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

August 1 and 2, 2005
Alexandria, VA

Minutes

MONDAY, AUGUST 1

Welcome and Opening Remarks

The Chairman welcomed everyone to the meeting. He reminded attendees that SACHRP's Charter, issued on September 8 of 2004, comprises protection of human research populations, especially vulnerable populations such as children, pregnant women, prisoners, and those who are decisionally impaired. The committee's work to date has focused on these vulnerable subject populations. In fulfilling its responsibilities, SACHRP works closely with staff members from the Office of Human Research Protection (OHRP), who act as liaisons on SACHRP subcommittees in addition to providing support to the SACHRP committee itself. In particular, he thanked OHRP Director Dr. Bernard Schwetz, and then recognized the efforts of Kelley Booher and Cathy Slatinshek. The Chairman also thanked *ex officio* members of SACHRP, who are important partners in the committee's work.

Report on Issues

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

Dr. Schwetz informed SACHRP of the following developments.

The final rule amending 45 CFR 46 was passed on June 13. Changes involve "cleaning up" and updating the rule; for example, references to OHPRR have been changed to OHRP, and there is an update on the relevant control number for the Office of Management and Budget (OMB). The Director noted that it has proved time consuming to get the various agencies and departments to sign off on even these nonsubstantive changes.

In late August or early September, OHRP plans to issue a Draft Guidance Document on reporting adverse events and on anticipated problems involving risks to subjects or others. Public comments will be solicited.

The OHRP Web site has posted new items, including:

- Guidance on the 45 CFR 46.407 process for research involving children, based on suggestions received from the SACHRP Subcommittee on Subpart D;
- Guidance on reporting incidents to OHRP;
- Answers to frequently asked questions; and

- A compilation of human subject protection laws, regulations, and guidelines of over 50 countries in which funds from the Department of Health and Human Services (HHS) are being used to conduct or support research.

OHRP has received comments in response to its posting in the *Federal Register* regarding the registration of Institutional Review Boards (IRBs). It is in the process of reviewing these comments and deciding on next steps.

The Director also offered an update on the status of new compliance cases OHRP is addressing. The Office receives about 100 complaints per year, of which about half result in investigation. This year, OHRP has about 20 open cases; since the last OHRP meeting, there have been 8 new cases and 2 have closed.

The Institute of Medicine (IOM) committee funded by OHRP to review the ethics of research involving prisoners has been active. Members have visited prisons to give them a clearer perspective on prisoner vulnerability.

A planning committee tasked with developing a workshop on models for central IRBs has developed an agenda and a spreadsheet that compares the pros and cons of IRB models. The Association of American Medical Colleges (AAMC) and the American Society of Clinical Oncologists (ASCO) will cosponsor the workshop, which will be an invitation-only event to develop recommendations on the selection and use of various IRB models. Comments from the workshop, to be held November 17 and 18, will return to SACHRP for review and possible action. An open conference to be held next year will provide an opportunity for further discussion of these recommendations.

Following the Director's remarks, Dr. Hauser asked him to identify next steps related to adverse reporting. Dr. Schwetz responded that these included integration of public comments, further review within HHS and with other Federal agencies. Dr. Mike Carome estimated that this process should be complete by the end of the year.

Overview of Charges to Subcommittees; Approval of Minutes

Ernest Prentice, Ph.D.

The Chairman provided an overview of charges to existing SACHRP committees and complimented the committees on their work. He highlighted the new subcommittee on Subpart A, which will review and assess all provisions of Subpart A and consider how to reduce regulatory burdens that do not contribute to the safety of human subjects. A second subcommittee deals with research involving children; it has issued seven reports to date, many of which have culminated in significant recommendations and changes.

Minutes for the previous meeting (April 18-19) were approved unanimously.

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

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

Mr. Nelson reviewed the charges to 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. The subcommittee will do so in three categories: interpretation of specific provisions, development of new OHRP guidance or modification of existing guidance, and possible revisions to Subpart A. Mr. Nelson said the subcommittee was interested in "pushing the envelope" with some of its recommendations, and recommendations for revisions to the rule are possible, though they would be a "last resort."

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.

To date, the subcommittee has had two telephone conferences and two face-to-face meetings, the last of which was held July 20-21 in Alexandria, VA.

Issues identified for review at the first meeting include continuing review, expedited review, assurances, multi-site research, recordkeeping and reporting, investigator responsibilities, elements of informed consent, exemptions, IRB review of exceptions and deviations, vulnerable populations, and definitions related to all these issues. Adverse event reporting will be discussed after a Federal working group addressing this issue has brought forward its recommendations. Criteria used in prioritizing these issues for subcommittee consideration included the importance of the problem, the ease of fixing the problem, the effect on human research protections, the contribution to regulatory burden, and the contribution to nonregulatory burden.

Working groups have been established for continuing review (chaired by Gary Chadwick and David Strauss) and for expedited review (chaired by Moira Keane and Tom Puglisi). At its second on-site meeting, the subcommittee reviewed draft reports from each working group, considered issues related to minimal risk, and heard input from Federal agency representatives.

The Co-Chair stressed that the working groups' presentations are recent and preliminary. Currently, however, recommendations are expected to follow, and feedback from SACHRP and from members of the public would be timely. He also emphasized that regulatory burden is not the same as work reduction; the subcommittee's focus is on where regulatory requirements may actually detract from human subject protection by diverting IRB time to issues that make no meaningful contribution to protection.

Remarks on Continuing Review by Gary Chadwick

Dr. Chadwick began by explaining that the requirement for continuing review (CR) of research is a legacy of the infamous Tuskegee syphilis study, which went on for decades without scientific or ethical review. Continuing review is intended to prevent the continuation of research activities in the face of unacceptable harm, futility, or technological or ethical obsolescence. However, the Belmont Report does not mention continuing review.

Continuing review, the speaker explained, is an important tool that plays a central and often understated role in the IRB process. Requirements for CR are addressed only in §109(e) of the Common Rule, which states: "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." The only regulatory requirement is that research be reviewed at least yearly; there is no regulatory direction about what the "review" must entail. The Preamble to the regulation states that procedures adopted by the IRB for continuing review should be left to the discretion of the IRB and adds that whatever procedures are used, they should not needlessly hinder research. In regard to the frequency of reporting requirements, the preamble states that they may vary according to the level of risk associated the research: "Reporting requirements may vary from a *simple annual notificatio*n in the case of research involving little or no risk, to more frequent reporting [or for] clinical trials, the IRB may require a special mechanism to carry out data and safety monitoring functions."

Currently, however, IRBs do not tend to use either of these reporting strategies, and the speaker said the guidance offered by HHS and the Federal Drug Administration (FDA) has not been helpful. FDA does not provide specific instructions for IRBs on how to set up their own rules for continuing review; however, HHS has detailed prescriptive guidance that requires IRBs to use all eight criteria in Section 111 for every review, defines the content of internal progress reports, rules out grace periods, spells out the documentation required in IRB minutes, states when continuing review should occur, and indicates what documents should be used to conduct each review.

The subcommittee raised a number of questions regarding continuing review. Dr. Chadwick presented preliminary thinking on these questions, which may evolve into recommendations.

1. *When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB can close it?*

The regulations do not address this issue. They simply state that the review is to be conducted "not less than once per year" (§46.109[e]). While there is no written guidance from OHRP on when a research study ends, OHRP has for some years held that as long as an investigator is controlling identifiable data, continuing review must be conducted at least annually. The subcommittee noted that there are studies in which ongoing risks are extremely low or nonexistent. Examples cited by the speaker included cooperative oncology studies sponsored by NIH that remain open solely to collect survival data. There is no new enrollment and no ongoing intervention. The only potential risk is a breach of confidentiality and with the typical safeguards in place, the risk of such an event is very low. The subcommittee believes that applying Section 111 to this type of low-risk research adds no value to human subject protection and is not justified. The subcommittee suggests a revision of existing guidance that states that a study has ended when all interventions are over and/or when the data collection is complete at the research site for which the IRB has oversight.

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

Dr. Chadwick pointed out that the preamble includes no explanation for selection of the one-year period. Many believe that for minimal risk research the requirement for yearly review should take the degree of risk into consideration. In reference to the content of such reviews, subcommittee members also questioned

whether §111 should be cited as a guide (as suggested by both HHS and FDA). This section, the Co-Chair suggested, seems to unduly limit the flexibility of IRBs to employ appropriate reviews and criteria for ongoing studies. Members also felt it was not in keeping with the original intent of the regulations. Instead, the subcommittee felt that IRBs should be permitted to develop their own policies and procedures regarding the selective application of §111 to continuing review.

Unfortunately, however, only a change in the regulatory wording would allow IRBs to use a longer review interval. Wide comment from IRBs, researchers, and the public on this issue would be helpful.

3. *Should categories 8 and 9 from the expedited review list (November, 1998) be expanded or clarified?*

Subcommittee members generally agreed that activities in these categories, such as follow-up of cancer survivors, can be of such low risk that even an expedited continuing review does not meaningfully add to human subject protection. The fact that there are exempt categories in the regulations acknowledges that not all research activities require the protection provided by IRB review or even informed consent.

Subcommittee members suggested that expedited review Category 8(b) should be interpreted so that expedited continuing review is permitted if no additional risks have been identified at any site in a multi-site research, no subjects have been enrolled since the prior review, and none are currently enrolled at the IRBs research site *since the proceeding review*. (Currently, guidance suggests that 8(b) refers only to instances in which no subjects have ever been enrolled at the site.)

Category 9 promotes flexibility in continuing review based on study risk; all minimal risk studies are eligible for expedited review, so long as "no additional risks have been identified." For minimal risk activities that are not on the list published in the *Federal Register*, however, the initial review must still be conducted at a convened meeting. The subcommittee felt this constituted an unjustified burden.

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

The regulations do not state any requirement for IRBs to perform or validate literature reviews; this is seen as the responsibility of the investigator. The subcommittee held that the IRB should simply receive the results of the review.

5. How should exempt research be handled at continuing review?

Subpart A defines some types of human subject research as having such low risk that the regulations are not applicable; therefore, there is no continuing review requirement for them (45 CFR 46.101[b]). However, OHRP has cautioned that investigators should not self-determine that their research is exempt; as a result, most institutions require the IRB to verify exemption claims. Some institutions process these claims through full expedited procedures and some even conduct annual continuing reviews. The subcommittee held that such review diminished IRBs' credibility and resources without benefit. It therefore suggested that OHRP should take steps to ensure that its caution concerning investigator self-determination of exemptions is not intended to imply that the IRB has any responsibility for oversight of these exempt activities.

6. What is role of review for unanticipated problems and adverse event reports?

While Section 103 requires written procedures to ensure prompt reporting of any "unanticipated problems involving risks to subjects or others." However, HHS guidance requires the IRB to consider "adverse events." The subcommittee finds no regulatory basis for this requirement; however, it has deferred further discussion and development of recommendations since several agencies are currently addressing the issue.

7. *What is the proper interface between data monitoring committees (DMCs) and the IRB during continuing review?*

Only Section 111(a)(6) addresses the subject of data monitoring. It simply states, "When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects." Because this issue is broader than just continuing review, the working group held that further discussion and development of recommendations on data monitoring committees should be addressed by the full subcommittee. Working group members did suggest that harmonizing HHS and FDA guidance with the many National Institute of Health (NIH) policies on data monitoring committees would provide a valuable opportunity to enhance substantive review, both initial and continuing. They also suggested that defining an appropriate role for data monitoring committees and clarifying the interface between IRBs and DMCs would reduce the burden on investigators and IRBs while enhancing human subject protection.

8. *What types of oversight are appropriate and reasonable in continuing review? What data or information improves human subject protection?*

Both accrediting organizations have standards that address continuing review. These standards list the types of documents and/or information that should be provided and reviewed by the IRB. These lists essentially evolved from the HHS and FDA Guidance Documents, but go beyond them in many cases. The subcommittee felt they focused on process rather than substance. Members held that Federal regulators and voluntary accrediting organizations should recognize and support the use of a variety of mechanisms to achieve safe and ethical research.

9. *Some IRBs have established as institutional policy a "resubmit- as- new review." Is this a best practices model?*

The subcommittee recognized that such policies represent one way to enhance the process of continuing review and generally endorsed the concept – but only as an option only for those institutions that would derive a value from that process. This policy in combination with a longer review period might, in fact, be a truly effective method for some IRBs. Nevertheless, the subcommittee cautioned against writing the practice into Federal guidance so that it becomes a hard-and-fast requirement. Rather, nonregulatory educational outlets are recommended to disseminate information on best practices like this.

10. *Does the current HHS guidance regarding setting the date of continuing review need to be changed?*

HHS guidance advises that "in order to determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs." The subcommittee viewed this guidance as placing an unnecessary regulatory burden on the review process without enhancing human subject protection. This policy, the Co-Chair asserted, results in artificially shortened review periods and sometimes causes floating expiration dates that are hard for IRBs and investigators to track. More helpful guidance would allow IRBs to set the date by referring to the date when the protocol receives final approval, not the date of the convened meeting. The subcommittee argued that the regulations support such a policy and that it would be

consistent with the regulatory authority given to the IRB to extend to the chair or experienced reviewers the full approval powers of the assembled board (i.e., through the expedited review process).

The subcommittee was also critical of HHS guidance that states that "when continuing review occurs annually and the IRB performs continuing 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." They felt that the "30-Day rule" sets an artificially short window for granting approval and that it is both practically and logistically problematic for IRBs and investigators. Members suggested that the rule should be changed to allow more flexible review schedules, as well as more timely and accurate reviews.

The subcommittee considered how temporary lapses in approval should be handled. They concluded that a lapse in approval because an investigator has not submitted a progress report should not automatically halt the study, so long as it is in the best interest of the subjects to continue. Separate requests to allow each individual subject to continue are unnecessary. OHRP is in agreement with this interpretation. The subcommittee also held that new enrollments should be stopped in lapse studies because the consent form has expired and because an assessment of risks and the adequacy of the new consent information has not been made for new subjects. This is another area of agreement with current OHRP thinking.

The subcommittee suggested that guidance should be changed to state that when continuing review is underway, study suspension is not required automatically when the expiration date passes before the review and approval process is complete. Suspension should be left as an IRB option on a case-by-case basis. Of course, IRBs should specify strategies to prevent delays in review and avoid extensive time in the lapse state. Their policies should specify what conditions and activities will be permitted in such circumstances.

11. *What does the phrase "verification from sources other than the investigators" mean for continuing review?*

Some IRBs have established audit programs that utilize IRB staff, chairs, and members to provide verification. Some research institutions that have established human research protection programs have included an audit function, usually separate from the IRB, for investigator site audits as well as for conducting IRB operational audits. The subcommittee held that such audit functions are appropriate as institutional mechanisms but should not be viewed as the responsibility of the IRB. Other techniques for verification exist that are useful in ensuring safe and ethical research. Auditing strategies should not be enshrined in guidance as best practices, which would risk creating a *de facto* requirement for their use.

12. *Does the continuing review need to be performed by the same board that made the initial approval? How do special continuing review IRBs impact the process?*

The current guidance says that CR does not need to be performed by the original board and the subcommittee agrees. The speaker also noted that if many IRBs are sending their CRs to the same special CR IRB, the work load could result in less substantive reviews. However the review is done, it is the responsibility of institutions to ensure that sufficient resources and effective procedures are in place to support full compliance with the regulations and to adequately protect its human subjects.

13. *What documents should the IRB be given in order to conduct continuing review?*

Current HHS guidance states that "all IRB Members should receive and review a protocol summary and a status report on the progress of the research and at least one member of the IRB should receive a copy of the

complete protocol, including any modifications previously approved by the IRB." However, it is not clear what is meant by the term, "protocol summary." The subcommittee suggested that guidance be clarified to state that a protocol summary may or may not be a separate document and that combinations of sources, such as consent forms and the CR application itself, could constitute a summary.

If a primary review system is used, there is no added benefit to requiring that all IRB Members receive an extensive summary, though the entire protocol should be available to all members on demand. The subcommittee also observed that regulations allow consultants to aid the IRB in the review studies, which some IRBs have read as including qualified IRB professional staff. Use of this procedure when full protocol review is required can enhance human subject protection by ensuring that sufficient time and attention is paid to the protocol. The committee therefore suggested that guidance clarify that qualified IRB staff may act as a consultant to the IRB in this regard. However, it observed that this is not a significant concern for IRBs that use electronic application, submission, and review, because all materials will be accessible to all members at all times.

14. Can existing guidance on continuing review be consolidated and integrated?

In an environment where concerns about litigation and consequences of noncompliance drive institutional behavior, the absence of clear and consolidated guidance results in unrealistic demands on IRBs and investigators without substantively enhancing protections for subjects. For example, because the guidance does not make any allowance for changes to an approved study without Board review, even typographical changes are receiving Board review.

Guidance that is not easily accessible or can only be interpreted by trained IRB professionals perpetuates the misperception that IRBs are primarily responsible for human subject protections. Now, IRB professionals must explore extensive case law in multiple forms for answers to questions related to daily operations and decision-making. This is inefficient and time consuming. The speaker held that "investigators and other members of the research community need to be put back in the picture." He stressed that simplified, unified, and practical guidance for continuing review is urgently needed. Such guidance should include examples, explanations of standards, and definitions of thresholds. The *substance* of the review should be the focus. Finally, the subcommittee cautioned that guidance should be permissive rather than proscriptive wherever possible.

Remarks on Expedited Review by Moira Keane

Ms. Keane observed that there is a good deal of overlap in Subpart A issues; for example, expedited review is interrelated in many ways with continuing review.

The regulatory basis for expedited review is found in 45 CFR 46.110 and in FDA regulations at 21 CFR 56.110. These rules permit the IRB Chairperson (or one or more other experienced IRB members designated by the Chair) to approve minimal research in nine listed categories or minor changes in previously approved research that occurs within a year of approval. IRBs are advised of issues to consider in determining whether the risk is truly minimal (risk of criminal/civil liability, financial risk, employment risk, stigmatization, insurability, or embarrassment) and admonished to ensure the review is just as rigorous as a review by the full board. Also, standard requirements for informed consent remain the same as in a non-expedited review.

The subcommittee identified a number of key questions, then consulted with various professional associations and colleagues who have expressed concerns about expedited review, using both in-person dialogues and electronic discussion lists. These discussions informed preliminary findings on each of the questions. As a result of these discussions, members also concluded that the use of the expedited process was limited for some IRBs by their fear of incurring regulatory sanctions if their decision to expedite a project should be questioned, as well as a concern that use of the process might seem to trivialize a proposal.

With the benefit of this input, the subcommittee addressed several key issues of concern.

1. *Use of a "stipulation" mechanism*

Many convened IRBs use a "stipulation" mechanism to define and permit timely verification by the IRB Chairperson (or designated IRB member) of clarifications or modifications needed for approval of proposed research. OHRP guidance currently limits the use of such mechanisms to situations requiring simple concurrence by the investigator to specific language dictated by the IRB. The subcommittee found that this limitation on the stipulation mechanism is needlessly restrictive and incompatible with the latitude permitted to Chairpersons in their review of other "minor changes" in research.

A possible recommendation from the subcommittee is that IRBs should be permitted to describe in their written policies and procedures stipulation mechanisms for defining minor changes required for approval of proposed research under which:

> (a) the IRB Chairperson, or a designated IRB member-reviewer, may exercise reasonable judgment in verifying that the stipulations of the convened IRB have been satisfied; and/or
>
> (b) 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 reviewer).

2. *Changes to the expedited review list*

Working group members found little enthusiasm in the IRB community for changing the existing list. However, they were concerned that current expedited review categories may unnecessarily restrict the use of expedited review procedures.

The working group identified two possibilities for expanding expedited review categories that will require additional discussion by the full Subpart A Subcommittee:

- Divide the current Category 7 (for research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies) into two categories and provide additional examples. The division of this category would assist IRBs in their review of social and behavioral research.
- In accordance with written policies in procedures, permit IRBs to utilize expedited review procedures for all minimal risk research.

3. *Minor administrative and clerical changes*

IRBs often receive changes to approved research that are entirely administrative or clerical in nature and have no effect on the conduct of the research, its underlying science or methods, associated risks and benefits, or the potential willingness of subjects to continue participation. The current requirement for approval of such changes by the IRB Chairperson or a designated IRB member-reviewer does not contribute meaningfully to the protection of human subjects and actually reduces such protection by wasting the limited time that IRB members have available for substantive review and oversight activities.

The subcommittee's preliminary recommendation is that IRBs be permitted to define in their written policies and procedures changes to approved research that can be implemented by qualified IRB staff. Such changes would be limited to those that are entirely administrative or clerical in nature and have no effect on the conduct of the research, its underlying science or methods, 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; or other changes, as defined in written IRB policies and procedures).

4. *Consolidated and integrated guidance*

Currently, multiple documents address expedited review, and new researchers or professional administrators are likely to be confounded by the many, many sources of authority. The subcommittee's preliminary recommendation is that OHRP and FDA should issue joint consolidated guidance on expedited review. Archived or obsolete guidance found in searches of the HHS Web site should be retired and removed from the searchable sections of the Web site or labeled as obsolete.

5. *Definition of "research"*

The working group explored a serious concern that lack of understanding about the regulatory definitions of "research" and "human subject" result in IRB review of activities that do not constitute human subject research. Review of such activities wastes time, generates resistance (even hostility) among investigators, and undermines respect for the IRB process. The subcommittee will consider a possible recommendation that the definitions of "research" and "human subject" be clarified as described below.

Regulations define research as **"**a systematic investigation … designed to develop or contribute to generalizable knowledge" (§46.102[d]). Key terms could be further defined as follows:

- *Systematic* means "carried out according to a plan that allows conclusions to be drawn."
- *Designed* means "intended or with the purpose of" (at least in part). Intention or purpose can be established either by the investigator's expressed intent or by the investigator's use of the information or conclusions resulting from the investigation.
- *Generalizable knowledge* means "information represented as applicable to persons in institutions (or other limited locations or contexts) beyond the institution (or other limited location or context) in which the information was obtained."

6. *Definition of "human subject"*

Regulations define "human subject" as "a living individual about whom an investigator … conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information …. Private information must be individually identifiable (i.e., the identity of the subject is, or

may readily be, ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects" (§46.102[f]).

The above provisions pose a significant problem for some social science researchers who work with very large data sets. Information may be deemed nonidentifiable where investigators provide a signed attestation that they will neither attempt to identify subjects nor knowingly obtain or accept information through which they may identify subjects. If subjects are identified through a code or other linking information to protect anonymity, information may be deemed nonidentifiable if investigators provide a signed attestation, countersigned by the individual or entity holding the key to any identifying code, that investigators will neither be given nor accept the key through which they may identify subjects. Further discussion with researchers is needed on how best to address this issue without creating unnecessary burdens or obstacles.

7. Activities not considered human subject research

Activities not encompassed within the above definitions of "research" and "human subject" do not require IRB review, approval, and oversight. Under normal circumstances, the following activities would not be considered "human subject research":

- Journalism interviews or investigations;
- Oral history interviews;
- Interviews or observations conducted by architects for use in designing a structure;
- Student activities conducted solely for pedagogical purposes;
- Quality assurance, program evaluation, or "institutional research" activities intended solely to evaluate and improve an organization's programs or services, with no application of findings outside the organization; or
- Feasibility studies to determine the potential utility or viability of a specific, proposed service or facility, with no application of findings to other services or facilities.

However, there are exceptions. For example, journalism interviews do not generally meet the definition of research with human subjects. However, the speaker suggested that if a journalist conducts a series of interviews not for news purposes, but to develop a theory of personality and social development, this could be considered human subject research. Institutions should ensure that their policies, procedures, and educational programs provide for and require appropriate IRB review, approval, and oversight on these rare occasions.

The working group also identified several questions on which it had reached preliminary conclusions:

- *Is there a need for clarification that expedited review is generally appropriate for review of recruitment materials, advertisements, etc.?* This is an area where IRBs have been reluctant to exercise the flexibility that is already available to us under FDA guidance. The working group suggests that it would be sufficient to stress the flexibility.

- *Can an expedited reviewer disapprove or require revisions and minor proposed changes to the ongoing research without referring the matter to the convened IRB?* In this instance, where an expedited review mechanism is employed, the reviewer, through professional judgment and a well-articulated review based on the regulations and requirements, determines that there are some aspects of the project that do need minor revision. In some very conservative interpretations, those revisions

would need to go back to the convened IRB rather than be handled through the expedited review mechanism. The working group believes that most IRBs are able to currently handle this situation through negotiation between the investigator and the IRB reviewer. However, there should be explicit permission for this approach in the guidance.

- *Is there a need to clarify the use of expedited review for minimal risk activities and research involving children or prisoners or will this be addressed by Subpart C and D?* The subcommittee will coordinate with other concerned subcommittees to receive additional guidance on this issue.

- *Is there a need for guidance on the appropriate use of expedited review of adverse events, serious adverse events and unanticipated problems?* The subcommittee does feel more guidance will be needed, but it now appears this will be handled outside of the Subpart A Subcommittee.

The Co-Chair stressed in closing that the expedited review mechanism is a mainstay of IRB operations and human subjects protection.

Considerations on Minimal Risk by Subpart A Subcommittee

While Mr. Nelson recognized that careful thought went into every word of every part of the regulation, he said that the changes that have occurred in the years since it was authored must now be taken into account. He stressed the importance of the definition of minimal risk, which is a factor in numerous important determinations that must be made by the IRB (for example, eligibility for expedited review, waivers, and the alteration of consent process or content). However, the subcommittee's thinking on this subject is very preliminary.

Inconsistencies are apparent in the definition of minimal risk throughout the regulations and in Federal guidance. The term is defined in Subpart A using "risks encountered in daily life" as the standard of comparison. The preamble to the 1981 regulations clarified that these risks were not those encountered in the lives of healthy persons, but rather those "encountered in the daily lives of the subjects of the research." Nevertheless, Subpart C specifically references "healthy persons" and their daily risks as the standard of comparison, a standard that the National Commission also used in reference to risks encountered by children, and OHPR recommends the use of the healthy person standard when asked (though it has not issued formal guidance to this effect). Subparts B and D do not include a definition of minimal risk, but SACHRP has recommended that it should be interpreted as referring to risks encountered by "normal, average, healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests."

The subcommittee has identified a number of key questions related to minimal risk:

- *Whose daily life is the standard of comparison – that of a healthy person or of a research subject (who may or may not be healthy)?*

Some members believe that using the research subject as the standard creates a "slippery slope" from an ethical standpoint. However, even if the healthy subject is used, where is the subject located? What degree of health and fitness is implied and what kind of daily activities are considered normal?

- I*s it essential to have the same interpretation of minimal risk for adults as applies for children?*

The subcommittee does not have consensus on this point.

- *Does the current definition imply equivalence between the risks encountered in daily life and those encountered during the performance of routine physical or psychological exams or tests?*

If the two are not equal, then perhaps the one that poses the greatest risk is the real standard.

- *Is it possible to downgrade greater than minimal risk to minimal risk research by means of minimization procedures?*

IRBs have sometimes imposed procedures to decrease the risks involved in research that was clearly, at the outset, greater than minimal risk.

- *Do we need to harmonize differences across the regulations?*

The subcommittee has pointed out differences in wording and references, as well as in how those are understood and applied. It is still considering whether this poses a real problem that needs to be addressed. Some would argue that inconsistency across the IRB system, within and outside this country, decreases credibility, undermines the system, and poses an impediment to conducting research, particularly multi-center studies.

- *Should differences in research types be acknowledged?*

There are clear differences between biomedical research and social and behavioral research. Under the Common Rule, the risks of social and behavioral research are likely to be overestimated. Should this tendency be acknowledged and addressed, either at a regulatory level or through guidance?

- *Would a list of examples be helpful?*

Some do feel this would be helpful.

- *Are we talking about all risks? Should that be factored in, as opposed to those that are reasonably foreseeable?*

Some risks are encountered infrequently or never. Should such risks be factored in, or is the scope of risks being considered limited to those that are reasonably foreseeable in the construct of this individual research study? The subcommittee is not yet ready to present preliminary recommendations on this issue.

Once the subcommittee has finalized its work on the topics presented, it will move on to issues related to exemptions and informed consent. It expects to continue to use a working group format.

DISCUSSION OF INITIAL ISSUES and FINDINGS, SUBPART A

Members raised the following questions and concerns.

Continuing Review. Dr. Prentice asked whether Dr. Chadwick knew the origin of the concept that IRBs are required to reapprove projects, as opposed the simply re-review them. Dr. Chadwick did not know, but noted that the regulations call only for an annual review. Dr. Prentice recalled that prior to guidance

being issued, IRBs were not strict about conducting the annual review with a 365-day period.

Dr. Prentice asked Dr. Chadwick to expand on his statement that it should not be necessary to consider all the approval criteria at §46.111 in a continuing review for every research project. Dr. Chadwick gave the example of ensuring that the research plan makes adequate provision for monitoring the data outlined to ensure the safety of the subjects. He felt that the adequacy of the plan should be thoroughly reviewed before the project is approved, but continuing reviews should only need to check that the plan was in place and working. The level of review that is required may differ for each criterion.

Dr. Prentice returned to the question of when a study ends. He asked for confirmation that the current position of OHRP is that a study ends when all interventions and the analysis of the data are complete. Dr. Carome stated that this was correct. The Chairman observed that this is a different criterion than the one presented by the subcommittee, which understood OHRP's position to be that as long as an investigator is controlling identifiable data, annual reviews must continue. Dr. Chadwick pointed to the example of a study that is kept open only for the purpose of collecting survival data. Some institutions combine these studies into an umbrella survivor follow-up protocol for the purpose of review.

Mr. Adams asked whether the committee had considered the possibility of lengthening the period of review for some studies. Dr. Chadwick responded that this had been considered, and the subcommittee felt that some levels of research should be allowed to go longer than a year within reviews. For example, in some studies it may be a year and a half before the first subject walks in the door. However, introducing such flexibility would require a regulatory change.

Literature Review. Dr. Prentice asked whether he was correct that the issue of whether the IRB had a role in performing or validating the literature review arose following the Johns Hopkins hexamethonium study, in which the IRB was faulted for not identifying the risk of pulmonary toxicity. Dr. Chadwick agreed. Dr. Prentice inquired whether OHRP had issued any formal guidance on this point. Mr. Nelson commented that determination letters can become *de facto* guidance, and Dr. Chadwick confirmed that the letter in which Johns Hopkins was faulted for not conducting an adequate review was the source of this requirement. Dr. Gyi observed, however, that many scientists would hold that the Hopkins group had done a fairly thorough review, but it was in a different committee structure than the full committee.

Dr. Fisher advised the subcommittee to give more extensive thought to the issue. She noted that Federally funded research will have a Scientific Review Committee that is looking at the human subjects section and the assumption that a legitimate review has occurred may be justified. She also raised the question of exactly what the review should examine, since much of the literature bears no relation to possible adverse events. She suggested that tracking other investigations that used similar methods that are ongoing or recently completed might be a better use of the IRB's time. She further proposed that the significant ethical question is, "What is the responsibility of the IRB to ensure that the information it has gotten from the investigator is timely and up to date in terms of what the risks are to participants?" She suggested that the investigator and the IRB each have responsibilities that should be considered.

Identifying Best Practices in Guidance. Dr. Prentice asked speakers to elaborate on the concern that best practices embedded in Federal guidance could become *de facto* requirements. He asked for an example of an instance in which this has occurred. Dr. Chadwick said that most of the specific requirements surrounding continuing review have no regulatory basis; they may be best practices, but they are prescribed only in guidance. The involvement of IRBs in validating the literature review is another example. A suggestion can quickly become an expectation. Dr. Chadwick suggested that guidance should

have examples, but they should be permissive rather than prescriptive in nature.

Informed Consent. Dr. Hauser raised the concern of how the risk profile of a study is updated. If a significant adverse event occurs, how does that become part of the informed consent process? Mr. Nelson and Dr. Chadwick said this point had not yet been considered. Dr. Fisher suggested the subcommittee review the kinds of data identified for presentation when renewing parental permission, as outlined by the Subpart D subcommittee.

Minor Changes. Dr. Prentice asked Ms. Keane to clarify what the working group considered to be a minor change. Ms. Keane said specific examples have not yet been developed. Ms. Kornetsky was cautious about developing lists, but said the impact on the risk benefit should be the key consideration in determining whether a change was minor. Dr. Puglisi, also a member of the subcommittee, added that the current guidance is that the IRB's written policies and procedures should define what constitutes a minor change. He felt this flexibility was appropriate. Accordingly, the subcommittee did not want a specific definition of "minor change" and also did not want to define stipulations for approval.

Definition of Research. Dr. Fisher questioned the examples used to distinguish does and does not constitute human subjects research. In regard to the journalist who is conducting interviews to write a book on a theory of personality and social development, she offered the example of a book on political development. The fact that the individual is writing a book does not mean the person is a social scientist. She suggested the subcommittee reconsider the meaning of research in reference to social, medical, and physical science. Ms. Keane found the point well taken, but noted there was a significant grey area that poses a challenge. Dr. Puglisi added that better examples are needed. An alternative is to define exemptions for certain disciplines, but this would be a controversial approach.

Additional Expedited Review Categories. Dr. Prentice asked Ms. Keane what the proposal to divide the current category 7 into 2 categories was designed to accomplish. Ms. Keane said this was an area the working group is still struggling with. Dr. Chadwick clarified that a reference in the list for this category indicates that some of the research in the category is exempt, but does not say what is and is not exempt. Splitting out the contents of the category might make this clear.

Use of Expedited Review for all Minimal Risk Research. Ms. Selwitz observed that this was a novel suggestion and said she was not yet sure of her own position. She invited Ms. Keane to elaborate on the idea. Ms. Keane said that the idea is a very expansive approach to expedited review that might not work out, given the conservative approach IRBs tend to take. Ms. Kornetsky cautioned that the definition of minimal risk should be considered hand-in-hand with this proposal. She noted that the advantage of multiple viewpoints may be lost in the expedited review process. However, Ms. Keane pointed out that IRBs could still determine that a study would benefit from review by the full committee and proceed on that basis.

Dr. Weiner noted that minimal risk procedures could be embedded in treatment protocols; such studies should be considered as a whole, and an expedited review process might not be appropriate. Dr. Gyi asked the subcommittee to give more thought to models of how risks are analyzed, especially in regard to minimal risk. He also asked them to consider how much authority and information is given to the IRB.

Harmonization of Regulations. Dr. Prentice asked representatives of OHRP and FDA how they would ensure harmonization of the SACHRP recommendations that are accepted. Dr. Lepay responded that

OHRP and FDA share guidance as they are being developed and have many venues for discussing emerging issues. The approach would be tailored to the individual recommendations to be coordinated.

Dr. Prentice asked about the extent of harmonization on §407 reviews. Dr. Lepay said that review panel processes for OHRP and FEDA are close to identical.

PUBLIC COMMENT, SUBPART A

Members of the public commented as follow.

Dr. Alva Schomisch of Citizens for Responsible Care and Research. (CIRCARE) called attention to issues not addressed by the Subpart A subcommittee. The first is that there is research being conducted on human beings without any Federal oversight, while in contrast, all animal research is now covered by Federal regulations. The speaker also expressed concern that flaws in the rule have been identified on the basis of anecdotal rather than scientific evidence. The speaker felt that the subcommittee was preoccupied with the issue of regulatory burden and had not proposed additional enhancement for the protection of human subjects.

Dr. Prentice asked if the speaker knew what percent of human research in the U.S. is unregulated. Dr. Schomisch responded that no one really knows, but probably at least 30 percent of it is unregulated. The Chairman observed that regulations governing animal research are relatively recent (1985 for the Public Health Service and 1989 for regulations from the U.S. Department of Agriculture). However, he granted that there is no gap in coverage for animals and "they are ahead of us."

Mr. Paul Gelsinger, also with CIRCARE, highlighted the issue of unreported adverse events, which he held responsible for the death of his son. That lack of reporting, he said, prevented the IRB and an advisory committee from halting the study. He felt the committee was continuing to "push off" this critical issue.

Dr. Prentice explained that adverse event reporting was one of the first issues addressed by the committee; its recommendations to the Secretary of HHS resulted in the establishment of a Federal task force consisting of representatives of all agencies that is currently examining the interface between IRBs and data monitoring boards. The subcommittee on Subpart A is not yet addressing this issue because it is waiting to see the conclusions of this task force. In response to a query from Mr. Gelsinger regarding the time frame and oversight of the task force, Dr. Prentice confirmed that the person in charge was Dr. Amy Patterson and said the group is making progress. He was hopeful that there would be a satisfactory resolution that would not only help protect human subjects, but also relieve the regulatory burden placed on IRBs that currently must attempt to analyze and respond to thousands of adverse events without data.

Report of the Subcommittee on Research Involving Children

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

KEY DISCUSSION POINTS, SUBPART D, §45 CFR 46.40

Parental Permission and Assent: What do the Regulations Say?

Dr. Kornetsky reviewed the regulations briefly. She noted that there is a large span of development in children from birth to adolescence, and the appropriateness of procedures will differ according to the age of the child.

She explained that "permission" may be given by a parent (biological or adoptive) or by a legal guardian. She stressed that for research conducted under §46.406 or §46.407, in which there is no potential for direct benefit and greater than minimal risk, permission must be obtained from both parents unless the parent is deceased, unknown, incompetent or not reasonably available or when one parent has complete legal care and custody of the child. IRBs often gloss over this requirement. Documentation required to prove permission has been given is similar to that required for consent under Subpart A.

HHS permits IRBs to waive parental permission in some circumstances, including when the child is abused or neglected. However, FDA does not allow this option, and many IRBs choose not to use it. Ms. Kornetsky also observed that State laws have a bearing on whether waivers are permissible.

"Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not in itself be construed as assent. Rather, assent means the actual engagement and discussion with the child at whatever level is possible and the child's agreement to participate in the research. The regulations hold IRBs responsible for determining that adequate provisions have been made for soliciting the assent of children when the IRB judges them to be capable of providing it. When the IRB determines that assent is required, it must also determine whether and how assent must be documented. The regulations specify instances in which assent is *not* required, such as when the child is too young to give meaningful assent (though no age guidelines are given, and the IRB must make this determination). The regulations do not prescribe the methods for obtaining or documenting assent. The regulations do not say that the assent must be in written form, though most IRBs do have written assent forms.

Regulations make the IRB responsible for the following decisions:

- Approve and document the informed consent process used to obtain permission from parent or legally authorized representative;
- Determine if one parent is sufficient;
- Determine if assent is required;
- Approve the mechanism to obtain and document assent; and
- Determine if parental permission may be waived, and if so, what additional protections must be put in place.

Clarifying Terminology and Procedures

Dr. Fisher reported that the subcommittee on Part D had met to identify terminology and procedures that required clarification and consensus. She outlined for SACHRP the related issues they plan to address and explained why they are areas of potential confusion.

Waiver of Parental Permission and Child Assent. The IRB is required to consider both Subpart A §46.116 and Subpart D §408(c). The subcommittee will be considering how these two regulations are similar or different as guides for investigators. Specifically, it will consider the following questions:

- What conditions would qualify as ones in which the IRB may waive this requirement on the grounds that "the research could not practicably be carried out without the waiver or alteration"?

For example, does this encompass difficulty contacting parents or instances in which the child will not participate if parental permission is sought?

- How does one assure that parental permission waiver "will not adversely affect the rights and welfare of the subjects" (§46.116 [d][2])? For example, does this mean it is acceptable to waive parental permission if the child is cognitively able to give informed assent or dissent?

- When is getting a child's assent not "practicable"?

- Under what conditions is it appropriate to waive child assent if parental permission has also waived under §46.116? How does one assure that in such circumstances the waiver "will not adversely affect the rights and welfare of the subjects" (§46.116 [d][2])?

Waiving Guardian Permission under §46.408(c). A guardian's permission may be waived if the IRB finds that this is "not a reasonable requirement to protect the subjects" and if "an appropriate mechanism for protecting the children…is substituted [that]…is not inconsistent with Federal, State, or local law." Questions that arise for IRBs in this area include:

- Besides neglect or abuse, what other situations could be considered as ones in which getting the guardian's permission is not "reasonable"? Could this apply, for example, to a study of psychosocial variables affecting the psychological, social, and academic development of self-identified gay and lesbian youth, in which some participants do not want their guardians informed of their sexual orientation?

- What is an "appropriate mechanism" to protect the child that could be substituted for the guardian's permission? Is this always a participant advocate? Is an individual assessment of each child required to decide what is appropriate?

Waiver of Parental Permission and Definition of Children. There are several questions related to who meets the regulatory definition of "children," which includes those who "have not attained the legal age for consent to treatments or procedures involved in the research" under applicable laws. These include:

- *Are emancipated minors children?* According to §46.402, emancipated minors are not considered children under Subpart D.

- *Are mature minors children?* State law may allow a child to be treated as an adult for certain purposes, such as consenting to receive treatment for venereal disease or substance abuse. Under §46.402, mature minors are not considered children if they can independently consent to the treatment or procedures involved under the research according to the jurisdiction's laws.

- *When is a child a mature minor under §46.402?* There is some confusion on this issue, since few States have specifically addressed the participation of minors who are adolescents in research. Often research that includes procedures to which the child is clearly allowed to give independent consent (such as receiving treatment for depression) also includes other procedures (such as identifying psychosocial correlates of depression) to which the mature minor is not specifically allowed to consent.

- *If a child is considered a mature minor for a specific treatment or procedure, but the research*

procedure is not normally conducted as part of the treatment, can parental permission be waived?

- *Is it "unreasonable" to require parental permission for research procedures that an adolescent could otherwise consent to outside of research?*

The Institute of Medicine (IOM) has made several recommendations regarding when waivers of parental permission could be granted for adolescents, and the subcommittee is generally in unity with these, though further consideration is needed before recommending their adoption.

The Emergency Research Waiver and Waiver of Parental Permission. Regulations say that both parental permission and child assent may be waived under certain circumstances, such as when subjects are facing a life-threatening situation that necessitates intervention. The subcommittee proposed that SACHPR consider clarifying that *the Emergency Waiver may also apply to research with children when parents are present.* An example in which this applies would be a situation in which there is clinical equipoise between two emergency treatments for a life-threatening pediatric seizure disorder, and their efficacy will be compared in a randomized clinical trial. The time required to secure parental permission would compromise the child's health. However, when children can be identified as having conditions that would make them eligible to participate in emergency research, the investigators could explain the procedures to the parents and secure their permission before the crisis occurs. The subcommittee recommends *that parental permission should be secured in advance for such research whenever possible*.

Documentation of Child Assent. Dr. Fisher highlighted this area as one that frequently causes problems for investigators, IRBs, and parents. The issue is when and how a child's assent should be documented. Key questions in this area include the following:

- *At what age, if any, should signed assent from a child be required?* Some have argued that signatures in general are coercive, because most children are not used to signing to give their permission for anything. Also, children are sometimes asked to sign long documents that they are unlikely to understand. Guidance in this area might be useful. The subcommittee plans to consider the ages at which children typically do sign medical and other forms and determine to what extent assent to research would be comparable.

- *What is developmentally appropriate?* While the issue of developmentally appropriate language levels has been addressed, there is little information on what elements of informed consent are appropriate for different ages. What should be shared with children at different levels of development?

DISCUSSION

Members raised discussion points related to the preceding presentation.

Waiver of Parental Permission. In regard to ensuring that a waiver of parental permission "will not adversely affect the rights and welfare of the subjects," Dr. Prentice asked Dr. Fisher to clarify the meaning of the fourth bullet: "Does the minimal risk nature of the research mean that points #1 - 3 are unnecessary?" Dr. Fisher explained that points 1-3 refer to the preceding points on the slide, not to the waiver criteria. If the study is minimal risk, is it still necessary to prove that the children are old enough to comprehend assent information at adult levels, that adequate measures are put into place to ensure

participation is voluntary, and that a participant advocate is assigned?

Emergency Waivers. In reference to the rationale for an emergency waiver, Dr. Prentice noted that the language of the regulation refers to "informed consent" even though the research subjects are children. Ms. Kornetsky agreed that the question is how the regulation applies to children, specifically in reference to an emergency waiver of assent. Dr. Fisher added that it is also applicable to conditions for waiving parental consent. She further explained that the subcommittee recommended that the waiver be specifically applied to conditions in which the parent is present, but it is not in the child's best interest to delay the treatment by taking time to get parental permission.

In regard to the subcommittee's recommendation that permission for a child to receive emergency treatment through a research protocol in advance wherever possible, Dr. Gyi noted that the emergency waiver under 21 CFR §50.24 is already associated with a "community consent" process. He questioned whether advanced permission should be necessary, given that parents with a child having the research condition should already be part of the §50.24 process. Dr. Fisher explained that this would depend on whether or not the population at issue can be identified in advance. If it can, then getting permission in advance is clearly preferable to having to waive parental permission in an emergency. Ms. Selwitz questioned whether the process of getting advance permission would be considered an emergency waiver. Dr. Fisher agreed and indicated the presentation would be changed to avoid this potential confusion.

Dr. Jones raised the issue of how to handle persons in an emergency situation who have indicated in advance that they do not wish to participate in a protocol. Dr. Fisher suggested a simple record system in which, for example, those who agree to participate each have a red dot in their records.

Dr. Prentice raised the issue of how a waiver can be granted without adversely affect the rights of the subject involved, particularly if both parental permission and child assent are waived. He asked whether appointing a participant advocate was the subcommittee's recommended strategy. Dr. Fisher responded that this might be too extreme a solution for minimal risk research. Dr. Prentice suggested that the subcommittee consider applying the "reasonable person" standard, used in malpractice law, to cases in which children are unable to assent. The standard, if invoked, would be whether a reasonable child of the same age would have given assent. Ms. Kornetsky pointed out this approach would be equally applicable to adults. However, Dr. Fisher raised the issue of how it could be reliably determined what a reasonable person would in fact say.

Emancipated and Mature Minors. Dr. Prentice asked whether State laws regarding emancipated minors and mature minors have been compiled. Dr. Fisher responded that the Institute of Medicine commissioned such a compilation and it has been published. She noted that a related issue arises for multi-site studies in which research is occurring in different States with different laws.

Obtaining Assent. Dr. Prentice asked whether the subcommittee had addressed the benefits and disadvantages of having children sign assent forms. He shared that he had recently asked a group of parents for their views regarding such forms, and they were unanimously opposed to them; however, the children seemed to like them, and the doctors saw them as a means of developing their autonomy. Dr. Fisher said the subcommittee had not yet addressed this issue, but plans to do so. She noted that even when children have the cognitive capacity to understand the research as adults do, they may have no experience in refusing adults. Dr. Fisher also questioned whether there was any empirical evidence on which to base a recommendation on the subject. Ms. Kornetsky added that cultural differences can be important in determining whether an assent form is appropriate and that having a child sign a form is not the only way to recognize that child's developing autonomy. Dr. Fisher reported approvingly a recommendation from the Children's Oncology

Group that everything said to a child and what the child said back should be documented, along with why signing a form did or did not appear to be appropriate.

Ms. Selwitz focused on the issue of when child assent is not "practicable." She questioned the relevance of Subpart A §46.116 (d)(3) to child assent. Dr. Fisher noted that §46.408, which addresses parental permission and child assent, refers back to §46.116 (d)(3). However, Ms. Kornetsky agreed that the §46.116 (d)(3) applied primarily to parental permission rather than child assent. She added, in response to a question from Dr. Gyi, that the only two instances in which assent need not be obtained are when the child is not capable of giving assent or when the research holds a possibility of direct benefit that is not otherwise available.

Clinical Equipoise and the Use of Control Groups

Dr. Fisher reminded SACHRP that the subcommittee was asked to identify and explore issues to be addressed regarding §46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects). These are in addition to the issues already presented to SACHRP, which resulted in approved recommendations to the HHS Secretary.

The subcommittee identified issues related to the application of component analysis to evaluate risks and benefits of randomized clinical trials, the definition of "available alternative approaches," vaccine trials, and placebo-controlled trials involving children.

Component Analysis of Risks and Benefits. The issue here is how component analysis (previously approved by SACHRP) applies to various types of clinical trials. The subcommittee suggested that SACHRP may wish to clarify how component analysis applies to each of the following instances.

- *Pre-randomization*. The component analysis approach means that the risks and benefits of placebo and treatment groups must both be assessed.

- *Risks of research procedures used in intervention as well as control groups (including, placebo, placebo with cross-over, treatment as usual, or alternative treatment controls)*. For example, how do you evaluate the risks and benefits of "treatment as usual"?

- *Ability to receive the intervention at the end of the trial.* The question is whether this is to be considered a benefit of the research itself.

- *Symptom management.* Should the assistance in system management a subject not receiving treatment receives when participating in research be construed as a benefit? How it should be evaluated from the standpoint of clinical equipoise?

Available Alternative Approaches. There has been confusion over the meaning of both "available" and "alternative." For example, must an alternative be affordable to be considered available? Does the alternative have to be empirically validated? Do strategies that are clinically accepted but untested qualify as alternatives? What constitutes evidence that a given alternative is effective or appropriate? Is treatment as usual in independent practice nonresearch settings considered an appropriate alternative?

Vaccine Trials. Such trials have the potential to help large numbers of children. IRBs may benefit from guidance to help them determine the appropriate Subpart D regulations: minimal risk (§46.404), minor

increase over minimal risk with direct benefit (§46.405), or minor increase over minimal risk without direct benefit (§46.406). It is not clear that there is a probability of direct benefit, since benefit to the individual child is different from benefit to the aggregate. It is also not clear whether the level of risk is minimal or minor increase over minimal risk. A smallpox trial some years ago was classified all three ways by different IRBs.

Placebo-Controlled Trials Involving Children. Dr. Fisher informed SACHRP members that the FDA Pediatric Ethics Working Group had a Pediatric Advisory Subcommittee that issued a consensus statement (2000) that contained recommendations worthy of SACHRP consideration. These include the following:

1. *Placebo-controlled trials may be acceptable if there are no approved or adequately studied therapies for children with the condition under study.*

2. *For serious or life threatening conditions, a Data Monitoring Committee (DMC) should be used with planned interim monitoring and stopping rules to permit early termination of a study that has shown clear evidence of ineffectiveness or unacceptable risks prior to completion of planned studies.* Dr. Fisher suggested that a significant question to explore is when a DMC should be required in placebo controlled or other §46.405 research.

3. *In studies of symptomatic therapy for less serious conditions, it may be helpful to build in individual patient discontinuation criteria (early escape) so that exposure to ineffective treatment is limited.*

4. *Add-on placebo-controlled trials that do not deny any element(s) of the standard of care (SOC) are generally acceptable if individual patient study discontinuation criteria are defined.* Dr. Fisher observed that IRBs do not often make the distinction between usual placebo-controlled trials and add-on, placebo-controlled trials that offer "standard of care plus." She suggested this clarification would be especially useful in social and behavioral sciences. Further, it is not clear how such trials should be assessed in terms of equipoise (risks and benefits).

5. *In placebo-controlled studies of minor illnesses and symptomatic conditions, exposure to placebo and patient discomfort can often be minimized by use of a randomized withdrawal design, usually with defined individual patient discontinuation criteria (escape rules) so that the time of exposure to ineffective treatment is minimized.* Dr. Fisher observed that the meaning of "minor illnesses and symptomatic conditions" should be clarified.

6. *These studies can be used to demonstrate long-term effectiveness when a long-term placebo-controlled trial would be unacceptable.*

7. *DMCs generally are not needed for studies of symptomatic conditions but would be desirable if there were important safety concerns.*

Dr. Fisher asked SACHRP to provide direction on whether the subcommittee should explore these recommendations further. She noted that the subcommittee plans to review the key literature on parental permission and child assent at its next meeting. It will also begin to consider the lack of harmonization between FDA and NIH criteria in this area.

DISCUSSION

Members raised a number of issues regarding the preceding presentation.

Component Analysis: Pre-Randomization vs. Post-Randomization. Dr. Prentice observed that the presentation included a pre-randomization application of component analysis, but there was no mention of post-randomization of component example. He explained that the analysis of risks and benefits would differ according to the point of view of the analysis. He gave the example of a clinical trial in which one arm is a placebo and the other is a study drug. A pre-randomization analysis might see a benefit in the 50 percent chance of getting some form of treatment. However, a post-randomization analysis would have to look at the risks and benefits of each arm separately.

Dr. Fisher indicated that her understanding of component analysis is that it must be post-randomization. Dr. Prentice asked the subcommittee to consider the issue further; he contended that some studies might be either §46.405 or §46.406 depending on which type of analysis is done. He also informed SACHRP that some IRBs consider the risks and benefits from both perspectives. Dr. Gyi agreed, explaining that from his perspective the two forms of analysis are both essential. Dr. Weiner found both the separation artificial from the standpoint of the subject's experience. However, she agreed that the issue should be explored in the context of Phase III trials.

Ms. Selwitz, however, stressed the difficulty of explaining this type of discussion to investigators and research staff. She advised that deliberations be framed in a way that they can be communicated and understood. Dr. Jones shared her concerns. Ms. Kornetsky agreed, and reminded SACHRP members that the presentation did not focus on recommendations, but rather on issues. Dr. Fisher added that it is the committee's practice to begin with ethical principles, which can be abstract, then move toward practical conclusions.

Serious and Life Threatening Illness and Other Illnesses. Dr. Weiner suggested that the subcommittee distinguish between these categories of illness, including grappling with the meaning of "minor" as needed.

Available Alternative Approaches. Dr. Gyi asked whether the subcommittee had given thought to instances in which study drugs are made available for subjects in placebo arms after the study is complete. Ms. Kornetsky said this was a recognized issue, and the subcommittee had considered whether or not this should be viewed as a benefit. Dr. Fisher said some study participants did not see it as such because the drug would not be likely to have been proven effective until more studies have been done.

The Chairman suggested that the subcommittee continue to explore issues such as waivers, emergency waivers, component analysis, and placebo controls and work towards recommendations to be presented at the November meeting. He saw parental permission and child assent as the most "doable." Ms. Selwitz and Dr. Gyi agreed.

PUBLIC COMMENT

Dr. Prentice invited public comment.

Ms. Cami Gearhard spoke as a member of the Quorum IRB, a central IRB that reviews both multi-site and single site studies. She responded to the proposal that an IRB be allowed to use expedited review to

review any research that this minimal risk. She observed that the proposal would offer flexibility, but suggested a more conservative approach in which expedited review procedures are allowed for any research that is determined by the convened full IRB to be minimal risk. She held this strategy would be especially useful to IRBs that review research on a multi-site basis.

Dr. Rick Herman, director of Human Research Protocol Office for the National Health Effects and Research Laboratory for the Environmental Protection Agency (EPA), expressed gratitude for the work done on protection of children, noting the "deplorable" lack of good data and information on what the best treatment modalities are for children. He stressed that children deserve the same degree of reliable scientific data available for adults. However, he stressed the importance of not discouraging scientific inquiries that could benefit children's health.

Summary and Wrapup
Ernest D. Prentice, Ph.D.

The Chairman thanked everyone for a productive meeting. He observed that the Subpart A subcommittee will continue its work on continuing and expedited review, which he hoped would culminate in some recommendations for SACHRP to consider at its next meeting in November. The Subpart B committee will address a variety of issues, including parental permission, child assent, and waivers; in addition, it will continue to address some particularly thorny issues related to the application of §405. He highlighted the importance of being able to approve ethically appropriate research with therapeutic intent under §405, since it might otherwise not be approved.

TUESDAY, AUGUST 2

The Chairman provided an overview of events for the day, which focused on perspectives from advocacy groups on issues in research subject protection. The Chairman noted this is the first time an entire day of SACHRP's deliberations has been devoted to public perspectives.

Panel #1 – Perspectives of Research Subjects, Representatives, and Advocates
Paul Gelsinger, President, Citizens for Responsible Care and Research (CIRCARE); Bob Huff, Editor, Gay Men's Health Treatment Issues, Gay Men's Health Crisis, New York; Carolina Hinestrosa, Executive Vice President for Programs and Planning, National Breast Cancer Coalition

Remarks by Paul Gelsinger

Mr. Gelsinger explained that CIRCARE has worked for nearly a decade to bring the need for major reforms in the protection of humans in research to the attention of Federal agencies, legislators, and the public. He noted that the scope of his remarks will relate to the current system of protection, as requested by SACHRP, rather that discussing strategies that might further strengthen human subject protection.

The speaker contended that society has a moral obligation not to exploit altruistic individuals who willingly serve the public good by acting as research subjects. However, he said the current human subject protection system does not effectively protect the rights and welfare of humans in research for many reasons.

First, he faulted the system for addressing compliance issues on a *post hoc* basis, coming into play only when a subject is harmed or an allegation of noncompliance is made. Another factor is the system's reliance on the good will of institutions and investigators, who often have a conflict of interest that affects their attention to human subject protection. The prestige and ranking of institutions are largely determined by the value of

research grants awarded, while investigators depend upon the research grants for career advancement, prestige, and often their salaries. These powerful motivators can conflict with the protection of research subjects.

Mr. Gelsinger also saw the system as misguided in that rather than protect the rights and welfare of research subjects, it only gives remedies to the regulator to make the noncompliance stop, using determination letters and infrequent prosecutions that proceed at a "glacial" pace. He attributed the slow pace, at least in part, to inadequate OHRP staffing, noting that, based on the number of assurances filed in February 2005, each of the Compliance Oversight's Division six staff members is responsible for the oversight of more than 1,333 institutions. Mr. Gelsinger faulted the process for holding institutions, rather than the investigator, responsible for compliance. As a result, no consequences befall an investigator who fails to protect research subjects. Finally, he said, it is clear that the system does not effectively protect the rights and welfare of research subjects because the same things keep happening over and over again.

Mr. Gelsinger has come to believe that the integrity of the research enterprise has been undermined. He held that the increased volume of research over the last decade or more has exacerbated the tension between institutions and investigators, on the one hand, and the need to protect human subjects, on the other. The IRB system is strained by the growing numbers of trials. The speaker cited OHRP determination letters as evidence of serious failures in human subject protection. He said they show that many of today's IRBs cannot reliably distinguish between research and medical care, approve consent forms without the required elements, approve proposed research on condition of revision without ensuring revisions are made, approve proposed research without adequate information, fail to maintain quorums at meetings, fail to review research at appropriate intervals, fail to make required determinations for review of research with children and prisoners, and don't have appropriate standard operating procedures. For their part, some investigators fail to obtain IRB approval, fail to supply material information to the IRB, fail to report unexpected serious adverse events, fail to obtain informed consent, fail to maintain records, engage in questionable subject recruitment schemes, and fail to follow research protocols. When these serious problems occur, he says, there are seldom serious consequences.

While there have been many generally accepted proposals for improvements in research protection, Mr. Gelsinger said no meaningful improvements have been instituted. In fact, he said, some problems documented in 2000 are even more pronounced today. As an example, he cited an inducement to recruitment whereby the order in which co-investigators would be listed as authors in the study publication dependent upon the number of subjects recruited.

Mr. Gelsinger next focused on the inadequate reporting of unanticipated serious adverse events (SAE) to OHRP. He said the failure to report unanticipated SAEs affects IRB review and approval of proposed studies because it prevents the IRB from minimizing the risk to the subjects and may lead to an inadequate informed consent process. He pointed out that subjects cannot consent to undertake risks which are not disclosed to them; nevertheless, he pointed to OHRP and FDA administrative actions as evidence of widespread failure to report unanticipated SAEs.

Mr. Gelsinger noted that an NIH reminder to institutions regarding mandatory reporting of unanticipated SAEs resulted in an overwhelming number of SAE reports (900). He encouraged SACHRP's interest in streamlining the importance of SAEs to reduce the administrative burden on IRBs, but said streamlining would not impact the problem of investigators who are unwilling to report them, who are unaware of their reporting obligations, or who are unable to distinguish between anticipated and unanticipated SAEs. For such investigators, he said, no consequences follow upon their noncompliance.

Failure to adequately report SAEs was responsible for the death of Mr. Gelsinger's son Jesse in a nontherapeutic gene therapy study. This Phase I clinical trial was being conducted at the University of Pennsylvania by the then- President of the American Society of Gene Therapists and overseen by the FDA and the NIH's Recombinant DNA Advisory Committee meeting. Jesse's decision to participate in this safety study was based on his entirely altruistic desire to help infants and others born with the homozygous variant of ornithine transcarbamylase (OTC) deficiency, which is invariably fatal. He was aware there would be no direct medical benefit for him. The experiment was designed to test whether this technology was safe to use in newborns with the worst form of OTC, of which Jesse had the mild heterozygous variant. He died of a massive immune response four days after receiving an infusion of a modified cold virus. Unanticipated serious adverse events in a previous dose cohort had not been properly reported, and the deaths of animals receiving test article also were not incorporated into the consent form.

In the case of the study that in which Jesse died, both the PI and the institution stood to profit from the research. The principal investigator owned a 30 percent interest in the biotech company that would profit if the research showed favorable results. The same company owned the patents on the investigator's gene transfer products and procedures. Finally, through the standard material transfer agreement, the University of Pennsylvania, the institution responsible for reviewing and approving the proposed research, owned stock in this company.

Mr. Gelsinger further explained that the University of Pennsylvania experiment was a dose escalation study. One-tenth the dose that Jesse received had caused four consecutive subjects in a previous dose cohort to develop liver toxicities that should have stopped this study. The FDA was aware of these reactions, but allowed researchers to continue with dose escalation; Mr. Gelsinger has never received an explanation for this that he accepts as adequate. In addition, he said, serious protocol violations went undetected, some of which were deliberately concealed from the oversight authorities. In February of this year, after nearly four years of investigation, the Department of Justice decided not to file criminal charges against the people Mr. Gelsinger holds responsible for Jesse's death. Instead, they paid a fine and were allowed to continue human research pending retraining and supervision of the investigators.

Mr. Gelsinger said that CIRCARE had many suggestions on how the system can be improved. The work of the many bodies that have addressed the problems that put human subjects at risk can be pulled together and implemented. He urged OHRP to "put teeth in the regulations by supporting a system for protecting research subjects that is codified in law."

Remarks by Bob Huff

Mr. Huff reviewed the history of AIDS in the gay community and the search for effective treatment through research. He said the community response was immediate when AIDS was first reported in 1981. Nevertheless, despite energetic attempts on the part of the gay community to share information on the disease and its treatment, people continued to die through the 1980s and treatment proved ineffective. In 1987, an organization called ACT UP responded to what they saw as slow research and unnecessary research methods. They surrounded the FDA in 1988, in a protest Mr. Huff saw as effective because the FDA sped up drug approvals. NIH was also "stormed" in 1990, and the ensuing dialogue resulted in AIDS patients receiving access to trial drugs as they were being tested. A Treatment and Data Committee formed to enable the gay community to educate itself on current research and the state of scientific knowledge. The committee often critiqued NIH when members felt the institution's methods were unfair or wrongly motivated. It also learned to be critical of industry methods and data.

Mr. Huff expressed appreciation for FDA's willingness to engage in dialogue with the gay community and help educate them. A group that brings together industry, academia, and researchers maintains an ongoing dialogue on issues, while advisory committee hearings are open to reporting.

Mr. Huff described several problems related to AIDS-related research. One difficulty has been enrolling a sufficient number of women in trials. This difficulty resulted in drugs being used for women's use that had not been tested in women, some of which have serious toxicities that do not exist in men. The difficulty of enrolling people of color is another serious challenge, since it is possible that race and ethnicity may also influence pharmacokinetic responses to treatment. The speaker also pointed to community consultations and informed consent processes with high-risk subjects in other countries that were poorly done. An important intervention is being stopped because of a failure to offer the best available prevention – clean needles – to study participants. Informed consent is also reportedly being "glossed over" in studies in eastern Europe, Russia, and China. The activist community has also been concerned about investigators who offer inappropriate inducements to enroll people as research subjects who are treatment-naïve, but at a state of low immune susceptibility.

The speaker drew attention to news stories about inappropriate enrollment of participants, noting that the pieces are being generated in association with a group of people who do not believe that HIV is the cause of AIDS. Since the public is generally unaware of the agenda behind the stories, the articles increase suspicion within the U.S. and internationally.

Mr. Huff emphasized the importance of community involvement and education, pointing to the Treatment Action Campaign in South Africa as a model. He stressed the importance of "informed, involved independent community participation in all the decisions from the development of the protocol forward."

Remarks by Carolina Hinestrosa

Ms. Hinestrosa focused her remarks on how the National Cancer Coalition, formed in 1991, approaches issues of patient participation and consumer involvement in the research process. The coalition was inspired by the previously described activism around HIV/AIDS and its successes. With this model in mind, it was felt that it was very important to have a group focus on political and systems change in order to move the research forward and end the disease. To accomplish this, it seeks to give consumers access to research and influence over it.

The coalition is proud of a number of significant accomplishments. It has substantially increased funding for breast cancer research. It was instrumental in the creation of NIH's Department of Defense Breast Cancer Research Program, which alone has brought close to two billion new dollars into breast cancer research. It developed a system of care for uninsured women who are diagnosed with breast and cervical cancer through the Centers for Disease Control (CDC) screening program. It also created an educated grass roots network of activists, survivors, and patient advocates, who are making decisions every day about research, about quality care, and about public policy.

The coalition stresses the importance of well-informed, educated consumers participate at every level where decisions are made about breast cancer. It believes that meaningful involvement will result in a system that is transparent and accountable to the patients who are its primary stakeholders. Participation provides opportunities to ask "dumb questions' that may lead to breakthroughs.

To prepare consumers for effective participation, the coalition educates them by providing a science course for consumers for survivors and patient advocates. Known as Project Lead, the course offers participants an

introduction to the language and concepts of science, as well as providing a basic understanding of the research process. The course is intended to prepare them to work alongside the research community on issues of breast cancer research. The coalition now offers an advanced course as well, known as Clinical Trials Project Lead, which helps consumers work with research organizations to design and monitor clinical trials. Consumers are now involved in developing research projects, developing research mechanisms, evaluating proposals as peer reviewers, and making funding decisions. Their involvement helps frame research in patient-centered terms. To further promote dialogue, the coalition provides reports and participates in regular meetings that offer opportunities for dialogues with scientists working in the field. For example, the Coalition is currently involved in helping to develop a strategic plan for biomarker research.

In addition to influencing research at the Federal level and serving on such key committees as the IOM Committee on Patient Protections, Coalition members work toward system change in the private sector. This area of effort involves not only developers of interventions for breast cancer in the pharmaceutical industry but also third-party payers of health care.

The Coalition has a clinical trials partnership that seeks to improve trial design, to monitor and monitor to increase access and accrual to innovative research, to educate the medical community and consumers about that research, and to promote the initiation of high-quality breast cancer trials. The speaker stressed that while there are many clinical trials, there are quite a few that are wasteful and unnecessary. Consumers are interested in access to important and innovative trials that will help achieve the goal of ending the disease.

The Coalition refuses to help recruit patients for trials in which it has not been involved in design from the outset. To win its support, the trial must be designed to answer an important and novel question, and the study must be well designed, scientifically rigorous, and conducted in an ethical manner. There must be sufficient data supporting the potential efficacy and safety of the intervention and the capacity to provide meaningful information to potential participants. There need to be safeguards for patient privacy. Of course, IRBs and data safety monitoring committees are needed. The Coalition also seeks to ensure that diverse populations are included. A final condition is that the results of the trial must be made public, whether they are positive or negative.

Ms. Hinestrosa closed by offering her observations of the current system of patient protections. Key points include the following:

- The current IRB system does not offer enough protections to patients. The system is over-burdened and inefficient, and it lacks adequate consumer participation.
- The U.S. system of health care is incentivized by profit. Combined with the fragmented system of care, this often puts the patient in a vulnerable position.
- It is critical to give consumers all available information and involve them in decision-making so that they can help ensure accountability.
- Researchers are eager to publish their results, and in the rush to be the first to publish, the patient may become vulnerable.
- The informed consent form is often a legal document designed to protect an institution rather than a means of informing and protecting patients.
- It is not clear whether data safety monitoring boards should be focused on protecting patients enrolled in the trial or on future users of the intervention.

- Post-marketing surveillance of drugs is often lax.
- There is a rush to approve drugs as fast as possible in order to save lives. Dr. Hinestrosa stressed the importance of maintaining a disciplined approach to the research process.

Ms. Hinestrosa's recommendations to address these issues included the following:

- Implement the recommendations of the IOM Committee on Patient Protections, including the "critically important" recommendation that review of research proposals include scientific review, financial conflict of interest review, and ethical review.
- Ensure that as information is exchanged with patient subjects, the focus is on truly informing the subject rather than protecting the institution.
- Continue to educate consumers and give them the tools they need to be peers with the scientific community.

DISCUSSION

The three panelists were invited to respond to questions from SACHRP members.

Systemic Improvements. After recalling the institutional shutdowns of the 1990s and the changes made in the years that followed, Dr. Prentice asked Mr. Gelsinger to clarify his position that no meaningful improvements to the system have been made. The speaker explained that he meant that the improvements that have been made are "minor in relation to the size of the problem." For example, in gene therapy, a reporting system for serious adverse event has been created, but it has not carried over to other research. While many IRBs have upgraded themselves, many have not, in part due to lack of either funding or a clear mandate for doing so.

OHRP Workload and Funding Issues. Dr. Prentice invited Mr. Gelsinger to elaborate on his observation that OHRP is seriously understaffed. The speaker responded that it is critical to infuse money into the oversight of research so that it is done ethically. At Mr. Gelsinger's suggestion, the Chair invited Dr. Adil Shamoo of CIRCARE to elaborate further. Dr. Shamoo noted that there are somewhere between 7,000 and 9,000 IRBs in the country, with an unknown number of additional IRBs that submit only to the FDA (which does not require registration). Many of these IRBs, he claimed, are "mom and pop operations" on which OHRP has no real data to show whether or not they have improved.

Dr. Jones asked whether the groups represented by any of the speakers have advocated for increased funding for human research protection and what percentage of research funds should be devoted to it. Mr. Gelsinger said CIRCARE does not have funding to do this kind of advocacy. Ms. Hinestrosa said her organization is primarily interested in supporting underserved research areas.

Community Representation. Dr. Prentice invited speakers to comment on Mr. Gelsinger's suggestion, made in PowerPoint slides he did not have time to present, that at least 51 percent of the membership of IRBs should be local community members. He noted that it is a challenge to get sufficient expertise to review highly scientific protocols. He said he would be worried about how the scientific and medical aspects of the review would be addressed with such a large percentage of community members.

Mr. Gelsinger responded that in fact 25 percent representation would be acceptable. He agreed that many IRBs lack the expertise to review cutting-edge technologies. For that reason, he suggested this should be done by an outside group working for the IRB. This would leave the IRB free to concentrate on the ethical rather than the technical review of the research. He pointed out the IOM made similar suggestions in *Responsible Research* (2003). Finally, he suggested that SACHRP itself should have more than one community representative.

Ms. Hinestrosa reflected on her experience serving on a "perfect IRB," a pilot central IRB of the National Cancer Institute (NCI) that had 20 to 25 percent consumer representation. Other members included pharmacists, surgeons, oncologists, general practitioners, and biostatisticians. Protocols were scored by a scientist and a consumer working together. A primary role of consumer participants was to keep asking, "why are we doing *this* trial?" However, she observed a high level of pressure from the investigator community to have the IRB approve their proposals quickly. Despite the idyllic experience, she added, the work had little impact because protocols were re-reviewed at the local level.

Mr. Huff said he had only limited experience with IRBs. However, he expressed concern about studies designed solely to help position pharmaceutical products in the minds of prescribers. He questioned whether this was an ethical use of human subjects.

Informed Consent. Dr. Gyi told Mr. Gelsinger that he himself had been a research participant and stressed the commitment of SACHRP members to make a meaningful difference in human subject protection. Speaking as the Co-Chair of the subcommittee on Subpart A revisions, he then requested guidance from panel members on the subject of informed consent.

Mr. Gelsinger said he went through the process only once, with his son, and the process failed. He said a critical focus should be whether the consent process actually reflects what is happening in the protocol, which is difficult to know if the investigator is not forthcoming. He said that great transparency and expertise is needed to analyze the protocol and ensure that what the subject needs to know is there. In this regard, the IRB at the University of Pennsylvania was inadequate, in that it approved a consent form from which material on animal deaths in previous trials had been removed. Combined with information on the toxicity humans had experienced at one-tenth the dose Jesse would receive, this information would have made a big difference in Mr. Gelsinger's decision about his son's participation.

Ms. Hinestrosa suggested that when information of this nature is not placed on a consent form, it is probably because the research community views the IRB system as a burden or obstacle and simply looks for ways to get around it. Another difficulty in ensuring key information is included is the large number of protocols IRBs must review in a single meeting. She stressed that to have a good consent form, the IRB must have a solid grasp of the research and its potential problems, and it is difficult for overburdened IRBs to manage this. She also emphasized the importance of publishing negative results so that potential participants have a more balanced view of what is possible.

Mr. Huff advised that informed consent is not really a matter of forms but a process that requires engagement between two or more people. What matters is whether the individual subject understands the research and its risks, and that understanding may develop in the interchange between the study nurse and the subject. A development that alarms Mr. Huff is the increasing use of study nurses who are able to speak the local language but have little or no scientific training.

Conflict of Interest. Dr. Hauser asked Mr. Gelsinger to comment further on investigator conflict of interest. He asked what level of participation an investigator should be allowed to have in the financial outcome of a study, if any. Mr. Gelsinger said unequivocally that investigators should have no financial interest in the work, because it will "put blinders up." Those who do have such interests should "recuse themselves from overseeing the work and give it to somebody else." In regard to institutions, those that have a financial interest in the study should ensure that an outside IRB is given oversight of the study to ensure that the proper ethical "firewalls" are firmly in place.

Mr. Huff added that the pharmaceutical industry is adept at "enmeshing" people with talent and influence into relationships, a strategy that is especially apparent in HIV/AIDS work. He stressed the importance of transparency.

Panel #2 – Perspectives of Research Subjects, Representatives, and Advocates

Wanda Jones, Director, Office of Women's Health, Office of Public Health and Science, HHS; Linda Wachtel, Children's Brain Tumor Foundation; Ron Honberg, National Director for Policy and Legal Affairs, National Alliance of the Mentally Ill (NAMI)

Remarks by Wanda Jones

Dr. Jones pointed out that every day women use medicines and take treatments that have never been tested with them. After years of exclusion, some have been injured or died as a result of using drugs that were not appropriate for women's bodies. She maintained that the risks associated with widespread exposure to drugs not tested with women are generally much higher than the risks of including them in research studies. With the research methods and statistical tools today, there should be no excuses; yet the problem continues to be serious.

While there are some legitimate barriers to including women in research, Dr. Jones dismissed many of them as "vestiges of old thinking." These include the ideas that women are harder to recruit, that contraceptives and hormonal states will confuse research results, and that women report more side effects. A more serious concern is the possibility for exposure of a fetus or of an effect on reproduction.

The speaker felt that women would be much easier to recruit if researchers would consider issues of concern to this population. Women may need information on how the study is meaningful to them, transportation to the site, day care, and an explanation of any required changes in contraception method. She recalled her own experiences as a research participant; in one case she had an engaging and interactive consent process, while in another the process was form-based and entirely bureaucratic. She noted that people would be much more likely to participate in studies if informed consent were more typically like the former study.

Dr. Jones noted that NIH's guidelines for funding insist that gender be considered when designing analyzing, and reporting findings from studies in all areas. However, she pointed out that most study-based primary and secondary papers do not report results by gender. Further, male-only studies are still likely to generalize their results to "people" while female-only studies do not make this leap. The Agency for Healthcare Research and Quality has attempted to get information on women participants from researchers on subjects of particular concern to women, but has often found investigators uncooperative or unable to provide these data.

Remarks by Linda Wachtel

Ms. Wachtel shared her story as the parent of a child named Tory who, at 18 months, had a large tumor in his brain stem that was assumed to be fatal. Following surgery, she found her son had become a valuable research candidate; the family received a number of recommendations for chemotherapy protocols. She stressed the difficulty of a family determining the best option in this situation. One protocol used 3 drugs, and another 8; one doctor advised the family to choose the 8-drug protocol on the grounds that 8 drugs would be better than 3. However, another doctor held that the 8-drug protocol would have too high a level of toxicity for a child so young. Eventually, the family took a third doctor's advice to wait and watch. Ms. Wachtel stressed the ethical responsibility of the treatment team to explain options to parents in an unbiased, factual, and understandable manner, explaining potential consequences. She also emphasized the importance of ensuring that research protocols in which children participate are specifically designed for children.

Later, when Tory's symptoms flared again, the family chose to enroll him in a study based on anecdotal data. She observed that parents do have an interest in such data. In the coming years, Tory received chemotherapy and radiation. At age 19, he is still very much alive, but faces secondary challenges and permanent disabilities, both from the tumor itself and from the treatment received. She underlined the urgent need for research to increase the survival rates from pediatric cancer and to address its long-term effects.

Remarks by Ron Honberg

Mr. Honberg explained that the membership of his organization, the National Alliance for the Mentally Ill (NAMI), primarily consists of persons with serious mental illnesses and their families. He noted that many members have become "research groupies" because of the hope derived through research breakthroughs in recent years. However, in the last several years there has been a crisis of confidence related to the research enterprise.

Major concerns stemmed from a University of California at Los Angeles (UCLA) relapse study in which people with serious mental illnesses were taken off their medication. In one situation, a family was shocked to find no one at the research institution who was available to respond when their son decompensated and became violent. Another study participant committed suicide. The "fine print" of the consent form probably explained what could happen, but it was not written in lay person terminology. Concern about this study also led to revelations of other disturbing studies in which symptoms of severe mental illness were deliberately provoked.

In addition to concern about unethical study protocols, Mr. Honberg pointed to a lack of mechanisms for interacting responsibly with potential study participants who have serious mental illnesses. He said regulations make no specific provision for capacity assessment and do not provide a means of determining what should happen if, indeed, the potential subject participant is unable to understand the potential risks and benefits of the proposed study. He said these critical issues were not addressed in regulations.

The speaker also shared his experience working on the intramural IRB at the National Institute of Mental Health (NIMH). He said that because panel members were evaluating protocols presented by colleagues, it was often uncomfortable raising questions or even deferring approval. He felt that he was able to bring

something valuable to the panel: an awareness of the day-to-day issues that people with mental illness experienced.

The perceived gap in the Common Rule regarding specific protections for persons with mental and cognitive disabilities concerned Mr. Honberg. He stressed the importance of safeguards and specific guidance for this population that will prevent abuse and guard against conflicts of interest than can harm subjects. While several attempts have been made to accomplish this on a State or Federal basis, none has been successful.

The speaker identified several steps that could improve protections for such vulnerable people without impeding research. These included the following:

- Patient advocates independent of the research institutions concerned should be available during all research projects greater than minimal risk. Research participants, their families, and advocates should be informed of the patient advocate and how to contact him or her. This individual should be independent of any conflicts of interest; his or her job should be solely to monitor and protect the best interests of vulnerable research subjects.

- IRBs that regularly review protocols involving research on mental illness should include public participants who are consumers and family members who have direct and personal experience with these illnesses. (NAMI is planning to reinstitute training to better prepare individuals to participate on IRBs).

- Whenever research is greater than minimal risk, procedures must be in place to assess the capacity of subjects with cognitive or mental disorders. The speaker said work has been done on capacity assessment and reliable guidelines now exist.

- Advanced directives may be relevant; these would give the subject an opportunity to communicate preferences in the event that the subject loses capacity during the research protocol. People authorized to make decisions on his or her behalf would be specifically identified.

- Research protocols involving persons with serious mental illnesses should specify mechanisms and procedures for responding to psychiatric emergencies.

Mr. Honberg pointed to a strong potential for coercion in this population, which stems from the difficulty in accessing care. He said only about 20 percent of people with severe mental illnesses have access to even minimally adequate treatment in this country. Researchers must be clear that they are offering a chance to participate in a research project rather than treatment. At the same time, they should ensure that participants do get treatment while they are participating and help to link them to treatment providers when the study is over.

DISCUSSION

Subpart E. Dr. Prentice commented that OHRP is in the process of developing a Subpart E that would address issues that arise when persons who are cognitively impaired participate in research. However, it is at an early stage; the next step would be to publish a notice in the *Federal Register* that includes such questions as, “Should there be a Subpart E? What should it look like?”

Mr. Barnes said SACHRP members would be glad to assist as needed. Dr. Fisher added that it would be helpful to see where the proposed Subpart is going in order to be able to address issues such as informed consent for persons with cognitive impairments as Subpart A is reviewed. Mr. Honberg advised OHRP to consult with various stakeholder groups as the Subpart is drafted in order to avoid a "firestorm."

Reporting Data on Women and Minorities. Ms. Kornetsky observed that NIH grant applications specifically ask researchers to specify whether or not women and minorities are included. She asked whether this information is actually reviewed. Dr. Jones (the panelist) said the information is reported on an annual basis, but she was not clear whether data are reviewed by study sections. Ms. Kornetsky reinforced Dr. Jones's contention that data that show differences must be reported.

Dr. Jones (SACHRP member) asked whether Subpart B contained appropriate protections for pregnant women or if it needed to be changed in order to include them more frequently in research. She also asked for input on how to change the research community to promote more inclusive research. Dr. Jones (the speaker) noted that Subpart B has been revised to respect the capacity of pregnant women to make their own decision regarding participation in research. While some would argue that women should be given complete autonomy in all cases, she advised caution, noting that there is a need for a higher standard of scrutiny and responsibility when pregnant women are involved.

In regard to changing the research community, she counseled that incentives work better than punishment. She looks forward to a day when IRBs are truly viewed as partners in research rather than as barriers. To accomplish this, it is important to seriously address researchers' issues and problems in addressing approvals, at the same time using incentives to promote the desired shift.

Cognitive Assessment. Dr. Fisher raised the concern that while persons with cognitive impairments do want protection, there is a potential for stigmatization. She also questioned the availability of adequate means of assessing capacity, noting that an individual could be impaired for some types of decisions but not for others. In addition, there are individuals whose cognitive capacity is transient. For all these reasons, Subpart E may not solve all related problems; a person might fall under this subpart sometimes and not others.

Mr. Honberg responded that Dr. Fisher's concerns were legitimate. Many people can recover, but capacity does fluctuate. However, the greater the risk, the more important it is to look at capacity and in doing so, to err on the side of caution. While there are no easy answers, the other ways of addressing this issue, including independent advocates and research advanced directives, can also help.

Panel #3 – Perspectives of Research Subjects, Representatives, and Advocates

Dr. Cora B. Marrett, Senior Vice President, University of Wisconsin; Darrell Forney, M.D., Johns Hopkins University; Jeffrey Henderson, M.D., Black Hills Center for Indian Health

Remarks by Cora B. Marrett

Dr. Marrett argued that the legacy of the Tuskegee study is not the sole reason for the relative difficulty in enrolling African Americans in research studies, though it is a factor in their reluctance to participate. In this study, African American men with and without syphilis were told they had "bad blood" (a local colloquialism covering a range of problems) and specifically excluded by arrangement with the Public Health Service from a campaign intended to wipe out syphilis in the area. They were denied information

about their disease and its treatment and allowed to infect their wives and children. The study received high visibility and led to a Presidential apology.

While a Detroit study in the late 90s found that 81 percent of African Americans and only 28 percent of whites were aware of the study, and that those who had this knowledge placed little trust in researchers, many people who have heard of the study do not understand the historical facts about the study. A survey of African American and white adults in Baltimore completed this year found that most respondents had not heard of the study; however, the higher mistrust of medical care among African Americans compared to whites did not correlate with knowledge of the Tuskegee study. A third study, also comparatively recent, found that while African Americans were less likely to say they would participate in a clinical trial than whites at the same age and income level, these differences could not be attributed to familiarity with Tuskegee.

The speaker explained that the issue of race and study participation is complex. There are differences by age, with African Americans under age 29 participating at a rate similar to whites. Other efforts have noticed that interventions that target African Americans of higher education and income levels are more apt to be successful; persons with low income and education are generally less likely to participate, regardless of race, and there are more of them in the African American population.

Trust is a serious issue, and the literature supports the importance of addressing it. The speaker suggested that it might be possible to increase trust by increasing understanding of the need for research among African Americans. She highlighted the success of projects that recruited through networks using outreach workers, community boards, and others to interpret them. She suggested that researchers and physicians communicate to the public directly about the importance of medical research and its potential benefits. It would also be helpful to encourage those who have participated to share their experience with others. In short, she said that the "broadening of public discourse is vital" if the situation is to be changed.

Dr. Marrett also pointed to the need for more information on the factors that lead African Americans to participate in research.

Remarks by Darrell Forney

Mr. Forney spoke as a well educated African American who has participated in over ten research studies. He explained that he joined a study in 1996 in which he was infected with malaria as part of the study. He stressed that a key factor was his trust in the research team and his perception that they were willing to answer questions without holding back information. He was motivated by a desire to help other people who were more likely to be exposed to the disease. He also stressed the major role played by support staff in his willingness to continue to participate in other trials. Finally, he noted that two clinical trials provided useful feedback on his own health and supplemented mental care.

The speaker explained that he made this decision despite the legacy of the Tuskegee study, which still "rang in his mind." In the Baltimore area, he said, many people are also aware of a study participant who died during a Johns Hopkins experiment. He did an informal survey of 20 individuals in the Baltimore area and found that the majority were able to tell him what the Tuskegee study entailed; further, fifty-six percent of them, regardless of educational or socioeconomic background, said they would not participate in a research study because of Tuskegee.

He suggested that for many individuals, a major barrier to participate is the lack of knowledge of what happens in a clinical trial. He stressed the importance of educating people on the benefits of clinical trials and why they are necessary. In order to communicate effectively, a good understanding of the subject population is essential.

Remarks by Jeffrey Henderson

Dr. Henderson, a Lakota Indian, works as President and CEO of a community-based nonprofit organization, the Black Hills Center for American Indian Health, with a strong research portfolio. Its $12.5 in studies include a study of risk factors for cancer among American Indians and Alaska natives, a survey of tribal college students about their participation in health-related studies, and a randomized clinical trial related to the prevention of Atherosclerosis among natives with diabetes. A new grant will provide an opportunity to conduct research in direct partnership with traditional healers. This experience has given his organization the opportunity to consent over 4,000 American Indians and Alaska natives.

The speaker explained how the historical experiences of Native Americans may impact their attitudes toward Federal research. He recalled the massacre of unarmed Lakota Sioux at Wounded Knee, South Dakota, by members of the U.S. Calvary, 18 of whom later received the Congressional Medal of Honor. He said a vibrant oral history about this and similar events fuels distrust of all Federal initiatives. He highlighted the Barrow study, which studied a northern Alaska municipality and wrote up its findings, generating sensational news coverage, without coordinating with the tribe. The municipality's bonds went from an A grade to junk overnight, costing the community millions of dollars in missed opportunities for capital. In yet another study, the Havasupai permitted researchers to study diabetes in their population, only to find the researchers were in fact documenting the prevalence of schizophrenia and studying the peopling of the Americas. Some Native American women were victims of coerced sterilization in the 1970s, and many middle-aged women are still grieving for this loss.

Dr. Henderson shared several unique features of conducting research on Native American populations:

- For legal purposes, the 565 Federally recognized tribes are considered domestic dependent nations with sovereignty. This has implications for data sharing.
- Unique types and levels of approval required vary by tribe. Research must almost always be approved by the tribe before individuals can be approached.
- An increasing number of tribes have their own IRBs.
- Tribes exist within the 12 regions of the Indian Health Service, which has a national IRB that reviews studies that cross regions, states, or tribes.
- Many reservations lack partner agencies that can collaborate on research.
- Researchers are often tested at tribal council meetings, where they must wait for hours or sometimes through multiple visits, showing their respect and talking with tribe members informally.

DISCUSSION

Dr. Prentice shared what he has learned about conducting research with Native American populations through his own work. He understood that many days may be spent talking with tribal elders about topics other than research until the elders are ready to discuss the proposed project. He also noted that researchers may have to go through multiple IRBs besides their own institution's IRB in order to conduct research.

The Chairman asked whether American Indians and Alaska Natives have a distrust of biomedical research and perhaps the white research establishment because of their history. Dr. Henderson said this distrust does exist. In one study, a surprising number of potential participants going through the consent process were aware of the Havasupai experience. Many of them are also aware of the Tuskegee study.

Dr. Prentice asked whether the system of oversight being developed through the Black Hills Center might help to dispel some of this distrust. Dr. Henderson hoped that would be the case. He stressed the importance of a unique feature of the Center's approach: the willingness to spend days, weeks, or even months sharing data with communities and their tribal health departments following a study.

The Chairman asked Dr. Marrett what institutions across the U.S. are doing to try to overcome the barriers she mentioned and enroll more African Americans in research that might benefit them. He also asked whether some leading institutions are involved in this effort. Dr. Marrett responded that problems cannot be solved solely by work on human subject protections; the experience of subjects in the medical and educational systems will also affect their attitudes toward participation. Mr. Forney added that for many African American community members, working through the church is similar to working through the tribe. Other informal but important links are fraternal institutions, societies, and lodges.

Dr. Prentice commented that a reasonable initiative might be for an institution to develop community-based programs in which they discuss research and present research projects that are available, and then ensure that communities are debriefed on the results. Dr. Marrett said that approach would be reasonable. She also mentioned the importance of checking in with the community's elders. Dr. Henderson gave the example of a dinner held by his organizations for all 138 research participants in one study, with staff members serving food.

Mr. Forney added that there will always be enduring legacies, including Tuskegee, but "it is how the present responds to the legacy with its current knowledge that may impact any future success." He stressed the importance of being frank and honest in discussing the historical context of Tuskegee. The speaker also pointed out that while the educational and socioeconomic status of African Americans has improved over the last 70 years, there are many who have difficulty understanding informed consent.

Ms. Selwitz asked Dr. Henderson whether the multiple layers of review associated with research on Native Americans serve to strengthen protections or simply constitute unnecessary bureaucracy. Dr. Henderson the principle value added is that more people become aware of the research in the process. He maintained that NIH could significantly increase the protections of Native American research participants by requiring applicants for research grants to have in hand the approval from the tribes with which they intend to work. He condemned the practice of researchers arriving at a poor reservation with research dollars in hand, which can be coercive; also, the study may be poorly adapted to the culture without preliminary groundwork. He felt that coordination would be improved if the tribal health director were routinely informed of all research.

Dr. Weiner commented that there are different levels of trust that are important: the trust between the family and the treating physician and the trust that pertains to government decisions and oversight. She asked whether the resistance to research persists even in "dire circumstances" when clinical trials may be "exactly what is called for" and a face-to-face dialogue with the physician ensues. Dr. Marrett suggested the importance of the Cold War phrase, "trust but verify." She pointed out that Tuskegee participants trusted the study nurse, but their trust was misplaced. Mr. Forney stressed the impact of face-to-face communication, noting that most study participants are unaware of what is occurring at the Federal level. He also re-emphasized the importance of sharing study outcomes as a means of building trust and an awareness of benefits.

Dr. Henderson added that there is "tremendous" distrust of the IHS delivery system in many reservation communities. He pointed out that this system of care is underfunded compared to other Federal health delivery systems and is also impacted by a high turnover. Further, the IHS facilities are largely limited to general care, with specialized services available on a contract basis only in situations where there is "imminent risk." Preventive care is seldom available.

Dr. Gyi drew attention to research by Dr. Nancy Kass on factors that motivate subjects to participate in research. He said she found that money was not a primary motivating factor, and issues such as socialization, social environment, and care and attention were more significant. He asked speakers to comment on compensation for participating in research and its relationship to trust. Dr. Marrett said that payment might help bring people in, but continued participation requires altruistic or other motivating factors. Dr. Henderson said his Center does compensate participants, but the level of compensation is not the most significant motivator. Rather, he said, the single leading factor among both men and women and across all ages was the salience of the research topic and how important it was personally to the individual subject. Mr. Forney said that motivating factors for him included the desires to learn about clinical research and benefit others, though compensation is also an important inducement that makes the subject feel valued.

Dr. Jones asked speakers to elaborate on the cultural relevance of protections for the particular groups they represent. Dr. Jones also inquired about the potential for coercion when the opportunity to receive medical care is an important influence on a subject's decision to participate. Dr. Henderson responded that his Center is sensitive to the possibility of coercion and addresses it by being "crystal clear" with constituents about the benefits offered. Mr. Forney said he did not feel his participation had ever been sought through coercive incentives. Dr. Marrett underlined the importance of considering what "group consent" means. She added that persons of low socioeconomic status, regardless of race, are subject to coercion whenever an opportunity for medical care is offered through research.

Mr. Adams asked whether accreditation of institutions or certification of individuals involved in research would increase trust for the groups represented. Dr. Henderson said that what matters most to American Indians is whether or not the group conducting the research is affiliated with the Federal government or sharing information with agencies they do not trust. He said accreditation would be unlikely to make a difference in "Indian country," particularly since the culture is one that values legitimacy conveyed through tradition rather than through bureaucratic or legal means. Dr. Marrett was also unsure whether this would make a difference, though it might become part of a larger system that works toward building trust. Mr. Forney felt that accreditation would not carry weight with individuals with low socioeconomic status and little education, though it might with more educated community leaders.

PUBLIC COMMENT

Mr. Michael Susko, President of CIRCARE, thanked SACHRP for the opportunity to have people who advocate for and represent research subjects present their perspective on the issues. He said that when the subject of human subject protection is addressed from the subject's perspective, the "big picture" becomes clearer, and larger issues come into focus: for example, the notion of building trust with subjects. Good protection of subjects is critical because it builds trust, without which good science cannot go forward. The presence of this perspective adds passion and reminds us of the altruism of study participants. Mr. Susko asked the Committee whether it would be possible to "institutionalize" and continue this dialogue.

The Chairman assured Mr. Susko that the dialogue is not a one-shot event and reminded him that the perspective of human research subjects and their families is also represented on each of SACHRP's subcommittees.

Ms. Elizabeth Woeckner, also of CIRCARE, explained her organization's assertion that "the human subject protection system is ineffective." She noted that the regulations talk about IRBs, but do not distinguish between good and ineffective IRBs. She said the committee's perspective is based on communications with participants. She highlighted a malaria vaccine study in China in which CIRCARE was contacted by families of infants who were harmed in clinical trials that tested unapproved medical devices in cardiac surgery without their parents' consent; an instance in which a principal investigator sold laetrile to an undercover agent; the Saturn trial; and a criminal case in Tennessee against an IRB member. Such instances highlight the fact that the quality of protection provided by IRBs is highly variable.

Dr. Prentice responded from a personal perspective that he believes the vast majority of investigators are ethical and well intentioned, but there are outliers and abuses that will persist in any oversight system and can only be minimized. He also observed that the vast majority of IRBs want to do right thing, but that protection is indeed variable – though he asserted that variation has been reduced over time, especially since 1998. While the system today needs improvement, he hesitated to describe it as broken, though he acknowledged that it may have been broken in 1998, when IRBs were more overloaded and under-resourced. Today, he sees more institutions, though not all, becoming more proactive. SACHRP is working to correct deficiencies, which cannot be done overnight. He agreed that at present we know more about how many animals are used in research than we do about humans, and data on this is needed. Registries of all clinical trials are being discussed, but it will take time to make this strategy a reality. In the meantime, he encouraged CIRCARE to be patient and continue to provide feedback.

Dr. Schwetz stressed that the IRB system is the only means of protecting human subjects currently available. He saw SACHRP as showing a significant commitment to reasonable improvements that can actually be accomplished, and to listening as well as talking. The input provided at this meeting is valuable and creates further incentives for such improvements. Ongoing feedback from the public is welcome, and each meeting provides an opportunity for comments on any topic of concern. In addition, he said OHRP was always open to communications. He is interested in OHRP doing an increasing amount of outreach to the public. He sees listening to the public, patients, subjects, and advocates as a continuing priority. He thanked all speakers.

Follow-up Discussions, Wrapup, Adjournment
Ernest D. Prentice, Ph.D.

The Chairman invited closing observations from SACHRP members.

Quality of Protection. Mr. Adams noted that most countries aspire to the level of quality in clinical research and human subject protection available in this country. It may not be perfect, he acknowledged, but it is the best in the world; it is therefore appropriate at this moment to celebrate success.

Subpart E. Ms. Selwitz asked Dr. Lepay to comment on the status of a possible Subpart E. He responded that FDA is working closely with OHRP in this area through a joint series of discussions aimed at providing better protection for individuals with diminished mental capacities. He said the best approach may be harmonized guidance on the subject rather than rulemaking. Dr. Prentice added that harmonized guidance is a major concern, but there is greater interaction between FDA and OHRP than there has been in the past. He expressed optimism that harmonized guidance would be achieved, though not in the very near future.

Equitable Subject Selection. The Chairman commented on the challenge of ensuring equitable subject selection, which is a requirement that he believes is not being adequately fulfilled by most IRBs. He encouraged the subcommittee on Subpart A to address the issue of ensuring diversity in the demographics of human subjects. Dr. Gyi agreed that this had not been considered by the subcommittee and asked how far IRB authority extended in this regard – should an IRB require a PI to halt a study that does not have a study with diverse participants? Dr. Prentice said his IRB enters this information into a data base, which will soon be searchable for all research protocols across departments and disciplines; when study lacks diversity, the IRB asks the PI for answers, which may be acceptable (for example, I approached everyone who came to the clinic) or unacceptable. This issue is important, because inequitable subject selection contributes to public mistrust. Many investigators have difficulty achieving racial and ethnic balance in their subjects, and they claim this is not their fault; therefore, it is important to reach out to the community.

Dr. Gyi agreed in principle with the Chairman, but noted that there is a lack of precision in what is required. He noted that FDA and NIH developed guidance related to equitable selection (in 1993 and 1994 respectively), but it is still not clear how the information compiled feeds into study sections. FDA's emphasis seems to be on retrospective analysis of data: if it does not look right, then further subgroup analysis is needed. Leverage and practical application seem, in short, to be limited. He expressed concern about the administrative burden additional responsibilities in this area might place on IRBs. He also questioned how much collection of such data would contribute to the minimization of risk or to the protection of human subjects.

Dr. Prentice said he understood the panel member's concerns, but suggested that the responsibility of ensuring equitable subject selection pertains more to the institution than to the IRB. A medical center ought to be able to provide the opportunity to participate in research that might benefit the community to all qualified community members. While the IRB may not be responsible for maintaining these data, he suggested, the institution should do so. At his own institution, the vice chancellor has asked for data on minority participation, and these data will be used as a basis for community outreach. Dr. Gyi rejoined that medical centers are not the only ones conducting research; other entities such as private practice groups must be considered as well. Dr. Prentice agreed, and further added that the leverage for ensuring participation would need to come from pharmaceutical companies. He suggested that it would be helpful if publications where research is reported would include demographic breakouts. Dr. Gyi questioned whether available technology and ethnography were sufficient to complete this type of analysis. Dr.

Prentice concluded with the observation that the issue of equitable selection needed to be “recalibrated” in a way that makes sense and holds everyone accountable.

Dr. Prentice thanked everyone and reminded all that the next SACHRP meeting will occur on November 1 and 2.

Secretary's Advisory Committee on Human Research Protections
August 1 and 2, 2005
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 by November 1, 2005

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