nelson highlighted the fact that harmonization of regulations, interpretations, and guidance across agencies is critical to the success of SACHRP efforts. He also noted that participation by agencies in addition to OHRP has been extremely helpful to subcommittee deliberations. However, members feel the subcommittee would benefit from more active participation. The subcommittee therefore brought forward this recommendation:

> **Recommendation. Harmonization of Guidance.** *SAS requests that representatives of ex officio agencies, including but not limited to the Food and Drug Administration (FDA), be encouraged to attend Subcommittee meetings.*

The Chair suggested that Dr. Schwetz encourage *ex officio* members to attend SAS meetings.

Recognition of Departing Members/Swearing in of New Member
Ernest Prentice, Ph.D.; Bernard Schwetz, D.V.M., Ph.D.; Admiral John O. Agwunobi, M.D., M.B.A, M.P.H.

Dr. Schwetz introduced Admiral Agwunobi, Assistant Secretary for Health of HHS, noting that the

protection of human subjects of research is a high priority for him. Dr. Prentice welcomed the Secretary and invited him to make comments.

Assistant Secretary Agunobi thanked SACHRP for the invitation and briefly reviewed some of the experiences in his career that increased his awareness of the importance of human subject protection. He explained that as a pediatrician, he served in a small hospital that treated children who had special health care needs, many of whom orphan diseases or particularly complex clinical situations. Through the course of their lives, they often were exposed to the benefits of research, and he would advocate in their behalf as their clinician. He later served as the chair of a hospital ethics committee, where he learned that no two situations were ever going to be the same and that the whole field of ethics was a moving concept that "rolls over time across changes in community values and principles," as well as across changes in science. In Florida, he joined an entity that was in effect an IRB for the State; it reviewed research protocols for both adult and children who were under the care of the State government. He was called to serve as Chair during a period when "clean up" was needed and was struck by the dedication and professionalism of the OHRP staff who were involved. As a "perpetual student of this process," he is interested in learning how it works, how things are deliberated, what the issues really are, what the priorities are, and future directions. He recognized the dedicated community of advocates and experts who serve on SACHRP and others present in the room and assured them that the subject is one of importance to the Secretary of HHS.

The Assistant Secretary told SACHRP that the Department is engaged in a number of "transforming initiatives." These include the American Health Information Community (AHIC), which seeks to transform the health system through a dramatic increase in the use of health information technology and the development of countermeasures to ensure pandemic influenza preparedness. He stressed that rapid change is occurring and SACHRP plays an important role in "making sure that we do it right the first time." Dr. Prentice responded with the observation that while the regulations have remained largely unchanged since 1981, their interpretation has been continually evolving, making everyone a "perpetual student" of human subject protection.

Dr. Prentice recognized departing members Felix Gyi, Susan Kornetsky, and Ada Sue Selwitz. He acknowledged Dr. Gyi as an analytical, thoughtful individual who helped resolve many difficult issues; Ms. Kornetsky as a well-recognized IRB administrator and expert on IRB review of pediatric research; and Ms. Selwitz as a "star" in the IRB world who is both intuitive and committed. He thanked each of them for contributing to SACHRP. Secretary Agwunobi presented plaques of appreciation to each of the departing members and expressed the Department's gratitude for their service. Dr. Mary Lake Polan, who was unable to attend, was also thanked for her contribution.

A new SACHRP member, Dr. Neil Powe, was sworn in by Admiral Agwunobi.

DISCUSSION

SACHRP members were given an opportunity to make comments or ask questions.

Ms. Selwitz said she was reassured by the Assistant Secretary's comments on HHS's commitment to human research protections. She explained that the Subpart A Committee is struggling to balance the need for protection of human subjects against the potential for unnecessary regulatory burden and invited the Admiral's perspective. He shared his reflections, based on his experience as the Chair of a Florida group seeking to improve access to research for minorities, that the system for regulatory

oversight appeared complex, with multiple layers. He has seen the need for balance first-hand and recognizes the need to reduce complexity where it is possible. In this effort, it is important to have feedback from those "downstream" of the regulations – the IRBs, the PIs, and the research subjects. He suggested that the Department will have the best chance of finding the right balance when engaged in appropriate dialogue.

Ms. Kornetsky thanked Admiral Agunobi for attending the meeting and highlighted the need for harmonization among the different sets of regulations promulgated by regulatory agencies. She said anything top-level administrators could do to help harmonize these regulations would be deeply appreciated. He responded that he was committed to working in that direction.

Dr. Prentice commented that the constructive relationship SACHRP has with OHRP also helps in finding the best balance. The Assistant Secretary thanked all SACHRP members for their work and hoped they would find their reward in a strengthened system.

Mr. Nelson then presented highlights of the work of the Subpart A Subcommittee over the past several months. He stressed that the Subcommittee is addressing some fairly major issues and he believes the recommendations will have a positive effect on the field. Dr. Prentice continued by highlighting the work of each of the other subcommittees and naming several of the panels that have addressed SACHRP and shared their expertise.

Discussion of IRB Workshop
Ernest Prentice, Ph.D.; Bernard Schwetz, D.V.M., Ph.D.

Dr. Schwetz began by informing SACHRP that Dr. Agwunobi was impressed by the committee's work and indicated a desire to attend one or two SACHRP meetings per year.

Dr. Schwetz thanked the committee that helped plan the IRB workshop recommended by SACHRP, which was held on November 17-18, 2005. Members of the planning committee included Amy Patterson and Alan Shipp from NIH, Lynn Cates and Genevieve Nowolinski from the U.S. Veterans Administration, Susan Ehringhaus of the Association of American Medical Colleges (AAMC), and Lowell Schnipper from the American Society of Clinical Oncology (ASCO).

About 50 people attended the conference, representing academia, business, government, independent IRBs, and subject advocates. The Planning Committee made a major effort to ensure all these groups were represented. Workshop time was allocated primarily to discussion, with both plenary and breakout groups used to elicit feedback. Attendees were charged with discussing the pros and cons of alternatives to local IRBs and addressing the need to encourage the use of the IRB model best suited for specific protocols and programs. Factors that influence the choice of model were identified.

The Director's observations included the following:

- People wanted to be heard, and they listened to each other.
- There was no evidence of a mass conversion to a particular view.
- Issues of real concern were identified, but some apparent barriers may be convenient excuses to maintain the status quo. It is necessary to address the real issues and separate out those that are really "smoke."
- There was evidence of interest in keeping the momentum.

- There was apparent interest in a national conference; many people stayed after the main workshop to contribute their ideas on what such a conference might look like.

Dr. Schwetz highlighted the barriers to the use of alternative models identified by participants. He noted that fears about liability were voiced the loudest, but in fact every model has some liability associated with it. Institutions are responsible for what happens at their institution, whether a nonlocal IRB is used or not. The need to address the local context appears to be a real concern; although some IRB mechanisms have worked hard at being able to address local context, others have further to go. Participants also voiced the concern that the use of an alternative mechanism might result in a net loss of resources; rather than freeing up time to do a better job on what remains, IRBs feared losing staff and funding. Attendees were concerned to ensure the quality of alternative mechanisms. Finally, they wanted more information on costs and the time required for review when alternative models are used.

Dr. Schwetz closed with several points for further discussion that arose from the workshop:

- Would more guidance from OHRP and FDA make a difference? Some participants thought it would, but this would be time consuming, and the Director wanted to be sure it would really be helpful.
- Some participants felt that workshops targeted to specific audiences might be more effective than a conference that did not allow such opportunities.
- Attendees clearly wanted information on the costs of alternatives; the performance of various models; and the quality, effectiveness, and efficiency of different options.

If more information is needed to convince people to use alternative mechanisms, then further questions arise: who could sponsor, collect, analyze, and publish these data so they are available?

DISCUSSION

The Chair invited sponsors of the workshop to add their comments. Dr.Ehringhaus said Dr. Schwetz had summarized the workshop well and that it was a privilege for AAMC to participate. Dr. Patterson agreed that the summary was on target, but added that she had been surprised at how little of the discussion was spent on the pros and cons of different types of review models for different research contexts. The conclusion seemed to be that almost any model might fit, given the right expertise. Dr. Cates added that the VA found the workshop useful and educational.

Ms. Kornetsky found the summary document useful. She wondered if the discussion addressed how to handle noncompliance and unanticipated problems, since her impression is that division of responsibility is a major concern. Dr. Schwetz said it did come up, and unfortunately many people wanted to believe that their institution is free of responsibility if another institution approved the protocol. Dr. Cates responded that many attendees stressed the importance of “crisp” agreements that delineate roles and responsibilities. Dr. Gyi, who was a public attendee at the workshop, said that those present had distinguished between the type of liability associated with financial litigation and the liability that is tied to public relations or to regulatory compliance. In the latter case, there is concern about which entity or entities might be subject to sanction. While FDA has a system capable of teasing out different components, HHS has an approach that holds the institution responsible regardless.

Dr. Ehringhaus added that she was surprised at the extent of misinformation about liability and responsibility and by the persistent myths about what might happen. She suggested that the workshop

had illuminated a number of areas, all of which could be considered as aspects of liability or accountability, that "cried out" for information and education. These could be addressed through a national workshop or through focus groups.

Dr. Fisher said that the models described in the summary were exciting, and she wanted to see the dialogue continue. She suggested it might be helpful to create models for shared liability with legal advice, since the fear of liability seems to be fueling resistance to the use of alternative models. It is possible that liability issues would differ on a multi-site project as opposed to the use of a centralized IRB for other circumstances.

Ms. Selwitz also found the summary document useful and congratulated the sponsors on their work. She observed, however, that developing guidance may be premature. She felt more solutions were needed first, including clarifying responsibilities and related ethical and regulatory issues. There are clearly major public relations concerns. She noted that the reality that centralized review is acceptable has not filtered down to many IRBs, and education is apparently needed.

Dr. Jones saw the concern that IRB resources would be jeopardized as a significant one. In regard to the need for data on the performance of various models, she wondered whether evaluation funds might be used to glean this information. Dr. Schwetz responded that there is money set aside each year to evaluate program performance, which is available on a competitive basis. However, evaluation is complicated by the lack of criteria to measure the performance of the IRB system. Dr. Jones responded that it might be possible to devise an evaluation tool that would help develop and test performance measures.

The Chair then introduced the question of next steps, highlighting major issues:

- To provide information on the cost of alternatives, it should be possible to collect information from a sample of institutions.

- Issues related to liability could be explored at a national conference or a targeted workshop.

- Issues related to dividing responsibilities could be explored further.

He added that there is no obvious way to get data on the performance of various models, particularly in regard to quality of performance. However, he felt there were enough issues explored that warrant further consideration to move to the next step. Dr. Prentice said his bias was toward having a national conference to give another airing of issues, followed by targeted workshops, including one on liability. Ms. Selwitz raised the issue of whether people would come. She also suggested that education could occur through channels other than workshops.

Members articulated a variety of suggestions relative to next steps:

- It is important to reach out to those who are hesitant about the use of alternative models.
- The workshop or conference should not be invitation only.
- Professional organizations may be willing to share lists of members so they can be invited.
- Areas in which there is misinformation should be addressed.
- It is important to articulate questions crisply to avoid repeating the same dialogue.

Dr. Jones observed that a conference could still have breakout groups on interest topics. Dr. Prentice agreed, noting that didactic presentations or panels could be followed by breakout sessions.

A Senior Policy Analyst from ASCO thanked the entire planning committee and reiterated the organization's "profound" continued interest in the subject.

Members agreed that an appropriate next step would be a national conference along the lines discussed, followed by targeted workshops.

Institutional Officials (IOs). Dr. Schwetz said that one of his priorities is reaching out to signatory officials and other IOs. Dr. Schwetz recently had an opportunity to talk to 40 IOs at a meeting of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) about their concerns. He said they were interested in talking to each other, which should be encouraged. He also highlighted the importance of the Signatory Official (the person who signs the Federal-Wide Assurance), who provides OHRP with its primary leverage over institutions. Dr. Schwetz said he believed more focus should be placed on the SOs because they are responsible for oversight of investigators.

Dr. Prentice added that there is interest in developing an organization for IOs. Ms. Selwitz was enthusiastic about the approach and characterized it as overdue. Dr. Powe was also positive, but thought the impetus for IOs getting together should come from professional groups rather than the government. Dr. Gyi agreed on the importance of leveraging the role of the SO, but reminded SACHRP that many research sites receive Federal funds that are not under an institutional umbrella.

PUBLIC COMMENT

The Chairman invited public comment.

Linda Ehler offered her personal observations as a staff member for the Regulatory Affairs Branch of the Division of AIDS, National Institute of Allergy and Infectious Disease, National Institutes of Health. She was interested in alternative IRB review models because the Division sponsors multi-site trials all over the world and hears complaints from investigators on related issues. She urged that members of the international IRB community be invited to participate in the forthcoming conference. National IRBs, industry representatives, and the Medical Control Councils in South Africa might have useful input.

Cheryl Ann Mathias also works for the Division of AIDS at NIH. She applauded SACHRP for considering the issue of a "60-day rule." She said the additional time provided would be extremely helpful in many international settings in which IRBs meet less frequently and barriers to communication lengthen the time required to work through issues.

John Mather of Chesapeake Research encouraged SACHRP to make full use of the interest shown by the Assistant Secretary of Health in its deliberations. He suggested asking for the Admiral's help in moving recommendations forward and also in addressing the staff shortage OHRP is experiencing. It might also be helpful to discuss with him the significance of accreditation and the need to promote the accreditation process.

Dr. Prentice thanked Dr. Mather for his comments. He also encouraged OHRP to make the Assistant Secretary aware of their staff limitations. He noted that SACHRP's recommendations regarding the §407 process have been implemented in a timely way and hoped the others would be implemented as soon as possible.

TUESDAY, MARCH 14

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

The Chairman provided an overview of events for the day. He also reminded attendees of future meeting dates: July 31-August 1, 2006 and November 2-3, 2006.

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

At the last meetings, there were many recommendations on parental permission and child assent that were approved. Dr. Fisher reviewed recommendations that were modified in response to feedback from SACHRP at its last meeting (see minutes of November, 2005).

Parental Permission and Child Assent

Dr. Fisher reminded attendees that Subpart A §46.116(d) regulations require the informed consent of all human subjects, with some exceptions for research involving no more than minimal risk. Subpart D §46.408(c) provides additional protections for children by requiring parent/guardian permission and participant assent, with some exceptions for research involving all levels of risk.

The subcommittee found the Subpart A language in need of clarification and sought to offer a decision-making tree that would assist IRBs in determining that an exception could be granted. Subpart A indicates that an IRB may "waive the requirements to obtain informed consent" if several conditions are met. One of these is a determination that the waiver or alteration "will not adversely affect the rights and welfare of the subjects." The subcommittee's first recommendation speaks to the factors that should be taken into account to make this determination. The third bullet in Recommendation 1 was altered based on feedback from SACHRP at the last meeting (November 2005).
Changes made in the recommendations that follow to address SACHRP concerns are underlined.

> **Recommendation 1. *"Adversely Affect," as Modified.*** *To determine that a parent/guardian waiver "<u>will not adversely affect the rights and welfare of the subjects</u>" under 116(d) the IRB should consider*
>
> - *Federal, state, or local laws pertaining to parent/guardian permission*
> - *Alternative mechanisms to protect the rights and welfare of child participants, and*
> - *When appropriate, whether the investigator has adequately considered the norms of the community from which subjects will be drawn.*

Consideration of local norms might be assured, for example, by having an unaffiliated nonscientific IRB member who knows the community speak to the issue or by engaging a consultant. An example of an approvable request for a waiver would be a survey on soft drink and fast food intake in which the investigator has worked with the local PTA to develop procedures, the middle school children who will participate are old enough to understand assent information, and arrangements have been made with school personnel to ensure that participation is voluntary. There are no laws that would be violated. On the other hand, a waiver could not be granted if the investigator also wanted to correlate eating patterns with student grade point averages, since the Family Educational Rights and Privacy Act (FERPA) does not permit access to school records without parental consent. Another example of a reason not to grant the waiver would be concern from an Orthodox Jewish community about questions related to pork.

Another finding that must be made to grant a waiver is that the research "could not practicably be carried out without the waiver or alteration." The subcommittee's second recommendation speaks to this requirement. The subcommittee worked to make the recommendation more understandable and cohesive

> **Recommendation 2. *"Cannot be Practicably Carried Out," as Modified.*** *To determine whether parent permission can be waived under **46.116(d)(3)** because the research cannot be "practicably carried out," the IRB should take into consideration issues such as:*
>
> - *A reasonable argument that scientific validity would be compromised if parental permission was required,*
> - *A rationale for why the research could not be conducted with a population for whom parental/guardian permission could be practicably carried out, and*
> - *A reasonable argument that alternative methods to obtain parent/guardian permission are not feasible.*
>
> *Guardian permission should not be waived under §46.116(d)(3) for convenience nor waived solely for reasons of cost or speed or other expedient measures if doing so weakens protection of subjects' rights and welfare.*

An example in which the permission of a parent or guardian could be waived under this recommendation would be an instance in which the PI proposes to waive parental permission for a national study of diet and after-school activities to predict census tract concentrations of middle school children's respiratory disease. To meet the requirement for scientific validity, a large random sample of children is necessary for statistical power. In regard to alternative methods, Census tract neighborhoods vary with respect to ability to contact parents through telephone directory or other measures; therefore, data would not be evenly spread out across the census tracks. All census tracts must be included for data to be meaningful.

The subcommittee sought to clarify the circumstances under which parental permission can be waived as "not a reasonable requirement" (other than instances of abuse or neglect). At the last meeting, SACHRP asked the subcommittee to craft a recommendation that makes it clear that the proposed guidance refers specifically to situations in which there is a conflict in the interests of the role of the parent or guardian as compared to that of the potential subject.

Recommendation 3. "Not a Reasonable Requirement," as Modified. *In considering parent/guardian waiver under 408c, IRBs should consider justifications for "not a reasonable requirement" beyond the example of "neglected or abused children" given within the regulation and include instances in which parent/guardian permission would jeopardize subject welfare or fail to provide additional subject protections.*

The subcommittee then attempted to define instances in which this would be the case.

Recommendation 4. ***Criteria for Waiver under §408(c), as Modified.*** *Assuming that an appropriate mechanism for protecting the children is provided, the IRB may waive parent/guardian permission under 408c by applying the following 3 criteria:*

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

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

3. *The research involves adolescents and satisfies all of the following:*

    a) *The research is important to the health, development or well-being of the subject population*
    b) *The PI has made a reasonable argument that the subject population is capable of understanding the research and their research rights*
    c) *Adequate procedures are in place to assure the voluntary nature of participation*
    d) *Involves experiences or procedures that are reasonably commensurate with those inherent in treatments that state laws permit adolescents to receive without parent/guardian permission*

An example of the application of criterion 1 would be an instance in which the PI seeks to identity patterns of psychological risk and resilience in high school students who consider themselves gay or lesbian, but who have not made this identity public. The PI might present literature on the social stigmatization of gay or lesbian youth, their potential confusion, and whether or not there is evidence of abusive reactions in particular populations.

An example of the application of the second requirement would be an instance in which a Principal Investigator (PI) seeks to study coping behaviors of adolescents who have joined an Al-Anon Group. If there were only one parent and that parent were an alcoholic, there might be a conflict that would render the parent unable to make a decision in the child's best interest.

A third example presented by Dr. Fisher is one in which a PI applies for a parental waiver to study adolescent girls' attitudes toward and use of different forms of birth control. Participants will be recruited from a clinic serving teenage girls 14 years and older who are permitted by state law to receive gynecology services and birth control without parental permission. To satisfy the third requirement, the PI would have to show that the research is important to the health and well-being of adolescent females who are sexually active and provide empirical evidence demonstrating adolescents of this age are capable of understanding informed consent at adult levels. The PI must also have assured during recruitment that it is clear to the teenagers that participation in the study is not related to their treatment and that a decision not to participate will not jeopardize their ability to get services.

Finally, the PI might show that asking subjects about their sexual practices and use of birth control is reasonably commensurate with questions asked during gynecology services they are permitted by law to receive without parental permission.

The subcommittee withdrew previous Recommendation 7, which requested OHRP guidance to clarify that IRBs may apply the Emergency Waiver to research involving children when parents/guardians are either present or not present

DISCUSSION

Recommendation 1. *"Adversely Affect," as Modified.* Dr. Powell questioned whether there is a requirement that the understanding of the norms of the community reflect its cultural and ethnic diversity. Dr. Prentice responded that this would depend on the study, noting that in some instances actual community consultation might be needed, and one representative on the IRB would not suffice. The IRB would have the responsibility of determining the acceptability of the information.

ACTION

Recommendation 1 was approved unanimously.

DISCUSSION

Recommendation 2. *"Cannot be Practicably Carried Out," as Modified.* The Chair pointed out that the recommendation would not support waivers driven solely by cost and convenience but would not exclude them from consideration.

Ms. Selwitz was concerned that the recommendation might be read as a requirement. Dr. Fisher said it was difficult to write any guidance that does not sound like a requirement. The following revised wording was proposed by the Chair:

> *To determine whether parent permission can be waived under **46.116(d)(3)** because the research cannot be "practicably carried out," the IRB should require investigators to provide the following, as appropriate within the context of the research…*

Dr. Fisher agreed with the wording, but added that she did not see the criteria as reducing flexibility or interfering with IRB judgment.

Ms. Selwitz was not convinced that each of the criteria spelled out in Recommendation 2 needed to be addressed in every circumstance. She gave the example of students getting Master's degrees and Ph.Ds; they might be working with records and have no way to reach parents. Dr. Fisher said there is flexibility to address this example. At the same time, students should be trained to do valid research and not to sacrifice the rights of children. Dr. Gyi, however, was concerned that the recommendation would place the IRB in the position of mentoring investigators in appropriate design instead of placing the responsibility on the investigator. Agreeing, Ms. Kornetsky said she was uncomfortable with the word "require"; she felt the criteria should simply be presented as things to take into account. Dr. Powe agreed with the new wording. He noted, however, that other considerations not listed could also be taken into account.

Dr. Fisher was concerned that the new language did not make it clear the burden was on the investigator to provide this information. Ms. Kornetsky, however, emphasized that the burden is always on the investigator, but the intent was to give the IRB flexibility in how the information was provided.

Dr. Jones suggested that guidance for investigators might also be needed in order to help them fulfill this requirement. The Chair observed, however, that a paper could easily be written on the first criterion alone. He observed that education and training will be needed to help investigators interpret this guidance, as on any aspect of the Common Rule. However, some flexibility must be left to investigators and IRBs.

Dr. Gyi asked whether any of the *ex officios* wished to comment. Dr. Bartlett noted that "such as," included in original wording, would be "softer," and the new wording was finalized as follows:

> *To determine whether parent permission can be waived under **46.116(d)(3)** because the research cannot be "practicably carried out," the IRB should take into consideration issues such as:*

ACTION:

Recommendation 2 was unanimously approved.

Recommendation 3. "Not a Reasonable Requirement and Recommendation 4. Criteria for Waiver under §408(c), as Modified. Both recommendations were discussed together because of their close relationship.

Dr. Powe asked whether there was still flexibility for the IRB to use its best judgment. Ms. Kornetsky responded that this would always be the case. Dr. Powe questioned whether item 3(d) of Recommendation 4 would be equally applicable to all research that falls under these recommendations, in that it appears to assume a study that involves treatment. Dr. Fisher agreed and suggested substituting the word "services" for "treatment." Ms. Selwitz was not sure that the provision would apply equally to social science research.

On the same criterion, Dr. Flanzer raised the question of what would happen if State laws were silent on the issue. While Dr. Flanzer was concerned about a "checkbox approach," Ms. Kornetsky explained that the intent was to be restrictive, because all the considerations listed are important, and some limits are appropriate. Dr. Fisher added that the intent was to provide the flexibility to do important research on adolescents that could not be done if parental permission is required and to allow decisions to be informed by the mature minor laws. Dr. Lepay added that investigational products are precluded by the current wording because the state law could not permit the use of an investigational product.

Dr. Prentice suggested that there were actually two situations that needed to be spelled out separately rather than blended into one criterion. A State law might exist that would prohibit a waiver of parental permission, or a State law might exist that permits a mature minor to consent to the type of services included in the protocol. Dr. Fisher said the situation in which State laws are silent must also be addressed. The following language was proposed:

> *d) Waiver is not inconsistent with federal, state, or local laws.*

e) When applicable, involves experiences or procedures that are reasonably commensurate with those inherent in services that state laws permit adolescents to receive without parent/guardian permission.

Dr. Jones strongly encouraged the use of examples to clarify the intent of the guidance.

ACTION

Recommendations 3 and 4 were approved unanimously.

Initial Presentation of Proposals on Key Issues Related to §46.405

Dr. Fisher presented proposals to address some of the key concerns identified by subcommittee members. She reminded committee members that this section of the regulations is related to research that may be greater than minimal risk but that provides the possibility of direct benefit for the child.

Acceptable Risk. The first question addressed by the subcommittee is what level of risk is acceptable under this regulation. The subcommittee proposed to underscore the risk benefit decision with the following guidance:

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

Available Alternatives. The subcommittee sought to provide IRBs with language that would help them weigh risks and benefits within the framework of the regulations.

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.*

Evidentiary Base for Available Alternatives. The subcommittee felt that guidance was also needed to help IRBs identify the type of evidence that would prove an alternative is effective or appropriate. They proposed the following, which is in keeping with the thinking of the National Commission on the need for scientifically sound expectation of success to justify risk.

Proposal 3. Evidentiary Basis for Evaluating Available Alternatives. *Evidentiary evidence can be defined in terms of scientific data or comparison to the standard of care for treating or monitoring the subjects' disorder.*

Monitoring Procedures as Benefit. Dr. Fisher reminded members that the regulations state that "direct benefit" can be shown if the intervention itself, the monitoring procedures, or both will have a direct benefit. Subcommittee members felt that the monitoring procedures should not count as having a direct benefit if they are simply "add-ons"; the procedure's efficacy should be a focus of the research and the benefit should be intended, not incidental.

Proposal 4. Monitoring Procedures as Benefit. *Any benefit of monitoring 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.

Phase 1 Studies. The subcommittee considered whether Phase I studies, in which drugs are introduced in humans for the first time, can be approved for pediatric patients under section 405. Such studies are designed to determine the absolute level of acceptable toxicity, not to test direct benefit. However, there is sometimes a benefit that occurs for a small percentage of subjects. The subcommittee recommends a conservative approach that places the burden on the PI to demonstrate that a Phase I trial qualifies under 405, using evidence and relevant prior studies:

Proposal 5. Approval of a Phase I Study under §46.405. *To be approved under 405, Phase I studies must satisfy the same criteria recommended for all 405 classifications:*

1. *The prospect of direct benefit for the subject must be proportional to the probability and magnitude of risk.*

2. *Even if the risks are balanced by anticipated evidence, a phase 1 study may not be approved under 405 if the anticipated benefits are not at least as favorable to the subjects as available alternative approaches.*

3. *Any benefit of a "monitoring procedure" must be an objective of the study (it must have the intended not incidental, potential benefit of influencing the child's management of the disease).*

PI s should have the burden of demonstrating that a Phase I trial qualifies under 405 and provide evidence and relevant prior studies justifying

a. *The dosages selected*
b. *Characteristics of subject population*
c. *The prospect of direct benefit to participating subjects*
d. *That the prospect direct benefit is balanced by the potential risks*

The subcommittee was concerned to make sure that participation in Phase I is voluntary and that both risks and benefits are made clear. They proposed the following:

Proposal 6. Additional Protections for a Phase I Drug Study under §46.405*. To approve a Phase I drug study under 405 (in addition to criteria under recommendations 4 and 5) IRBs should also consider:*

1. *Whether the risk-benefit balance is accurately reflected in the consent documents,*

2. *That recruitment does not offer inappropriate incentivization for children and families, and*

3. *That collateral benefits of monitoring are calculated in relation to the subject inclusion criteria and disorder being studied.*

Phase 1 Vaccine Studies. Dr. Fisher stressed that vaccine trials are research with the potential to save the lives of large numbers of children. In the past, such trials have saved more lives and benefited more children than many other types of studies.

> ***Proposal 7. Additional Protections for Approving a Phase 1 Vaccine Trial under §46.405.*** *To approve a Phase I drug study under 405 (in addition to criteria under recommendations 4 and 5) IRBs should also consider:*
>
> 1. *The benefits demonstrated by related studies*
>
> 2. *The risk of contracting the disease under investigation*
>
> 3. *The dosage justifications provided by the PI in terms of the immunological susceptibility of the participants, and*
>
> 4. *No participants should deliberately be subjected to the illness under study*

Applying Component Analysis under §46.405

Dr. Fisher suggested that while SACHRP has already recommended component analysis – specifically, it recommended that each research procedure in a study must be evaluated independently in terms of its potential benefits and risks to subjects – it may wish to clarify how component analysis applies to pre-randomization and post-randomization, the risks of research procedures used in the intervention as well as control groups, the ability to receive the intervention at end of the trial, and symptom management. Specific proposals brought forward include the following:

> ***Proposal 1. Approving Multi-Arm Studies.*** *To determine approval of multi-arm studies under §46.405 IRBs should use component analysis where:*
>
> a. *The direct benefit of any arm is in question, or*
>
> a. *The risk-benefit balance and/or comparison to available alternative treatments of any arm is in question.*
>
> ***Proposal 2. Trial Arms without Direct Benefit..*** *Trial arms that do not provide direct benefit cannot be classified as meeting 405 criteria using benefits from other arms of the study.*
>
> ***Proposal 3: Reducing Regulatory Burden.*** *The investigator has the responsibility to demonstrate to the IRB which procedures or study arms do or do not have the prospect for direct benefit.*
>
> ***Proposal 4: Consent for Treatment Studies that Include Procedures or Arms Approved under 404, 406, or 407.*** *If the IRB has determined that the research cannot be reasonably conducted without procedures or arms with no clinical relevance for the child's treatment, the informed consent must clearly explain the nature and rationale for such procedures.*

These proposals were not discussed further at this meeting. Rather, the subcommittee chose to focus its remaining time on recommendations related to wards of the State.

Wards of the State

Ms. Kornetsky discussed issues related to wards of the State as subjects, noting that the issue is a timely one. A recent compliance investigation focused specifically on the issue of wards, and the OHRP Web site posts 15 to 17 letters to institutions throughout the United States about wards and pertinent regulations. OHRP has found that in particular studies, IRBs failed to obtain sufficient information regarding the selection of wards and foster children as research subjects, failed to obtain sufficient information regarding the process for obtaining permission from parents or guardians, and failed to consider safeguards related to their enrollment. The subcommittee has considered how to assist IRBs in ensuring adequate protection for these subjects under the regulations.

Under §46.409, regulations require the following:

If the research is approved under paragraph (a) of this section, (§46.406 or §46.407) the IRB shall require

- Appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*.
- One individual may serve as advocate for more than one child.
- The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research
- The advocate is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization

More generally, Section §46.111 (b) requires IRBs to consider extra protections for vulnerable populations, which might include wards.

Ms. Kornetsky highlighted a number of practical issues that affect the involvement of wards in research. These include the following:

- Physical custody may be different from legal custody. This may mean that the person who brings the child to the doctor and takes care of the child might not be the same person who has actual legal authority.
- The legally recognized guardian may not be involved in the day-to-day life of the ward. The child may be in a foster care situation, for example, with a case worker representing the State.
- There may be different arrangements regarding decision making *(i.e.*, when the child is in foster care, the biological parents may retain their rights in this regard, or the State may have legal authority). Knowing who has authority may require review of legal documents.
- There could be frequent fluctuations in guardianship.
- The child may have transient relationships with guardians and decision makers as they move among foster homes or are restored to parental custody.
- State regulations vary, when they exist.
- Safety of wards involved in research requires appropriate oversight, which may become difficult and complicated.

The subcommittee considered how best to avoid exploitation of wards as a vulnerable population, while assuring that wards are not excluded as beneficiaries of research that offers direct benefit. Members also sought to assure continuity of care, safety, and oversight of research for wards who are involved in research, despite the challenges cited above. Their deliberations also addressed key questions:

- Are all wards vulnerable, not just those subjected to greater than minimal risk research with no prospect of direct benefit?
- Should extra protections be implemented for any ward who is a subject, regardless of the type of research? If so, what should they be?

Definition of a Ward. The following recommendation is designed to synchronize FDA and HHS regulations regarding wards; it proposes that HHS adopt the same definition of a ward already in use by FDA.

> **Recommendation 1**. *A ward should be defined as: A child who is placed in legal custody of the State or other agency, institution, or entity, consistent with other applicable Federal, State, or local law.*

Appointing an Advocate. The subcommittee sought to give guidance to IRBs on the selection of an appropriate person to assume an advocacy role for wards of the State, though the guidance is not intended to be prescriptive.

> **Recommendation 2.** *In appointing an advocate, the IRB should take into consideration the following regarding the advocacy role. The advocate should*
>
> - *Have appropriate qualifications in order to take into consideration the nature of the research and understanding the advocacy role,*
> - *Have appropriate time to commit to the expected ongoing role, including meeting with each ward, caregivers and researchers,*
> - *Have the ability to make a decision regarding each ward's participation in research that is autonomous and independent of any contractual requirements concerning the number or types of subjects to be enrolled,*
> - *Have independence from the research for the entire period of the advocacy role, and*
> - *Become familiar with the child's health, behavior, and social and physical environment and act as a neutral intermediary between the child and the research efforts.*

Appointing an advocate. Ms. Kornesky commented that a subcommittee involved in some of the early HIV trials appointed an advocate for wards in the study even though it was not required because it seemed the right thing to do. The subcommittee recommends this step be considered, regardless of whether the research is beneficial or nonbeneficial, since wards are vulnerable by nature of their status regardless of the research category.

> **Recommendation 3**. *Although not required by the regulations, the IRB should consider appointing an advocate for wards of state participating in research approved under §46.404 and §46.405.*

Becoming a Ward. When a child already engaged in research becoming a ward of the state, decisionmaking authority may change and the implications of participation in the research might change as well.

> **Recommendation 4.** *If an individual child/adolescent becomes a ward during the course of the research, the requirements of §46.409 should be implemented. This includes the appointment of an advocate to determine that it is appropriate for the ward to continue research participation.*

Anticipating Subjects Becoming Wards. In order to avoid disruptions to research, the subcommittee suggested giving a "heads-up" to encourage investigators to think about this possibility at the outset.

> **Recommendation 5.** *Investigators who work with research populations for whom there is a reasonable possibility that subjects may become wards during the course of the research should consider meeting the requirements of §46.409 as part of the initial protocol review. This includes identifying a potential advocate in the event one becomes required.*

Guidance to the Research Team on Wards. The subcommittee felt that IRBs should be sure that investigators and research personnel are aware that they should let the IRB know when wards of the State will be involved, or may become involved, in research.

> **Recommendation 6.** *IRBs in collaboration with their associated institutions (including legal counsel offices) should provide guidance and education to investigators and their associated research personnel regarding*
>
> - *Who is defined as a ward of the state*
> - *The need to notify the IRB when a ward is initially considered for research*
> - *The need to notify the IRB when a child/adolescent already participating in research becomes a ward of the state.*

Component Analysis. The rationale for this recommendation is that component analysis applies to all pediatric research; therefore if any part of the protocol fits the criteria of 406 or 407, the special protections for wards must be applied.

> **Recommendation 7.** *If component analysis of a study finds that one arm or procedure is approvable under 404 or 405 and another is approvable under 406 or 407, the most restrictive component will govern. Therefore any ward participating in that research will need to included in accordance with the provisions of §46.409, which include the appointment of an advocate.*

DISCUSSION

Recommendation 1. Definition of a Ward. Dr. Jones wondered how the term would apply internationally. Dr. Fisher was uncertain, but suggested that this should not stop the effort to harmonize the definition with FDA. Dr. Prentice saw flexibility in the definition and saw nothing to preclude its application.

ACTION

Recommendation 1 was approved unanimously.

Recommendation 2. Appointing an Advocate. The SACHRP discussion focused primarily on conflict of interest. Dr. Powe suggested broadening the concept to encompass other areas in which a conflict of interest might occur. The Chair suggested the following rewording for the third bullet of the definition:

- *Have the ability to make a decision regarding each ward's participation in research that is autonomous and independent of any employment, professional relationship, or contractual*

requirements, financial gains, or other conflicts of interests concerning the number or types of subjects required for recruitment, enrollment, and ongoing participation.

Members were concerned that nothing in the recommendation be read to imply that paying advocates is a bad idea or constitutes a conflict of interest. Rather, the intent is to ensure that advocates are not "paid by the head."

Another concern was whether the reference to financial gain would encompass a situation in which the advocate is the spouse of the investigator. The Chair suggested the following wording, which would leave the IRB free to determine what does and does not create a conflict of interest.

- *Have the ability to make a decision regarding each ward's participation in research that is autonomous and free of any conflicts of interest.*

Dr. Powe also raised the question of what is meant by "appropriate qualifications" in the first bullet. However, Co-Chairs responded that they have seen many people fill the role successfully and did not want to be overly prescriptive or shut doors.

Dr. Jones asked for clarification of what was meant by "appropriate time to commit…" Dr. Fisher explained that the advocate needed to be able to meet with each child and understand that child's specific situation. Co-Chairs considered the possibility of combining the second and last bullet to make it clear that the point is to enable the advocate to "become familiar with the child's health, behavior, and social and physical environment."

The subcommittee determined to table the recommendation to consider the committee's input.

Recommendation 3. Appointing an Advocate. Dr. Jones was concerned that the guidance might amount to an "unfunded mandate" by raising the bar of expectations for advocates. Dr. Prentice rejoined, however, that if wards are a vulnerable population, extra protection for them is already required.

Dr. Schwetz questioned whether the recommendation was one that was aimed at OHRP. He felt the remaining recommendations did not appear to constitute subjects for guidance, but rather more general suggestions for the IRB community. OHRP is not specifically asked to take a position. Also, he did not want to be perceived as increasing regulatory burden.

The recommendation was tabled to allow further consideration by the subcommittee.

Recommendation 4. Becoming a Ward in the Course of Research and Recommendation 5. Anticipating Subjects Becoming Wards. Dr. Fisher suggested that this issue is similar to issues related to persons who become prisoners during the course of a study. She said it would helpful for OHRP to clarify whether an IRB or investigator could be considered to be in violation of the regulations if this occurred and they were unaware the child had become a ward. Dr. Carome said OHRP had not issued formal guidance on this point. Ms. Kornetsky reminded SACHRP that "case law" is not the best way to communicate OHRP expectations on such issues.

Dr. Prentice asked whether the subcommittee felt the issue was an important one that needed to be addressed. Ms. Kornetsky responded that something has changed in the child's status, and something

is needed in response. Depending on the type of study, the change in the child's status could effect the child's participation in significant ways.

The recommendation was tabled to allow further consideration by the subcommittee.

Recommendation 6. Guidance to the Research Team on Wards. Dr. Prentice was uncertain of the meaning of the second bullet. He also wanted it made clear who is responsible for notifying the IRB (the investigator). Dr. Flanzer added that a subject becoming a ward may be analogous to an adverse event; in each case, the PI has certain reporting responsibilities.

Dr. Powe saw the third bullet as putting the burden on the investigator to know this information, and it is not clear how the investigator would make sure he or she did know about this type of change. Ms. Kornetsky responded that she would need to talk with legal counsel and some investigators to get a sense of the practical issues and processes involved.

In light of Dr. Schwetz's earlier comments, Dr. Fisher pointed out that this recommendation may be an insight rather than a recommendation that should go to the Secretary.

The recommendation was tabled to allow further consideration by the subcommittee.

Recommendation 7. Component Analysis. There was no discussion of this recommendation.

PUBLIC COMMENT

Cami Gearheart with Quorum Review, an independent IRB located in Seattle, Washington, observed that SACHRP is airing issues of importance that are creating difficulties and issues for the IRB's Board. The solutions are appreciated.

Ms. Gearheart had the opportunity to observe the workshop held last fall on alternative modes of IRB review and found it helped her understand the pressures and concerns of institutions that are looking at the centralization process. She was pleasantly surprised by the level of acceptance and encouragement for the centralization process in some quarters but taken aback by the level of hostility in others. She came away with the understanding that as academic medical centers move toward centralization, independent IRBs may or may not be part of the solution, since the centers have issues of financial support and liability to work through. It may be that collaborations within and among institutions will help address those concerns. She expressed willingness to share lessons learned with academic colleagues as the process moves forward.

Dr. Prentice assured her that independent IRBs would be represented at the upcoming conference on the topic.

Linda Ehler identified herself as a nurse consultant in the Regulatory Affairs Branch of the Division of AIDS, National Institute of Allergy and Infectious Disease, National Institutes of Health. She asked SACHRP to broaden references to State laws in guidance to encompass Federal, State, and local laws. She noted that this change was made in the new section 3(d) of "Recommendation 4: Criteria for Waiver under §408(c), as Modified" but not in (e). Consistency in this regard would be helpful to the international community.

Ms. Ehler also offered comments in regard to wards. She noted that in some international settings, when children become wards, physical custody may be different from legal custody. Also, while the committee has considered the implications of a child becoming a ward during the course of research, it has not considered what happens when research is suspended (again, with an international setting in mind). This should be addressed. It is possible that the IRB would then need to reconvene and reconsider the research with an advocate in place. When children are receiving benefits as a result of participating in a trial, this situation can be problematic.

Ms. Ehler also observed that the Division has found that in some of its pediatric trials, IRBs are not properly documenting their determination of pediatric risks. The Division has responded with training. She emphasized the need to train IRBs and investigators about the needs to document their pediatric risk determinations.

Dr. Prentice thanked the speaker for her comments and assured her that her input would be considered by the subcommittee.

Ed Bartlett of OHRP commended the children's subcommittee for its work. However, he pointed out an inconsistency related to recommendations passed by SACHRP earlier in the day. He noted that the regulatory language related to the waiver of parent or guardian permission under §46.116(d) says the waiver or alteration *will* not adversely affect the rights and welfare of the subjects. Recommendation 4, however, says that the IRB may waive permission under 408(c) if "the investigator has provided a reasonable argument that informing parents *may* result in harm to the child. Mr. Bartlett argued that this is a very important discrepancy because the regulatory language sets quite a rigorous standard to meet and the recommendation appears to weaken it.

DISCUSSION

Ms. Selwitz thanked the Chair for his "excellent job" and thanked the OHRP Director and staff for "how you consistently listen to what we're trying to do." Finally, she thanked her colleagues on SACHRP and expressed the opinion that "what this committee has done and will continue to do is of significant importance for human subjects' protection." Ms. Kornetsky agreed. The Chair thanked them for their comments and added that subcommittee members are dedicated people who work hard, noting that the enthusiasm they bring to the committee's deliberations is infectious. He was grateful that the members leaving SACHRP will continue to be active on subcommittees. Dr. Schwetz also thanked each of the three departing members and said he had learned from each of them.

Dr. Prentice commented that in the months between this meeting and the next (in July) subcommittees will meet to consider issues raised by SACHRP so they can bring modified recommendations back to the committee. Also, OHRP will be planning to implement the latest recommendations sent to the Secretary, which have just been accepted. A progress report is expected in July. Also by the July meeting, it is hoped that progress will have been made in the development of a national conference on alternative models of IRBs. A report is also expected on issues related to adverse event reporting, as well as a status report on the IO initiative.

Dr. Schwetz reported that there have already been several planning meetings for the national conference. Based on the current status of planning and recent input from SACHRP, he said the conference would probably be open to everyone and use breakout groups to reach specific audiences, such as signatory officials, institutional attorneys, IRB members, and investigators. Since the conference sponsors provide

links to key audiences, OHRP will seek to ensure wide enough representation on the planning committee to move the agenda forward.

Panel on Status of Research Ethics/Training Internationally
Moderator: Robert Levine, M.D.
Panelists: Melody Lynn, Ph.D.; David Lepay, M.D., Ph.D.; Jean-Louis Saillot; Maureen Power, R.N., M.P.H.; Barbara Sina, Ph.D.

Dr. Schwetz commented on the expectations for the panel. He recalled that SACHRP has benefited from two previous panels on international research. As the subject is large and complex, it was decided to focus this panel on a topic that was narrow enough that a handful of people could address it from their experience. This smaller slice of the topic is training in the area of ethics. The subject encompasses ethical issues relative to the investigator, the institution that is supporting the research, the IRB, the review process, and the Ethics Review Board. Voices represented on the panel nclude not only U.S. regulators, but also those in the medical product industry, funding agencies, and those already involved in training related to research that occurs in the international setting. These speakers were asked to address several key questions:

- Whose responsibility is it to do the training for ethics of research conducted in developing countries. Who is responsible for that?
- What type of training is already available and what type of training is needed but not yet available? Where are the "cracks" between what is being done and what is needed?
- What innovative models exist that could be used to scale up the training of ethics in the international setting?
- What has been tried and didn't work? What is working?

The Chair introduced Dr. Levine, who served as moderator for the panel.

Remarks by Robert Levine, M.D.

Dr. Levine began by stressing that the "worst thing we can do is dictate ethics." Guidelines set forth by the Council for International Organizations of Medical Sciences (CIOMS) are intended to guide sponsors and investigators from wealthy countries as they carry out their work in developing countries, not to dictate to collaborators in those countries how they "ought to behave." Rather, it is important to learn from them about what works in their cultural context.

CIOMS Guideline 11 has proved the most controversial. This requires that each subject be provided with an "established effective intervention" (EET) – not necessarily the best intervention. Placebos may be used only under the following circumstances:

- When no proven intervention exists,
- When withholding EEI results in only temporary discomfort and no serious harm,
- When EEI as comparator would not yield scientifically reliable results, and
- When studies are designed to develop an effective alternative to an EEI that is not locally available.

Dr. Levine said many people saw the fourth bullet, in particular, as representing a double standard. He felt, however, that the results of the research should be responsive to the health needs and priorities of the community of subjects, and the products developed should be reasonably available.

He agreed that this provision violates the fiduciary standard, under which physicians must have no interest of equal or higher priority than the patient's wellbeing; however, he felt the guidelines put strict limits on the degree of violation tolerated.

Dr. Levine highlighted several other key guidelines:

- ***Guideline 3: Ethical review of externally sponsored research***. *An external sponsor…should submit the research protocol for ethical and scientific review in the country of the sponsor… and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ERC, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards. Division of labor is permissible.*

Dr. Levine added that "stringency" is interpreted in the context of the country where the research is carried out. Division of labor may allow the ethical review committee or IRB in the host country to see that certain universal standards are applied appropriately in the context of the local culture. For example, the local IRB will know what constitutes undue inducement in the light of local traditions.

- ***Guideline 6: Informed consent***. *Sponsors and investigators have a duty to…seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate.*

In regard to Guideline 6, however**,** Dr. Levine observed that in some tribal villages it is almost unthinkable that an individual will refuse to participate in an activity to which their governing body has agreed.

Dr. Levine also briefly reviewed Guideline 10: Research in populations and communities with limited resources; Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects; Guideline 16: Women as research participants; Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research; and Guideline 21: Ethical obligation of external sponsors to provide health-care services.

Dr. Levine closed by reflecting that while the distribution of wealth among the nations of the world is inequitable, "research did not cause this and research cannot fix this." While it is tempting to use international research documents as a means of correcting these inequities, he said, it is important to avoid developing guidelines that would impede the efforts of sponsors and investigators in industrialized countries to help countries with less resources develop treatments and preventions that they can afford.

Remarks by Melody Lin, Ph.D.

Dr. Lin addressed each of the questions posed to panel members in turn:

- *Are regulators in U.S satisfied with the current level and nature of training of research ethics?* Dr. Lynn said this was true in some cases, but there is little data available.

- *Is the medical product industry comfortable with the training of research ethics?* These are questions

for industry and the FDA; however, if they are not comfortable, the next question is what is being done to compensate for that lack of training.

- *Are funding agencies satisfied that grantees and contractors are adequately trained in research ethics?* Dr. Lin wondered what is being done to compensate if the answer is "no."

- *How do we know what's "out there"?* Dr. Lin suggested that the international workgroup of the human subject research subcommittee might be able to develop an inventory of teaching materials.

- *How can specific needs be met?* Dr. Lin proposed illustrating ethical concepts using locally acceptable scenarios.

- *How can we achieve a uniform level worldwide?* Dr. Lin proposed establishing a public-private partnership that would make s standardized curriculum with locally customized content available worldwide. A sister institution arrangement might also be possible.

- *How can the effect of the training be made durable*? Dr. Lin advocated the use of video training that can be repeated and given frequently. She stressed the importance of intensity and frequency of review, given that many research ethics committees have a low volume of research and could lose expertise due to lack of practice.

- *Whose responsibility is it to assure adequate training?* While there are no explicit regulations on the subject, conduct of training could be required by research sponsors.

- *Would more rigorous training of ethics decrease the risk to subjects?* Dr. Lin clearly saw a need for improved training and communication.

- *How do we accomplish the training so that subjects of research are protected?* Dr. Lin felt that training should be widely available and endorsed by an international organization. Refresher training is also important to ensure that new people become familiar with concepts. Research ethics training should be considered an integral part of research.

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

Dr. Lepay began by explaining that FDA is essentially a regulatory agency. It funds very little clinical research, with the exception of some domestic research in the areas of orphan products, women's health, and epidemiologic surveillance. In connection with this research, FDA has sponsored training for program coordinators, investigators, and its own IRB.

FDA has no legal authority or jurisdiction outside the U.S. However, it does have authority to set conditions for accepting non-U.S. data that will be used in support of research or marketing permits in the U.S. for the U.S. population, which gives the agency some significant leverage. FDA can accept this non-U.S. data in two ways: the non-U.S. studies may voluntarily operate under a U.S. Investigational New Drug application (IND), in which case all U.S. regulations apply, or the data may be submitted under separate FDA regulations that apply to non-U.S., non-IND studies. FDA can reject studies that do not meet applicable requirements.

In regard to IND studies, FDA has general regulations that require "qualified investigators"; however

they do not specify a single core curriculum or a set of core competencies. There is no regulatory requirement from either FDA or OHRP that anyone serving on this committee have any basic ethics training. In regard to non-IND studies done outside the U.S., the Declaration of Helsinki currently serves as a minimum standard. FDA has a proposal out for public comment that would instead reference internationally recognized standards for good clinical practice similar to those in place in the U.S. However, there would still be no specific requirements for curricula. Instead, FDA requires documentation showing how standards have been met, including a description of how investigators were trained.

FDA's ability to conduct international inspections is a criterion for accepting non-U.S. non-IND studies. This authority is embedded in IND regulations. Since 1980, FDA has conducted over 600 non-U.S. inspections in nearly 60 countries. These international inspections encompass investigator qualifications as well as training. Dr. Lepay added that as broad international standards have been articulated, differences in GCP between domestic and international locations have become increasingly small. A forthcoming handbook from the World Health Organization (WHO), built on CIOMS guidelines, will further advance education related to ethics and GCP.

FDA leverages and promotes ethical conduct and ethics training through partnership with other regulatory authorities. Information sharing helps to identify ethical issues and provide a basis for targeted education and outreach. Dr. Lepay highlighted four international strategies as particularly helpful in promoting ethical practices internationally. These include:

- International harmonization of Good Clinical Practice (GCP) Standards,
- Capacity building for international regulatory authorities,
- Information sharing among regulators, and
- Education and outreach for regulated parties/professional organizations.

Discussion. The Chairman asked whether it was FDA's intention to eliminate any reference to any version of the Declaration of Helsinki in its revised guidance. Dr. Lepay explained that this would be true of the regulation itself, but in practice the principles of the document that are also common to good clinical practice will be promoted.

Remarks by Jean-Louis Saillot, M.D.

In regard to industry-sponsored trials, Dr. Saillot stressed the need for global approaches based on standards that ensure that the dossier that presents the scientific evidence is acceptable by all relevant health authorities, including by the FDA. At this point, however, the vast majority of clinical research is still conducted within the U.S. and the European Union; only about a third of such activity is outside these countries.

In practice, all global clinical development programs are based on full compliance with International Conference on Harmonization (ICH) guidelines. Sponsors fulfill their obligations under the guidelines not only through training, but also through monitoring, quality assurance, and selection of investigators with the appropriate credentials and experience. In general, the same global standards are applied whether the project is an IND or non-IND effort, though there are some procedural differences between the two.

In such studies, both the sponsor's personnel and investigators are targets for training. Sponsor personnel such as monitors visit sites regularly, as do investigators. Important ethical principles are communicated

through publications and training. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) has put together a document called "Principles of Conduct of Research Study." Many companies have internal codes of ethics or credos that are communicated through training to monitors and to the people in charge of the programs. Sponsors typically have a curriculum and Standard Operating Procedures (SOPs) that proceduralize the requirements of GCP and the ethical principles behind the protection of patients in clinical trials. All the monitors of any company would receive significant training to be sure they understand these requirements. Dr. Saillot referred to this training as encompassing "applied ethics" rather than abstract principles.

Sponsors have a large impact on investigators. A typical study would have what is called an investigator meeting, which is to go over the protocol for all the investigators included in the sites. Frequently, a significant proportion of this time is spent on GCP and specific ethical expectations applicable to the study, including training on the reporting of adverse events and safety issues. In addition, monitors visit to examine the way the study is conducted. These visits are considered a training function as well as a means of oversight. Whenever things are not done according to the protocol, it is the role of the monitor to identify problems to the investigators and sometimes to the ethics committee or the IRB, should there be repeated deficiencies at the level of the investigators. Dr. Saillot added that the international context is a dynamic one in which the level of experience of investigators varies widely.

Discussion. Dr. Jones asked how much "crosstalk" occurred among companies of different sizes in terms of how ethics education should be approached. Dr. Saillot responded that there was some level of interaction through working groups of the Pharmaceutical Research and Manufacturers of America (PhRMA), including a BioPhRMA working group that shares best practices. The Drug Information Association (DIA) offers good training in ethics, while fora such as the Association of Clinical Research Professionals and the American Association of Pharmaceutical Physicians and Investigators pursue a certification and training agenda.

Dr. Powell asked whether differences exist between the larger patient trials and smaller Phase I studies. He also wondered there are a wide variety of standards that would govern these types of sites. Dr. Saillot observed that the issues relate to proof of concept, and Phase I trials are so specific that they are traditionally made in either the U.S. or Europe and only rarely in other countries. He suggested that might be because of the level of comfort that exists with particular sites, academic institutions, or centers. He believed that requirements, including SOPs and monitoring requirements, are very consistent across the board.

Remarks by Maureen Power, R.N., M.P.H.

Ms. Power described approaches used by the National Institute of Allergy and Infectious Diseases (NIAID) in conjunction with the Fred Hutchinson Cancer Research Center and Family Health International to build IRB capacity in resource-limited settings. NIAID has been increasing its international research portfolio in recent years and has participated in many global partnerships in this endeavor. This has resulted in ethical challenges, often in complex situations.

While international locations differ widely, resource-limited settings often have a very limited understanding of U.S. requirements, including limited access to information and guidance. People are often in remote locations without the convenience of ready Internet access and are not sure where to turn for guidance. Ms. Power stressed the need for ongoing, sustainable training in order to have real impact.

In 2001, NIAID embarked on a research training activity that was specific to ethics for the first time. This was a four-day workshop conducted in Malawi called "Ethical Aspects of Clinical Research." Attended by 70 or 90 participants, the training was very well received. A number of similar interactive workshops have followed for widespread audiences with an interest in clinical research, including investigators, members, chairs of IRBs, and institutional officials.

At the request of African colleagues, the training program has also been modified to focus specifically on the needs of IRBs. Through meetings with OHRP, other research sponsors, other parts of NIH, and target audience members in Africa, specific training needs were identified, including the following:

- How to interpret and implement regulations, directives, and guidance,.
- How to write and standard operating procedures,
- How to run effective meetings,
- How to divide up the workload of the IRB so that it could be effectively performed,
- How to overcome obstacles associated with making and distributing copies of thick documents,
- How to adapt training for the local culture so they develop their own approach,
- How to achieve institutional buy-in in settings where IRBs are relatively new,
- How to network IRBs in remote areas to get advice and support, and
- How to access financial resources needed to manage IRBs.

NIAID is addressing these needs in three ways. First, it offers training opportunities in the United States, where selected individuals are brought to the United States to attend national IRB conferences. This tends to make the issues IRBs struggle with more real and provides an opportunity to network, reducing isolation. Foreign visitors can also meet IRB members or observe IRB meetings through exchange visits. These visits also help domestic IRBs gain an appreciation for the realities of research in international settings.

Another approach to addressing the needs of low-resource international settings is to have local and regional training in their own regions. Karen Hansen, through the Fred Hutchinson Cancer Research Center, has utilized her NIH enhancement grant to reach out to a number of the international IRBs in Botswana, Malawi, Haiti and the Dominican Republic. She did a needs assessment survey and developed in-country training to meet identified needs and issues. This included developing tools to help IRBs organize their work, such as audit checklists and templates for IRB minutes.

NIAID has also helped organize regional training on a larger scale through the Partnership for Enhancing Human Subject Protections (PERHP). The Partnership has developed a standard curriculum for IRB training that presents the fundamentals of U.S. regulations and international standards, offering practical assistance and tools that can be adapted to meet local needs and interests. Training is interactive, with frequent use of panel discussions and case studies. NIAID has also offered a follow-up workshop that focused on developing local papers of regional interest and a workshop specifically for administrators (one and a half days). Finally, to further disseminate training and tools, NIAID has also used Web-based approaches.

Remarks by Barbara Sina, Ph.D.

Dr. Sina represented the Fogarty International Center, which is part of NIH. She explained that its primary mission is to support collaborative research and research training between U.S. and developing country scientists. Therefore, it has been doing IRB training for many years. It does not support clinical trials, but it does support other research involving human subjects. All faculty mentors involved in this

research have human subjects education similar to education U.S. investigators would receive that addresses responsible conduct of research. Grantees, primarily people from the U.S. working in international sites, set up IRBs and related training.

Dr. Sina highlighted a training program on international bioethics that has been delivered in developing countries since 2000. Recently, the Center decided to review the program and identify lessons learned and directions for the future. The training seeks to foster "homegrown" expertise and leadership in designing national and international guidelines to be used in those countries. It addresses bioethics, research ethics, and international guidelines; in addition, it includes practical experience. Trainees sit in on IRBs and design their own courses to teach bioethics when they return to their countries, including conducting small research projects in ethical issues of high importance to the trainees.

The speaker noted that while U.S. institutions tend to have fewer trainees per year because of tuition costs, developing countries can really reach much further and support more people. Africa has been a primary focus because its capacity was relatively low. All the PIs are brought to the U.S. annually to discuss training-related issues and receive resources. Some institutions that are trying to build up capacity internationally in research ethics, such as the Wellcome Trust, come regularly. So far the program has given 167 people intensive Master's-level training. Many IRB members have also benefited from short courses related to these programs.

The program has chosen to target those in positions that could have the most impact on changing their ethics situation when they returned home. Even though the trainees are getting short-term training compared to the training provided other research trainees who are working on research related to molecular biology and malaria or similar subjects, they have already contributed 80 publications to the literature. Also, many of them have moved into prominent positions. For example, one trainee returned and was immediately asked by the government to set up a national ethics review board in Nigeria, receiving a presidential medal. Another example is a trainee from Ecuador who served as the consultant for a national commission on bioethics. Partners are working to match the trainees to places where they are most needed, such as where IRBs are reviewing particularly difficult protocols.

DISCUSSION

Dr. Gyi asked Dr. Lin to expand on the subject of funding sources for ethics training. Dr. Lin saw the need for pooling resources to develop a systematic and global approach, rather than having each organization do its own. A public and private partnership might develop a Web-based approach that would be more cost effective.

Ms. Mathias asked Ms. Power to explain how protocol registration works at the Division of AIDS and elaborate on investigator training. Ms. Power explained that the Division AIDS provides a variety of training resources, including training on good clinical practice for its institutions. All key personnel are required to take training on human subjects protection.

Mr. Borasky of Family Health International posed several general questions. First, he asked for more clarity about the training audience and its goals. He asked specifically whether the intent was to make Western or Northern bioethics principles global. He also wanted to know whether the purpose was to help people comply with regulations or to train them in bioethics or philosophical ethics. Ms. Hansen responded that U.S. regulations inform training because international collaborators need to understand what is expected and required. The next step is to embrace the values of the host country setting and

allow them a platform for comment and input. A further step is to bring these international participants to the United States where they can meet with investigators and sponsors conducting research in their countries. It is important that growth occurs in the U.S. setting in terms of international needs and views.

Dr. Levine commented that the question of whether there are universal ethical principles or whether there is legitimate cultural pluralism in the field is an ancient debate that began in the times of the classical Greeks. However, while Aristotle could say ethics were universal, his universe had clear boundaries; Spartans were barbarians and didn't count. Dr. Levine maintained that ethics are developed within particular cultures and are directly connected to traditions and experiences. Recognizing this, the successful international ethical codes do not aspire to universalism. Instead, the CIOMS document aspires to "global applicability." This means that as far is known, the guidelines apply around the world today; still, as more is learned, it will be necessary to continually revise and improve the standards.

Ms. Tobin asked whether there were situations in which it is unethical to train international researchers and enable them to become more competitive players in the world economy. She cited the example of training closed cities in Russia on IRB procedures, where they are now overseeing biochemical research. However, no one participating sees the whole picture of the research. Dr. Saillot responded that clinical research activities in Russia are limited. Dr. Levine asked Dr. Lepay whether there were not some components of clinical investigations that FDA maintains as secret or proprietary information, and Dr. Lepay confirmed that there is some proprietary information cannot be disclosed by government officials. There is also classified research sponsored by the intelligence community in which the purpose of the research may be unknown to IRB members.

Dr. Jones returned to the question of whose obligation it is to deliver training and provide the necessary resources. She also asked about issues that arise in the PI-subject relationship that are different in international settings. Dr. Levine responded that little is known about that relationship. even in the U.S. In regard to responsibility for training in how to become an effective IRB member, Dr. Sina responded that all IRB members are responsible for training themselves and providing training to others to the extent possible. She also said, however, that more resources are needed to expand the work being done in a wider sphere.

Dr. Levine added that funders have an obligation to see to it that when American funds are being spent, they are used in accord with what we would consider ethically acceptable procedures. Dr. Lin rejoined that those who fund research generally, whether they represent the U.S. government or the U.S. pharmaceutical industry, have an interest in providing research ethics training. This will help ensure the research is of good quality.

Dr. Powell asked what should be done to determine whether an investigator has a sufficient understanding of ethics to be able to do different types of research. Ms. Power said that competency testing was difficult; NIAID relies on the fact that training has been provided to effect an appropriate behavioral change, especially in combination with other checks and balances within the system. Dr. Levine added that it is not possible to know for sure what is actually done when the researcher and subject are alone together.

Dr. Schwetz observed that capacity can be built either on demand or independent of demand. Primarily, he noted, the current approach is the former. Knowing that there is a significant increase in the amount of research being done outside the U.S. that's funded by various U.S. institutions, both private and non-private, he asked whether we are approaching a point at which the need can no longer be met by simply arriving a few months before the medical team arrives to do the experiment – in other words, one study at

a time. Dr. Levine called this issue a serious problem. Currently, he said, it is assumed that different types of programs will call for different levels of capacity building. Dr. Sina added that the approach of the Fogerty Center has been to provide the deep, long-term, sustainable expertise within developing countries. Over the long run, she felt, this is a stronger system. Dr. Saillot highlighted a challenge, however: studies occur at a particular site to which the sponsor may never return. It is easier to make a long-term strategic investment when working wuth the same institutions over and over, as NIH does. It would take a significant paradigm change to motivate industry to develop reliable sites that can be used repeatedly with reduced risk; no mechanism currently exists for this approach.

Dr. Schwetz asked whether the public and private systems could be designed to help each other's efforts to build capacity. Ms. Power said a degree of collaboration is already in place, but more partners could be involved. Ms. Homman of the Fogarty Center added that capacity building has been successful in several countries. For example, at the University of KwaZulu-Natal, there is now a group of about 30 people (lawyers, philosophers, psychologists, researchers, medical doctors, and community members) who form the core of a bioethics group. Many countries are now seeing the need to build this expertise for themselves and to acknowledge the need for high standards. Dr. Levine confirmed that the Center is building an "impressive list" with considerable momentum for sustained change.

Dr. Lepay added that the FDA has tried to use its inspection program as a means of working with industry over time to develop standards. In the long term, he sees the most promising strategy is to help develop and train other regulatory authorities that have legal jurisdiction within their own countries. The World Health Organization (WHO) will shortly issue a handbook for implementation that reflects a "higher level of thinking" about good clinical practice and will help in this regard.

Dr. Prentice was impressed by the "substantial" initiatives to provide research ethics training internationally. He highlighted the fact that 70 to 75 percent of all clinical research is conducted by private practice physicians in local settings where there is no requirement for ethics training, other than investigator meetings that may be required by a pharmaceutical company. He felt more effort may be needed in our own country. Dr. Sina responded that several NIH initiatives include ethics training in training for clinical researchers. She felt more could be done, however, to infuse undergraduate science curricula with an appreciation for ethical issues in human subjects research.

Dr. Prentice asked for the percentage of investigators trained overseas, but Dr. Sina said she was unable to make an estimate because she had no idea of the total number of international investigators. Dr. Levine ventured to guess, however, that training is reaching slightly under a 100th of one percent.

The Chair then turned to the issue of how SACHRP would use the information presented. He asked panel members to comment on what, if anything, SACHRP might do to help resolve the issues identified in international ethics training and address stated goals. Responses included the following:

- Ms. Hansen suggested that academic centers that hold Federal-Wide Assurances (FWAs), within and outside the U.S., should be made aware of the resources already available.
- Dr. Lin wanted SACHRP to endorse the development of a public-private partnership to identify a core curriculum that can be blended flexibly with local content and made available as a distance learning tool. Ms. Power agreed that a core curriculum would be helpful, but encouraged the use of multiple training modalities (not just the Internet). She also suggested working within a larger framework that would met a range of needs for an institution developing a human subject protections program.
- Dr. Sina felt that SACHRP had already sent a message by inviting a panel on the topic.

- Dr. Saillot also felt having the panel helped air the issues. He noted that discussions were underway on the certification of investigators; this would result in a minimum curriculum. There have also been discussions about including clinical research and ethics as subjects in the regular medical curriculum.
- Dr. Levine suggested forming a committee of people engaged in this work to develop recommendations. He added that a core curriculum will not work without the personal involvement of dedicated teachers.

The meeting was adjourned.

Secretary's Advisory Committee on Human Research Protections
Meeting
March 13-14, 2006
Alexandria, VA

Certification of the Summary of Minutes

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

Original signed July 31, 2006

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