Secretary's Advisory Committee on Human Research Protections
July 31 and August 1, 2006 – North Bethesda, Maryland

Minutes

MONDAY, JULY 31

Welcome and Opening Remarks
Ernest Prentice, Ph.D.

The Chairman welcomed everyone to the meeting and acknowledged the presence of the Assistant Secretary of the Department of Health and Human Services (HHS), John Agwunobi, M.D. He reminded attendees of SACHRP's Charter, issued on September 8 of 2004, which comprises protection of human research populations, especially vulnerable populations such as children and prisoners.

Dr. Prentice then introduced several new members, including Jeffrey R. Botkin, M.D., M.P.H.; Myron Genel, M.D.; Daniel K. Nelson, M.S., CIP; Francine C. Romero, Ph.D., M.P.H.; and Samuel J. Tilden, M.D., J.D., LLM.

The Chairman stressed that SACHRP works in partnership with staff members of the Office of Human Resource Protections (OHRP), who act as liaisons on SACHRP subcommittees. Dr. Prentice thanked *ex-officio* members of SACHRP, who often attend subcommittee meetings in addition to meetings of the main committee. He also expressed appreciation to all OHRP staff who work in partnership with SACHRP.

The Chairman provided an overview of charges to existing SACHRP committees. He noted that the subcommittee on Subpart D has produced a series of recommendations related to protections for children. He also observed that the new subcommittee on Subpart A is looking at all aspects of Subpart A. He thanked all members of the subcommittees for their hard work.

Minutes for the previous meeting (March 13-14, 2006) were approved unanimously, but with a note that a small error identified by Mr. Nelson does need to be corrected; documentation will be provided to the Executive Secretary. Dr. Prentice then reviewed the agenda for the day.

Remarks
John Agwunobi, M.D., Assistant Secretary for Health

The Chairman introduced the Assistant Secretary, who is the primary adviser to the Secretary of Health. He also oversees the U.S. Public Health Service. Dr. Agwunobi is a pediatrician who has dedicated himself to work on behalf of underserved populations.

Dr. Agwunobi said he saw the work of SACHRP as critical and its members as both highly qualified and diverse. He complimented the committee on its progress, noting that ethical issues tend to evolve over time and require interpretation. He said he looks forward to reviewing its future work and recommendations, which are followed closely not only within HHS and by the research community,

but also by other Federal agencies. He assured committee members that their recommendations are taken very seriously and that their "solemn" charge is extremely important to research subjects.

DISCUSSION

The Assistant Secretary entertained questions from SACHRP members and audience members. These included the following:

How is the preparation for bird flu coming? It is progressing reasonably well. The Federal government is investing in the science and in advancing the industry associated with vaccines, including issues related to stockpiling and development. He highlighted the need to find, manufacture, and stockpile new antivirals needed to respond to the next pandemic, whenever it may occur and whatever its nature. The Department is also addressing the issue of surveillance, both global and domestic, and working with international partners to further their capacity to respond. In addition, the Department continues to work to help states and local communities prepare for the possibility of a pandemic that could affect every community simultaneously. Finally, Dr. Agwunobi said we must continue to find ways to improve our lab diagnostic capabilities, which means we need to test and manufacture new diagnostics that will allow for rapid identification and management of individuals with diseases such as pandemic influenza.

Is HHS working with Congress to further antibiotic development? Dr. Agwunobi agreed that this is a priority area, noting that nature is "keeping up with us" in terms of resistance. He said the Department is aggressively investing in the science related to antibiotics and pursuing investments in clinical science that may help slow down the march of resistance to antibiotics over time.

Does HHS anticipate children being involved in any of the research just described, such as work on a vaccine for avian flu? There are risks associated with not doing research with children, as well as risks involved with doing it. In protecting our nation, we must protect our children. Research suggests that children and congregations of children (such as schools and daycare centers) are a major way that influenza viruses spread through a community. Both industrial and nonindustrial research efforts are underway that seek to broaden data and information related to children. There are two main areas of effort. The first is the development of a pandemic influenza vaccine. HHS's goal is to have 300 million courses of such an antibiotic within 6 months and a vaccine within 6 months of the start of such a pandemic, with the goal of vaccinating every citizen, children included. A discussion is underway about who should be given priority, an issue SACHRP is welcome to deliberate. It is also important to consider what variables would affect prioritization (for example, whether or not the needed drugs are licensed). The second area is a pre-pandemic vaccine. Today, for example, vaccine for H5N1 is being stockpiled, although it may not be the source of the next pandemic. The most appropriate uses of this vaccine to protect specific populations are debatable.

In its report on prisoner protection, the Institute of Medicine (IOM) points to the fact that much research does not fall under the oversight of OHRP, and the IOM committee was concerned about protections for such research. The committee also sees a need for a person to serve as a liaison in prisoner research. The solutions are associated with cost. How does HHS see the issue of increasing resources allocated to human subject protection? The OHRP does have responsibility beyond the walls of HHS in terms of oversight of human research protections, at least where Federal dollars are involved in supporting the research. As in the recent debate on stem cell research, the parameters of ethical issues, human research, and subject protection overlap. Our obligation is to do the right thing and not look at it as an "additional expense. It's not extra; it's the cost of doing research in our value system. As research

expands, research protections need to keep up. Dr. Agwunobi assured SACHRP that he would work with Dr. Schwetz on funding strategies about the long-term challenges of maintaining human subject protections.

The Chairman thanked Dr. Agwunobi for his visit and expressed the hope that he would find it possible to attend future meetings as well.

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

Dr. Schwetz noted that Assistant Secretary's support for OHRP's work and mission is reassuring. He added that Dr. Agwunobi understanding of issues related to the protection of human subjects is especially impressive in light of his many responsibilities.

Dr. Schwetz provided updates on activities of concern to SACHRP. First, he noted that SACHRP has made recommendations regarding Adverse Event reporting and will shortly hear a report on the progress that has been made in implementing them. Also, the IOM Report on issues related to prisoners as subjects is now in hand and will provide a basis for decision-making. OHRP anticipates SACHRP's advice on next steps.

Plans are in place for a national conference on alternatives to local IRBs and related issues, to be held November 20-21. The day-and-a-half meeting, which will follow up on the workshop last fall that addressed the same topic, will address such issues as liability, quality of review, cost, timing, and local context. Attendees will include institutional officials, institutional officials, investigators, IRB members, and others involved in decisions on review options.

In July of 2006, OHRP published a notice in the *Federal Register* clarifying that the requirements of 45 CFR 46 apply not only domestically, but also when HHS funds are used to conduct research overseas. If other alternate guidelines are followed, they must be shown to provide "equivalent protection." To date, however, no other guidelines have been evaluated to date to make this determination. Other signers of the Common Rule will make their determination on how they wish to handle this issue.

OHRP has also been working toward guidance to address the question of "what is research?" A draft document has been prepared for review by an internal council of HHS agencies. Other agencies under the Common Rule are also reviewing and commenting on the document.

OHRP is also reaching out to the public, including minority and ethnic groups, to provide education on research. A trifold document – available in English, Spanish, and Vietnamese – will carry the message that research is important, and you have a choice whether or not to participate. The document is intended to help people understand both the opportunities and risks associated with participation.

OHRP has made an effort to interview the people involved in writing the landmark *Belmont Report*. Links to 19 of these interviews are now available on the OHRP Web site so they can be viewed. Four additional interviews are planned.

Questions:

The Director responded to questions from SACHRP members.

Have the recommendations defining minimal risk in Subpart D been approved by HHS? Secretary Leavitt accepted the last set of recommendations, which included this definition.

Has there been any thought about further dissemination of the Belmont Report interviews beyond the Web site – either freestanding or as a publication in an ethics journal? We will consider this possibility.

Federal Adverse Events Task Update on New Coordinated Federal Policy Initiative
Amy Patterson, M.D., NIH; Michael Carome, M.D., OHRP

Remarks by Amy Patterson, M.D., NIH

Dr. Patterson, the Director of the Office of Biotechnology Activities at the National Institute of Health (NIH), provided an update on a Federal policy initiative aimed at harmonizing and optimizing the reporting of Adverse Events (AEs). She pointed to the multitude of Federal forms for reporting AEs as indicating the divergence among Federal policies, which differ in significant ways regarding the threshold, scope, and timeframe for required reports. This divergence creates confusion, can lead to noncompliance, and may also increase costs by requiring clinical coordinators and investigators to learn how to comply with the various policies.

One of the greatest costs, however, is the potential cost to human subject protections as a result of the lack of standards, incomplete reports, and poor quality of information attributable to these diverse policies. Valuable information is being lost that could lead to improved design for future studies or alter plans for studies already underway.

Recognizing the importance of these issues, SACHRP requested that a task force be assembled with the following charge: "To propose specific means for promoting harmonized and streamlined Federal requirements for reporting, analyzing, and communicating adverse events in clinical research." The Federal Adverse Event Task Force (FAET) was formed with the following member agencies: NIH, the Veterans Administration (VA), the Department of Defense (DOD), the Food and Drug Administration (FDA), OHRP, the Centers for Disease Control (CDC), and the Agency for Healthcare Research and Quality (AHRQ). Members agreed on three primary objectives:

1. *Agencies will speak the same language.* At present, there is a lexicon of varied terminology related to safety information that contributes to confusion. Examples include the terms "related" vs. "associated," "unanticipated" vs. "unexpected" and "adverse event" vs. "unanticipated problem." FAET has conducted an inventory of terms and mapped them to determine whether they are rooted in the regulations, originated as guidance of individual Departments, or entered the vocabulary of safety in other ways. The good news is that many of the differences were found to be rooted in policy rather than regulations, making them much easier to bring into alignment.

2. *Develop a best practices blueprint for reporting, analysis, and application of safety information.* Each agency agreed to examine its own activities, looking at the information it collects, how it is analyzed, and what is done with it. Members then agreed to identify the best practices among

them, identify critical control points in the workflow process, and seek ways to optimize information flow, use controlled vocabularies to support analysis, and promote standardized reporting.

3. *Develop one core AE report that Principal Investigators (PIs) can sent to multiple agencies, to be called the Basal Adverse Event Report (BAER).* This report would feature a baseline set of core information (both medical and administrative) that could be adopted by all agencies, incorporating HHS standards for data transmission and vocabularies. It would also be used to report "unanticipated problems."

Progress made toward accomplishing the third objective was the focus of the remainder of the report. The process used to develop the BAER including not only focus groups within each agency, but also limited outreach with stakeholders. Meetings were held with about 35 IRB chairs and administrators and with groups of principle investigators, with clinical research coordinators engaged in running large multi-center trials, and with industry representatives engaged in developing standards for handling healthcare and research information.

FAET members reviewed the various forms currently in use and asked agency representatives to identify their data requirements and approaches to data analysis. These conversations yielded about 4,000 concepts and elements, within which there was considerable redundancy. It proved possible to reduce the 4,000 elements to 300, not all of which must be filled out for every AE. The computerized form will allow the investigator to pull up the data elements relative to the trial, many of which are "static" elements that need be entered only once (such as the PI's name). Other elements are dynamic and will change according to the nature of the event and the trial.

The BAER draws on existing standards for AE reporting, such as ICH E2B, and can be used to report AEs and unanticipated problems that occur in the context of a variety of research types. The BAER may enhance protection of human subjects by providing standards that enable a more uniform and streamlined approach to AE reporting. FAET members agree that the draft BAER represents a single, baseline set of core information acceptable to their agencies and believe that it will promote completeness of data, improve quality of data, and facilitate analysis of information.

Next steps planned by FAET included further engaging the user community, seeking formal HHS clearance, and a initiating a phased approach to Federal implementation. The committee expects the report to be in use in 2007, with an initial period in which adoption of the BAER is voluntary.

Remarks by Michael Carome, M.D., OHRP

Dr. Carome provided an update on the status of OHRP's "Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems." The guidance has been developed and circulated in tandem with the initiative described by Dr. Patterson.

In March 2004, SACHRP recommended that OHRP and FDA promptly issue clear and consistent joint guidance on IRB review of adverse events. The scope of the charge was broadened by OHRP to encompass both internal and external AE reports. To accomplish this, the Federal Adverse Events Task Force (FAET) was formed from among *ex officio* members of SACHRP and chaired by NIH. OHRP prepared and shared several iterations of the draft guidance on AEs and unanticipated problems (UPs) with FAET members for review and comment. When agreement was reached among FAET members, the draft was posted on the OHRP Web site for public review and comment.

Comments were accepted for a 3-month period extending from October 13, 2005 to January 13, 2006. The draft was divided into ten sections that contained questions for response. OHRP received comments from 54 sources, including 26 organizations (research institutions, IRBs, academic organizations, human subject advocacy groups, and patient advocacy groups) and 28 individuals (IRB members, investigators, institutional officials, and consumer advocates). Of these, 35 comments were explicitly supportive of the guidance, and 19 were strongly supportive. Another 15 did not offer a statement of support, but only suggested minor edits and may be presumed supportive. Four were not supportive. The most frequent comment received was a call for joint harmonized guidance from OHRP, FDA, NIH, and other Federal agencies.

Dr. Carome highlighted comments received on selected questions of interest:

- *What are AEs?* Of the seven commenters, several recommended inclusion of a clearer definition of adverse event and definitions of serious, harm, and discomfort.

- *What are Unanticipated Problems (UPs) and how do they relate to AEs?* Of the 22 commenters, several recommended inclusion of definitions of serious, non-serious, and possibly related. Several recommended that for AE assessments, "related or possibly related" be changed to either "probably related" or "definitely related."

- *What should the IRB consider at the time of initial review with respect to AEs?* Two of the nine commenters recommended that the guidance state more strongly that monitoring plans should be adjusted to fit the degree of risk.

- *How should reports of external AEs, internal AEs, and UPs be handled?* Some of the 19 commenters suggested that external AEs that represent UPs should not be reported beyond the IRB for each site. Two persons specifically recommended that the guidance address circumstances in which an IRB wants to change a protocol in response to an UP, but the sponsor disagrees with the proposed changes.

- *What is the appropriate time frame for reporting UPs to the IRB, appropriate institutional officials, the department or agency head, and OHRP?* Several of the seven commenters recommended that the guidance include a clearer definition of *prompt* and include more specific time frames for reporting.

In addition to comments from the general public, OHRP is also responding to comments from FDA. Next steps will be to revise the document in response to comments and in consultation with FDA, FAET representatives, and other Common Rule departments and agencies. Revised guidance will then be issued and additional feedback will be assessed.

DISCUSSION

Relation to GEMCRIS. The Chair initiated a discussion of the presentations. He observed that the BAER system appeared to resemble the Genetic Medical Clinical Research Information System (GEMCRIS) developed by NIH and FDA for reporting AEs on gene transfer or gene therapy clinical trials. Dr. Patterson said the BAER is quite similar to GEMCRIS, but GEMCRIS does not contain many of the elements the BAER should have.

Data Base Use. Dr. Prentice noted that the number of clinical trials that would feed into the BAER would be significantly larger than the 130 reported through GEMCRS. Dr. Patterson agreed, but added that the FAET is not envisioning a single data base into which all trials report. There might still be a data base for each agency. Dr. Prentice asked whether investigators would be able to access the information in these data bases. Dr. Patterson agreed this would ultimately be possible, but the focus at the moment is on determining what is reportable.

Dr. Powell asked whether private industry sponsors had commented on the draft guidance. Dr. Carome said that AvaMed and one other industry group had commented. Dr. Powell speculated that having several databases with information on AEs would have a real impact on industry, which might impact product development or even labeling. He asked whether at some point people would be able to search AE data. Dr. Patterson reiterated that a system with a central repository has not been conceptualized. However, she noted that when the AE database for gene therapy trials is conducted, it will have a public face that will allow people who follow the field to determine what events have occurred in a trial. She added that while making AE data publicly available might help prevent similar events in the future, making data available too early could result in faulty conclusions. Streamlining and standardizing reports, however, does facilitate the development of local and Federal databases capable of comparing events within or across trials.

Internal and External Events. Dr. Prentice asked Dr. Carome to clarify whether there is a difference in the threshold for reporting for internal as opposed to external events. Dr. Carome responded that the threshold does not differ, and it would be hard to justify such a difference. However, there is a difference in where the report must flow and who is responsible for making such the report. He further clarified that the criteria for what constitutes a UP do not differ depending on whether the event is external or internal.

Altered Risk-Benefit Relationship. The Chairman asked whether the concept of an "altered risk-benefit relationship" as the result of an AE would be clarified. Dr. Carome said this was under consideration. Dr. Prentice added that he was concerned that there be a lower-risk or lower-harm threshold for reporting at the institutional level. Dr. Carome agreed, noting that AEs can occur in a series or group; they may not rise to the level of "serious," but still should be reported.

Testing, Evaluation, and Roll-Out. Dr. Powe asked Dr. Patterson to comment on plans for pilot testing the BAER in the user community. Dr. Patterson said there were plans, but the tool is not yet ready. FAET is looking for opportunities to present the BAER for BETA testing.

Dr. Weiner asked whether there were plans to validate the instrument with respect to individual agencies to be sure that the culture and priorities of each agency are being met. Dr. Patterson observed that some might be concerned that going from 4000 to 300 elements might mean stripping protections; however, this reduction reflects the elimination of redundancy. She also stressed that the thresholds and criteria for reporting are separate from the BAER itself; agencies are still able to have differing criteria for when reports are required.

Mr. Nelson invited further discussion on how the tool will be rolled out. Dr. Patterson said that a period of initial voluntary adoption was being discussed as an option (as opposed to beginning by making it required). Some feel it would be best to test and debug the tool during a voluntary period of one to three years rather than imposing something that may still need work. Others argue for completing the BETA testing, making a reasonable approach to what is needed, and requiring its use

so that the completeness and quality of reports can be enhanced and buy-in achieved. Mr. Nelson doubted that people would use the BAER voluntarily. Dr. Prentice agreed.

Dr. Botkin queried whether any evidence-based performance measures for the system were known that could help assess the process and determine whether it is succeeding at identifying true positives and eliminating or reducing the false negatives and false positives. Dr. Patterson observed that while this was an important question, a good baseline may not exist. Plans are "on the table."

***Independent IRB Participation*.** Dr. Fisher wondered how and whether independent IRBs would participate in such reporting. She also drew attention to the need to reduce the burden on IRBs, but at the same time to maintain local subject protection with respect to AEs. Dr. Patterson hoped the BAER would decrease the burden, but said the tool itself makes no assumption about what the local policy might be on the threshold for reportable AEs.

The Chair said he was delighted with the progress that has been made on this issue.

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

Mr. Nelson reviewed the charge to the subcommittee, its goals, and its membership. He explained that in this meeting the Co-Chairs will review some of the recommendations previously presented to SACHRP in order to set the new proposals in a global context, help orient new members, and highlight revisions suggested at previous meetings.

To date, the Subcommittee has developed 20 recommendations that have been approved by SACHRP, 15 of which were related to continuing review (2 of these were marked for possible revisiting at a later time) and 5 of which related to expedited review. These have been developed over the course of four in-person meetings, four telephone meetings, and a number of working group meetings. The Co-Chair expressed appreciation for the contributions of ex officio members to the committee's deliberations.

Continuing Review

The Co-Chair reviewed previously approved recommendations on CR (see the minutes of November 1-2, 2005 and March 13-14, 2006). Previously approved recommendations have addressed the issues of when CR begins (IRB approval of a study "sets the clock" for CR); when CR can stop ("when all research interventions and interactions with subjects are over and data collection for research purposes is complete as described in the approved study plan/protocol, at the research site for which the IRB has oversight"…); the timing of CR (unnecessary restrictions on IRBs in scheduling CRs should be removed, using a 60-day rather than a 30-day time window if one is needed); and how temporary lapses in approval should be handled (a general request for all subjects is permissible rather than individual requests for each subject).

Mr. Nelson then presented the following new recommendation:

Recommendation: *On suspension of all study activities when continuing review is underway:*

OHRP should modify guidance on continuing review so that, when the study has been reviewed by the IRB (at a convened meeting or through an expedited process, as appropriate) and there are no substantive concerns that impact human subject protections, automatic study suspension is not required when the expiration date passes, provided that IRB review is completed within 30 days past the expiration date.

Mr. Nelson emphasized that the subcommittee is not suggesting an open-ended approach; rather, it is acknowledging that such an automatic suspension is likely not to be in subjects' best interest and could in fact have detrimental effects.

DISCUSSION

The Chair opened the floor to discussion.

Duration of CR. Two members had questions in regard to a previously approved recommendation (March 13, 2006):

OHRP should clarify its guidance on the required duration of continuing review. Continuing review may end when all research interventions and interactions with subjects are over and data collection for research purposes is complete as described in the approved study plan/protocol, at the research site for which the IRB has oversight…

Dr. Botkin raised a question about what would happen in an instance in which a large study is in a relatively dormant stage and a new investigator, such as a graduate student or faculty member, wants to access the data set to continue with the previously defined study goals. Would this require a new IRB application for a second investigator? Mr. Nelson said it would.

Dr. Powe wondered whether more guidance was needed to clarify whether *all* data collection, enrollment, and analysis needed to stop. Mr. Nelson said that the recommendation referred to instances in which the investigator and study team are ready to stop the study, plans for protecting confidentiality have been reviewed and are in place, and IRB oversight is no longer needed.

Dr. Tilden whether a blanket exclusion of data analysis under all circumstances was prudent in all instances. Mr. Nelson observed that there had been a good deal of debate before the recommendation was approved.

Dr. Genel commented that the recommendation would not be enforceable.

Study Suspension Not Required. In reference to the newly proposed recommendation, Dr. Fisher said she liked the recommendation very much, but wondered how the conclusions of the review would be documented. She felt the communication of these conclusions should not be simply oral. Mr. Nelson responded that a formal review document would be communicated to investigators as IRBs do now, but the report would indicate that minor issues remain to be addressed. Dr. Fisher asked what would ensure that these concerns would be addressed, especially since they would be labeled nonsubstantive. Mr. Nelson said the 30-day window was retained to allow time to make the required changes, but after that the opportunity for change would be understood to be exhausted.

In response to a question from Dr. Powe, Mr. Nelson agreed that data analysis, which a previous recommendation would allow to continue at the end of study, should also be allowed to continue if

the same conditions are met in the event that a temporary lapse occurred while the study is underway. Dr. Fisher agreed, noting that the guidance is intended to protect human subjects rather than punish the investigator. It is better for the subject if monitoring continues.

Dr. Tilden saw the recommendation as having a positive impact in the setting of international research. He observed that difficulties with communication and transportation could result in a delay in getting approval. The recommendation addresses a sometimes significant administrative problem.

Dr. Fisher wondered if there would be confusion around the issue, "30 days after what?" Mr. Nelson said the period in question would always be 30 days after the expiration date. This date would not shift depending on when the CR took place.

Dr. Prentice asked whether a clarifier was needed to indicate that the IRB review was completed and the protocol reapproved. Mr. Nelson pointed out that a previous version of the recommendation contained the language, "when CR was underway." However, the subcommittee wanted to address the instance in which the study has been reviewed by the IRB – the important review has taken place – and only minor issues remain to be addressed.

Dr. Flanzer raised the question of how this 30-day window relates to the 60-day window. Mr. Nelson saw them as related but separate parts of the same recommendation. Many IRBs do not maintain the anniversary date year after year; however, for those that do, the 60-day period allows a more reasonable time frame to complete the review before the expiration date passes. This is, however, a separate idea that addresses a separate problem.

A motion was made and seconded to approve the recommendation. This was followed by further discussion.

Dr. Powe was troubled by the language, "automatic study suspension." Mr. Nelson explained that this language refers to what happens now, under the current guidance.

Dr. Tilden suggested the following (underlined) change:

> *OHRP should modify guidance on continuing review so that, when the study has been reviewed by the IRB (at a convened meeting or through an expedited process, as appropriate) and <u>the IRB finds that</u> there are no substantive concerns that impact human subject protections, <u>automatic cessation of study activities is not required</u> when the expiration date passes, provided that IRB review is completed within 30 days past the expiration date.*

Mr. Nelson and Dr. Gyi noted that suspension may be formal regulatory term that is in current use. Dr. Prentice suggested clarifying the meaning by writing "automatic study suspension (cessation of all activities)…" In regard to Dr. Tilden's insertion that "the IRB finds," the Chair noted that the process might be an expedited one in which the finding is not that of the entire IRB. Dr. Prentice then suggested instead, "<u>the IRB or its appointed delegate finds.</u>" She also proposed specifying, at the same place, "<u>and communicates to the PI.</u>"

ACTION

The motion was tabled for further consideration and revisions. The Chair observed, however, that the concept has been endorsed and only adjustments in language are needed.

Expedited Review

The Co-Chair reviewed previously approved recommendations on Expedited Review (see the minutes of March 13-14, 2006). They addressed the processing of administrative changes ("clerical and administrative" changes can be processed by "qualified IRB staff" rather than requiring "convened or expedited IRG review"; replacing the term "expedited review" with "delegated review," which more accurately captures the intent of the process; and final approval of stipulations from convened IRB review.

Mr. Nelson then presented new recommendations, each of which was followed by discussion.

Expanding Types of Research Eligible for Expedited Review under Category 7

The subcommittee addressed the question of whether the 1998 list of "categories of research that may be reviewed by the IRB through an expedited review procedure" should be updated or revised (63 FR 60364-60367, November 9, 1998). In developing its recommendation, it considered the fact that social and behavioral science investigators and IRBs that oversee this work frequently perceive difficulty fitting their research into the current regulatory structure. The subcommittee polled a number of social and behavioral science organizations to get input from the field, and contacts indicated a need for greater specificity in identifying the research that may be appropriate for expedited review.

Recommendation: To revise category #7 as follows:

> *(7) Research*
>
> *(a) on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, affective states, interpersonal relationships, identity, language, communication, cultural beliefs or practices, and social behavior); or*
>
> *(b) employing methods commonly used in social, behavioral, epidemiologic, health services, and educational research, such as survey, interview, oral history, participant observation, ethnographic, focus group, program evaluation, human factors evaluation, or quality assurance methods.*

DISCUSSION

Dr. Fisher thought the social behavioral community would be pleased and that the recommendation would make a difference. She suggested adding to (a) <u>health promotion or compromising behaviors.</u> She also suggested adding <u>noninvasive physiological and biometric measures</u>. Both of these areas have been a source of confusion. Last, she suggested adding <u>observational</u> to participant observation (as a separate category). Dr. Prentice asked her to indicate at a later time where she felt this language should be added to the list.

Dr. Weiner was concerned that an imaging study aimed at understanding cognitive behavior might be retrofitted into an expedited review category by calling it minimal risk, which would not always be appropriate. Dr. Fisher added that such procedures may involve PET scans or MRIs. She suggested that the subcommittee consider how this category would be addressed. Dr. Genel proposed addressing

this concern by using "*and"* instead of "or" as the last word of (a). Mr. Nelson and Dr. Prentice thought this would cause additional problems by binding the two together and would also change regulatory language.

Dr. Powe questioned whether interventional studies were included. Mr. Nelson said that they would be only if there were minimal risk interventions in a listed area. Mr. Nelson thought that a behavioral intervention the IRB believed constituted no more than minimal risk might fit, but the categories would not encompass typical biomedical interventional studies, clinical trials, or anything of that nature.

ACTION

The recommendation was tabled for further consideration by the subcommittee. Members were encouraged to e-mail any further concerns to the Co-Chairs.

Adding a Category of Expedited Review for "Other Minimal Risk Research"

Mr. Nelson explained that in regard to the same 1998 list of categories eligible for expedited review, IRBs have indicated that valuable time in convened meetings is being spent on *pro forma* reviews of research that is clearly minimal risk but for which there is no specific category. The wording used for Category 9 provides a model for how a new category might be created. The subcommittee envisioned a tenth category for "other minimal-risk research" under which the convened IRB would be allowed to define additional categories of this type of research that would be eligible for expedited review. IRBs could use this option for types of minimal risk studies they see routinely that would not otherwise be eligible for expedited review.

> **Recommendation:** To establish new category #10:
>
> *DHHS and FDA should publish in the Federal Register a revised list of Expedited Review Categories that includes an additional category for "Other Minimal Risk Research." Under this category, IRBs should be permitted to develop written procedures through which the convened IRB may define additional categories of minimal risk research (not conducted under an investigational new drug application or investigational device exemption) that may be reviewed and approved using expedited procedures, based on the particular nature and context of research routinely reviewed* by the IRB.

Dr. Prentice observed that it would not be possible to vote on this particular recommendation yet because it is closely to the issue of what constitutes minimal risk, a subject the subcommittee is discussing. He said it was important to craft the recommendation carefully, because some IRBs do not have a reliable grasp of the concept of minimal risk. Dr. Jones also found the recommendation too open-ended.

Dr. Gyi added, however, that Charles MacKay and others involved in crafting the original language for expedited review had shared with the subcommittee that they assumed these categories would be revisited regularly; they were not intended to be "cast in stone." Mr. Nelson added that the same approach is shown in category nine, which has not been seen as opening the door too widely. Dr. Prentice pointed out, however, that the language of category nine specifies that the decision that research can be expedited is made at a convened meeting with a quorum of the IRB.

Dr. Botkin asked the Co-Chairs to indicate whether there are specific domains in this area that have proved especially problematic. He thought examples would be helpful. Mr. Nelson says a common example is a study that involves a single chest x-ray.

ACTION

An informal poll was taken in which one member believed this approach was a good idea, five thought it was not, and two abstained.

The recommendation was tabled for further consideration by the subcommittee, with the understanding that they would need to look at it carefully because of a lack of existing support.

Defining Human Subjects Research

Mr. Nelson highlighted the need to define what is meant by "human subjects research." He noted that OHRP is currently engaged in developing draft guidance. He did not ask for further discussion and response, but said that the recommendation captured the subcommittee's stance and asked that it be considered.

> **Recommendation:** *On Defining Human Subjects Research*
>
> *OHRP should define more precisely the boundaries of IRB responsibility under DHHS regulations, including criteria for determining when activities "cross the line" to become human subjects research. Examples of steps that might help define these boundaries include issuing guidance on*
>
> *(a) the definition of research, particularly explicating the meaning of the terms "systematic," "designed," and "generalizable knowledge."*
> *(b) the definition of "human subject," clarifying the meaning of "readily ascertained"*
> *(c) research-like activities that typically do not constitute human subjects research and thus do not typically require IRB review, approval, and oversight (e.g., journalism; some types of oral history; some educational activities conducted for pedagogical purposes; activities that interview informants to gather information on their organizations but to not collect individual data; some quality assurance and program evaluation activities; feasibility studies solely to determine the potential utility or viability of a proposed service or facility).*
>
> *OHRP should also consider making an Advanced Notice of Proposed Rule Making (ANPRM) to solicit public comment regarding a regulatory change to add additional exemption categories for human research activities in such areas a s journalism, oral history, quality assurance and program evaluation, public health outbreak investigations, etc.*

Future Work of the Subpart A Subcommittee

The subcommittee sees considerable difficulties in the current definition of minimal risk. It suggests that the next step is the development of a short guidance document on the topic and is proposing to draft guidance for review. A regulatory rewrite is not seen as essential for clarification.

Two issues were proposed as the next priorities to be addressed. The first relates to IRB membership (for example, number of members, diversity, expertise, and other considerations). The second

involves definitions related to vulnerable subjects (such as the meaning of vulnerable and what would constitute adequate safeguards). However, he noted that the subcommittee is not properly constituted to consider the issues that arise in regard to decisionally impaired subjects.

DISCUSSION

Dr. Fisher observed that the topic of vulnerability is complex, since people may be vulnerable in some circumstances but not others. It may be necessary to narrow the topic.

SACHRP agreed to discuss the topic of next steps for the subcommittee further on the second day after hearing from the panel on issues related to decisionally-impaired research subjects.

Working Lunch/Ethics Training For New Members
Michael H. Wolf, Ethics Division, Office of General Counsel

All SACHRP members attended ethics training to assist them in avoiding conflicts of interest and other violations of their ethical obligations as Special Government Employees (SGEs).

Report of the Subcommittee on Research Involving Children
Celia B. Fisher, Ph.D., Co-Chair

Dr. Fisher explained that the presentation was intended to address two issues previously raised with SACHRP. First, the subcommittee will lead a re-examination of §46.409, regarding Wards of the State. SACHRP requested some revisions, which the subcommittee addressed. The presentation will continue by revisiting issued additional issues relevant to §46.405.

Children who are Wards of the State as Research Subjects

Dr. Fisher explained that under existing regulations, children who are wards of the State or any other agency, institution, or entity can be included in research under §46.406 and §46.407 only if the research meets one of two criteria. It must be either:

- related to their status as wards, or
- conducted in schools, camps, hospitals, institutions, or similar setting in which the majority of children involved as subjects are not wards.

Dr. Fisher reminded SACHRP that the research in question under §46.406 and §46.407 is research that is greater than minimal risk with no potential for direct benefit.

If the research is approved, the IRB is required to appoint "an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*." The regulations further specify that "one individual may serve as advocate for more than one child"; that "the advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research"; and that "the advocate is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization." The Co-Chair also pointed out that wards may be considered a vulnerable population, thus falling also under the provisions of Section §46.111 (b) of the regulations.

Dr. Fisher observed that the term "ward" is not defined by HHS regulations, but is defined in FDA regulations. She said it is challenging to identify who should be considered a ward. Also, the person who has physical custody of the child on a day-to-day basis may be different from the entity that has legal custody. It is important to recognize that the legally recognized guardian may not be involved in the day-to-day life of the ward. Further complicating the issue, there may be frequent fluctuations in guardianship. Ensuring the safety of a ward who is involved in research requires appropriate oversight (for example, ensuring the child arrives at appointments for follow-up) that may become difficult and complicated. Finally, state regulations regarding wards, where they exist, may vary.

In deliberating the subject of protection for wards as human subjects of research, the subcommittee sought to accomplish the following:

- Avoid exploitation of wards as a vulnerable population,
- Assure wards are not excluded as beneficiaries of research that offers direct benefit, and
- Assure continuity of care, safety, and oversight of research for wards while involved in research and guardianship/physical location changes.

In developing its recommendations, the subcommittee wanted to avoid being overly proscriptive and bear in mind the potential impact on the international committee. Members also tried to bear in mind the differences between recommendations appropriate for OHRP guidance versus issues related to best practice within the IRB community that could be addressed or promoted in other ways.

Defining a Ward. The first related recommendation is based on the fact that there is currently no definition of ward in the HHS regulations. The subcommittee recommended adopting the one FDA uses to ensure a consistent approach.

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

ACTION:

Recommendation 1 was approved without further discussion.

Approving an Advocate. Dr. Fisher stressed that Recommendation 2 does not suggest that all the conditions listed must be satisfied; rather, it provides guidelines for what might appropriately be taken into consideration. It is intended as guidance regarding the type of questions an IRB should be asking about people who become advocates.

> **Recommendation #2.** *In approving the advocate for a specific protocol the IRB should take into consideration the following. The advocate should:*
>
> *1) have appropriate education and training, in order to take into consideration the nature of the research and the expectations of the advocacy role.*
>
> *2) have the ability to make a decision regarding each ward's participation in research that is independent and free of any contractual requirements or financial gains or other conflicts*

that depend upon the number or types of subjects required for recruitment, enrollment, and ongoing participation.

3) *have independence from the research for the entire period of the advocacy role*

4) *act in the interests of protecting the safety and welfare of the ward by assuming an intermediary role between the child and the research efforts. This may include meeting with the ward, caregiver, and researchers as deemed necessary and having the time and ability to become familiar with the child's health, behavior, social and physical environment.*

DISCUSSION:

Mr. Nelson asked for clarification of the similarities and differences between what the current regulations require or say under §409 and the wording used in Recommendation 2. Dr. Fisher saw the recommendation as a more detailed articulation of what is in §409. Mr. Nelson found the recommendation in harmony with the spirit and intent of the regulations.

Looking ahead to recommendations regarding children who may become wards after research initiation, Dr. Weiner felt it was overreaching to expect an IRB to keep on file references of people who could be advocates because of their knowledge of the child. Dr. Fisher clarified that the advocate would not have to have *a priori* knowledge of the child; rather, the requirement is that the person must have the ability to know the child individually. The intent is to identify someone able to make a recommendation in the child's best interest.

Dr. Weiner found the language, "the advocate should" overly prescriptive. This was replaced with "whether the advocate…" (see below).

The Advocate's Role. Dr. Tilden asked for clarification of the role of the advocate. Dr. Fisher said that the subcommittee had not articulated the roles, in part because there may be either more or fewer in specific instances. Dr. Prentice agreed, noting that an advocate acting in the best interests of the child might have a variety of different responsibilities and functions, from deciding whether or not the child should participate in the research to determining whether the child should withdraw from it. Dr. Fisher added that in defining the role of the advocate as an "intermediary" one, the guidance is communicating that the advocate should play a role every time contact is initiated with the child.

Dr. Tilden observed that the role of advocate was "quite a big obligation." He also suggested that the advocate would need direction on how to raise questions about the research if the person had concerns. Considering Dr. Tilden's comments, Dr. Flanzer saw a need to clarify to whom an advocate would report concerns or questions. Dr. Tilden added that the advocate's ability to observe the research on behalf of the IRB is a safeguard, but suggested the advocate should have a way to report back to the IRB. Dr. Fisher saw this as a critical issue. Dr. Prentice suggested additional language to clarify the advocate's responsibility to report back in (4). (See revised recommendation below.) Dr. Fisher added that if the guardian and the investigator do not heed the advocate's advice, the advocate can go to the IRB to arbitrate the final decision.

Dr. Botkin suggested adding language to (4) to further clarify the advocate's role as intermediary (included below).

Dr. Powell wondered whether limits should be recommended for the number of children an advocate could effectively represent. Dr. Fisher and Dr. Prentice saw it as the responsibility of the IRB to make sure the advocate was able to fulfill this role, which requires an understanding of a particular child.

Advocate vs. Guardian. A member observed that in the context of state and local law, guardians have varying levels of decision-making capability. The member asked for clarification of the role of the advocate in relation to that of the guardian. Dr. Fisher responded that the advocate does not have a legal role in regard to the child. The person who can consent is still the legal guardian. The advocate provides an additional layer of protection, but cannot "veto" the guardian's decisions. However, the advocate can tell the PI that the child is not a suitable research subject and should not be recruited; this adds protection because the legal guardian may be far removed from the child and may have no individual knowledge of the child's best interest.

To remove the possibility of a conflict between the advocate's decision and that of the guardian, members decided to replace the word "decision" in (2) with "determination."

Advocates, Foster Parents, and Natural Parents. Dr. Weiner asked whether it would be legitimate for a foster parent who is not technically the child's guardian to be appointed an advocate by the IRB. She felt this would not be comfortable. Dr. Fisher responded that the regulation specifies that the advocate must be independent of the guardian organization, which might rule out foster parents. Dr. Weiner was concerned that this would take power away from the foster parent, since the foster parent is precluded from serving as the child's advocate. Dr. Fisher noted that the specifications to which Dr. Weiner objects are embedded in the regulation.

Dr. Jones asked how advocates are paid for their services and questioned whether the language of (2) would preclude their being paid for their services from the research grant. Dr. Fisher responded that the onus is on the study investigators to demonstrate to the IRB that payment is not tied to recruitment – specifically, that the advocates are not being paid "by the head." They could receive a yearly salary, for example, that is funded by the same source as research activities.

Dr. Porter suggested including the natural parent as another person who may retain some legal rights to make a decision on behalf of the child. Dr. Fisher said, however, that the retention of rights was variable. Members agreed to add both the biological parent and foster parent to the persons the advocate might meet with under (4). The words "as appropriate" were added as a qualifier, since the specific circumstances will vary.

The following revisions were incorporated in the recommendation considered for approval:

> *In approving the advocate for a specific protocol the IRB should take into consideration the following.*
>
> *<u>Whether the advocate</u>:*
>
> *1) <u>has</u> appropriate education and training, in order to take into consideration the nature of the research and the expectations of the advocacy role.*
>
> *2) <u>has</u> the ability to make <u>a determination</u> regarding each ward's participation in research that is independent and free of any contractual requirements or financial gains or other conflicts*

that depend upon the number or types of subjects required for recruitment, enrollment, and ongoing participation.

3) *has independence from the research for the entire period of the advocacy role*

4) *can act in the interests of protecting the safety and welfare of the ward by assuming an intermediary role between the child, investigator, guardians, and the IRB. This may include, as appropriate, meeting with ward, biological parents, foster parents, and researchers as deemed necessary; having the time and ability to become familiar with the child's health, behavior, social and physical environment; and notifying the investigator and IRB of any concerns about the child's participation in research.*

ACTION

Recommendation 2 was approved as revised with one abstention.

Additional Safeguards for Wards in Research under §404 and §405. This recommendation has not previously been voted on by SACHRP. The Co-Chair pointed out that wards are vulnerable by nature of their status regardless of the research category and should be considered a special population. There are no special protections for wards under either §404 or §405, so this is an important consideration.

Original Recommendation 3. *In reviewing research that falls within category 404 and 405 and includes or will potentially include wards, IRBs should consider the inclusion of additional safeguards to protect the rights and welfare of these subjects in accordance with the provisions of subpart A part 46.111(b). This may include actions such as the appointment of an advocate or any other safeguard deemed necessary to protect the safety and welfare of the ward taking into consideration the nature of the research.*

DISCUSSION

One change was considered to reduce the prescriptive quality of "IRBs should consider." Instead, the language should read, "…IRBs may consider…".

ACTION

The recommendation was approved without further changes.

Becoming a Ward after Enrollment. The subcommittee considered the question of whether there should be requirements to address the situation of a child who becomes a ward after enrolling in a study. The issue came before the subcommittee because it is of concern to IRBs. The issue is complicated by a number of considerations: What procedures/requirements should exist such that the PI will know about a change in status? How practical would these procedures/requirements be to implement? What will they cost?

When a child becomes a ward of the state while participating in the research, the legally recognized decision maker may change. Informed consent is an ongoing process and as a result, the logistics of

who can make a decision on the child's behalf and the implications of the child's participation in research may also change.

While the subcommittee believes the following recommendation is consistent with the regulations, many IRBs and PIs are not aware of this requirement. The point of this guidance would be to highlight to IRBs the need to give special consideration to populations that are especially likely to become wards during the process of their oversight. While the first part of the recommendation refers to the IRB's mandatory obligation under the regulations, the second is intended as guidance.

> **Original Recommendation #4.** *If an individual child/adolescent becomes a ward while participating in research that falls under category §46.406 or §46.407, the requirements of section §46.409 must be implemented in order for the ward to continue participation.*
>
> *If an individual child/adolescent becomes a ward while participating in research that falls under category 46.404 or 46.405, the IRB may consider requiring additional safeguards to protect the safety and welfare of the ward as specified in Subpart A §46.111(b).*

The subcommittee also sought to provide guidance for IRBs and investigators on what to do to make it easier to deal with populations in which there is a large possibility that a significant number of the research subjects may become wards. This could happen suddenly, so it might be best dealt with in advance, by carrying out different levels of review simultaneously. Such a procedure could reduce unnecessary delays or interruptions in the research and in the subject's participation.

> **Revised Recommendation 5.** *If an IRB reviews a protocol for which there is a reasonable possibility that the investigator that some subjects may become wards during the course of the research and the research falls into category §406 and §407, the IRB may consider reviewing and approving the protocol in accordance with §409. This would include identifying a potential advocate in the event one were needed.*

DISCUSSION

Recommendation 4. Mr. Nelson was concerned about the appropriateness of saying the protections described in the first part of recommendation 4 "must" apply but those in the second paragraph "may" apply. Dr. Prentice explained that under §406 and §407 the IRB really does have no choice under the regulations. However, the IRB is not required to apply additional protections to wards under §404 or §405, but the IRB could decide to do so.

Dr. Botkin observed that the recommendation is silent about how one determines that a child has become a ward and whose responsibility it is to inform the investigator of the child's change in status. Dr. Fisher responded that the answer would differ depending on the state and which ward population is involved. Dr. Prentice said it could be assumed that the investigator would soon find out about the child's change in status and that the IRB would have guidelines specifying that the investigator should notify the IRB when this occurs. Dr. Genel differed, observing that it is not always apparent that a change in guardianship has occurred.

Dr. Prentice added that OHRP may further clarify the issues that have been raised if the recommendation is approved by the Secretary and it issues guidance on the subject.

Recommendation 5. Revisions were suggested to clarify the intent of the recommendation (see below).

Dr. Fisher asked Dr. Prentice to clarify requirements for a study in which some children in the study are wards and some are not. Are the children who are not wards approved under §406 or §407 and the other children under §409? Or should all of them have wards? Dr. Prentice responded that the subjects who are not wards are not subject to §409. However, the recommendation suggests that it would be helpful to approve the protocol in advance under §409 if it is expected that a substantial number of nonwards who may become wards. Dr. Fisher added that it is her understanding that this would help IRBs by avoiding unnecessary delays to comply with requirements. There should be a plan in place to identify a potential advocate in the event that one is needed.

Members clarified that the circumstance in which children are already wards does not have to be addressed in the recommendation because there is already a clear regulatory requirement that the protocol must be approved in accordance with §409.

> **Recommendation 5 as approved.** *If an IRB reviews a protocol for which the investigator may reasonably anticipate that some subjects may become wards during the course of the research and the research falls into category §406 and §407, the IRB may consider reviewing and approving the protocol in accordance with §409. This would include identifying a potential advocate in the event one is needed.*

ACTION:

With one abstention, Recommendation 4 was approved without changes.
Recommendation 5 was approved with the revisions shown above.

Guidance and Education for PIs and Research Personnel on Wards. The following recommendation may be addressed in a variety of ways – it is nonprescriptive – but is intended to prevent the kind of problems that IRBs and OHRP have been seeing when IRBs and investigators are unprepared for changes in a child's legal status.

> **Revised Recommendation 6.** *IRBs in collaboration with their associated institutions (including legal counsel offices) should provide guidance and education to investigators and their associated research personnel regarding*
>
> - *who is defined as a ward of the state in accordance with state regulations*
> - *specific state regulations and requirements if they exist*
> - *the need to notify the IRB when a ward is initially considered for research in category §406 and §407 research*
> - *the need to notify the IRB when a child/adolescent already participating in research categorized as 406 and 407 becomes a ward of the state.*

DISCUSSION

Dr. Tilden suggested reversing the opening words to rest the primary responsibility on the institution: "Institutions in conjunction with their IRBs…." Members decided on the rewording below, noting that OHRP will look at the issue in more detail when it drafts the final guidance.

Revised Recommendation 6. *Institutions and IRBs in collaboration with other operating units (e.g,, office of legal counsel or legal counsel) should provide guidance and education to investigators and their associated research personnel regarding*

- *who is defined as a ward of the state in accordance with state regulations*
- *specific state regulations and requirements if they exist*
- *the need to notify the IRB when a ward is initially considered for research in category 406 and 407 research*
- *the need to notify the IRB when a child/adolescent already participating in research categorized as 406 and 407 becomes a ward of the state.*

ACTION:

The recommendation was approved as revised.

Component Analysis and Protection for Wards. Since component analysis applies to all pediatric research, the subcommittee saw the following recommendation as following logically.

Recommendation 7. *If component analysis of a study finds that one arm or procedure of the research falls within category §46.406 or §46.407 and other arms or procedures are approvable under §404 or §405, the most protective component will govern and the research needs to be reviewed and approved in accordance with the provisions of §46.409.*

DISCUSSION

Dr. Fisher asked to withdraw Recommendation 7, finding the terminology unduly complicated.

ACTION

Members agreed to withdraw the recommendation.

Topics for Discussion under §46.405

Dr. Fisher reminded members that this section includes research that can be greater than minimal risk that has the probability of direct benefit for the individual child. The subcommittee sought to clarify the language and processes associated with the regulation.

Dr. Fisher then presented the existing regulation, highlighting the elements of the regulation that the subcommittee saw as requiring clarification:

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) **the risk is justified by the anticipated benefit to the subjects;**
(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

Acceptable Risk. The subcommittee sought to provide guidance on what is meant by "acceptable risk."

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

DISCUSSION

Dr. Powe pointed out that it is possible to have low probability of benefit and high magnitude of benefit, or vice versa. In other words, it is the product of two rather than either one separately that is at issue. Mr. Nelson, however, argued that the process cannot be reduced to a mathematical equation. Dr. Prentice observed that there could be specific data regarding probability – e.g., one chance in a hundred or one chance in a thousand of something occurring – and those two possibilities are distinctly different. Members agreed on the revised language below.

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

ACTION:

The recommendation was approved unanimously as revised.

Recorder's Note:

The following recommendation was approved in April, 2005:

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

Available Alternatives. Dr. Fisher explained that Proposal 2 is not really new, but articulates what is in the regulations.

> **Proposal 2**: **Available Alternatives.** *As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be independently approved by an IRB if the anticipated benefits are not at least as favorable to the subjects as available alternative approaches.*

The subcommittee went on to consider what is meant by "available alternative approaches." Are these, for example, intended to be affordable, empirically validated, clinically accepted but untested treatments, or treatment as usual in independent practice (non-research settings)? The subcommittee felt the correct approach was not to list all these possibilities, but rather to provide guidance on how to determine whether an alternative is appropriate. The contribution of the proposal is to stress the

need for an evidentiary basis for saying that an alternative is or is not as good as prospective participation in the study.

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

DISCUSSION

Proposal 2. Mr. Nelson found the word "independently" to be awkwardly placed; it could be misconstrued as applying to the IRB rather than factors.

Dr. Jones felt the language should refer to the risk-benefit relationship rather than the risk. The proposal was revised as shown below:

> **Proposal 2**: **Available Alternatives (amended).** *As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be approved by the IRB under §405 if the anticipated risk-benefit relationship is not at least as favorable to the subjects as available alternative approaches.*

Proposal 3. Dr. Prentice was concerned that Proposal 3 was too closely tied to clinical research. He wondered whether there might not be applicable studies that were nonclinical. Dr. Fisher could not think of such an example. However, she noted that the general term "scientific data" would be applicable to a social science study.

Mr. Nelson noted that in many cases a practice is standard of care, but there is little to support it. . Dr. Jones proposed alternative language (below).

> **Proposal 3 (as revised):** The evidentiary basis for evaluating available alternatives should be defined in terms of scientific data, when available, or by comparison to the standard of care for treating or monitoring the subjects' disorder.

ACTION:

Proposals 2 and 3 were tabled.

Recorder's Note:

The following recommendation was approved in April, 2005:

> **Proposal 2: Available Alternatives.** *As an additional protection, even if the risks are balanced by the anticipated benefits, a study may not be independently approved by an IRB if the anticipated benefits are not at least as favorable to the subjects as those presented by available alternative approaches.*

The concept of an evidentiary basis for risk-benefit decisions was also presented as **Proposal 3: Evidentiary Basis for Risk-Benefit Decision.** However, specific wording for the proposal was not presented at that time.

Monitoring Procedure. This proposal is intended to address an instance in which the intended intervention does not have the prospect of direct benefit to the child, but the monitoring procedure itself might have a benefit. The subcommittee felt there should not be simply a general benefit from monitoring to maintain the wellbeing of the subjects, but rather evidence that the monitoring procedure holds out the prospect of direct benefit. Its intent was to discourage "piggy-backing" greater than minimal risk procedures onto treatment trials if these procedures do not in and of themselves have a prospect for direct benefit or the efficacy of the procedures themselves is not a focus of the research.

> **Proposal 4: "Monitoring Procedure."** *Any benefit of monitoring listed in a §46.405 application must be an objective of the study.*
>
> *For approval under §46.405, the monitoring procedure must have the intended, not incidental, potential benefit of influencing the child's management of the disease.*

ACTION

The proposal was found to have been approved at a previous meeting (November 2005) with alternative wording as follows:

> **Proposal 4. Monitoring Procedures**
>
> *a. Any benefit of monitoring listed in a §46.405 application must be an **objective** of the study.*
>
> *a. For approval under §46.405, the monitoring procedure must have the **intended**, not incidental, potential benefit of influencing the child's management of the disease.*

The Chair thanked the Children's Subcommittee and asked its Co-Chairs to formulate the next letter to the Secretary.

PUBLIC COMMENT

The Chairman invited public comment.

Ms. Sarah Putney, who is with the IRB Administration of the Harvard School of Public Health, offered two comments. First, she observed that Dr. Fisher said her recommendations were aimed at the development of guidance, but the Chair had described one of the recommendations as requiring a revision to the regulation. In response, Dr. Prentice affirmed that no recommendations require an amendment of subpart D.

Ms. Putney then expressed surprise that some of Subpart A's recommendations were dismissed without much discussion, especially the proposal for a new expedited category 10. She felt there would be a good deal of support for the recommendation in the IRB community. She argued that today, more oversight and available help than ever before are available to help IRBs to do things well. For example, many are becoming accredited. She believed more trust should be shown for IRBs.

Dr. Prentice responded that the Subpart A Subcommittee plans to revisit this particular issue. In regard to Ms. Putney's point about accreditation, the Chair observed while there are hundreds of IRBs that are in the process of applying for accreditation from the Association for Accreditation of Human Research

Protection Programs (AAHRPP), to date there are only about 35 institutions that have been accredited of the 3,000 to 5,000 IRBs that exist. Many of these IRBs may be in a poor position to be able to interpret and apply the regulations in a consistent way. These IRBs must be considered when it is suggested that IRBs should be allowed a great deal more flexibility. He noted that even at a prestigious institution he visited, he found that the data base contained many studies the institution had expedited believing they were minimal risk that unquestionably were not.

Ms. Putney continued by giving examples of the types of studies that might be included in the proposed new category for expedited review. These included environmental sampling and air sampling when it intrudes on private space, as well as researchers wearing global positioning system gadgets while roller blading through public parkways.

In regard to the issue of the proposed new category for expedited review, Dr. Genel suggested inserting the phrase "subject to concurrence by OHRP." However, Dr. Prentice felt this would constitute a logistical problem in terms of the demands placed on OHRP. He agreed that the list of what could be subject to expedited review could be expanded.

Discussion and Wrap-Up
Ernest Prentice, Ph.D.

Dr. Prentice shared thoughts based on a discussion with Dr. Fisher related to next steps for the Subpart A subcommittee. He said it was desirable to encourage the subcommittee to tackle issues that will allow it to develop a work product in a reasonable period of time, culminating in the development of a letter to the Secretary. Dr. Fisher felt that taking on the entire topic of vulnerable subjects would be overly complex and time consuming. She suggested addressing smaller issues such as consent and waiver of consent. Dr. Prentice asked members to consider this approach for discussion the following day.

He added that in terms of addressing major topics, SACHRP cannot support more than two subcommittees at a time. As of this meeting, the work of the Subpart D (Children's) subcommittee is all but complete, so it would be possible to start a new subcommittee to address the needs of decisionally impaired subjects if that seemed appropriate.

TUESDAY, AUGUST 1

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

The Chairman provided an overview of events for the day.

Dr. Prentice invited Dr. Schwetz to remind the group of the history of the IOM report. Dr. Schwetz said he was pleased when SACHRP decided to look at Subpart C, since OHRP had received many questions about it from the IRB community that clearly showed there was confusion about what the regulations meant and how they could be applied. The subcommittee concluded that there were changes required in Subpart C that could not be addressed through guidance alone, but would require a process to change the regulations themselves. However, because the current context of prisoners is so different today compared to time when Subpart C was written (in 1978), it seemed best to begin by

exploring the ethical considerations that surround the use and involvement of prisoners in research. The IOM panel was formed to examine these issues.

Presentation of IOM Prisoner Report
Wendy Visscher, Ph.D., RTI International; Andrew Pope, Ph.D., IOM

Dr. Visscher, Director of RTI International's Office of Research Protection and Ethics, served as spokesperson for the IOM Committee.

She explained that the committee's charge was "to examine whether the conclusions of the National Commission in 1976 remain appropriate today, specifically considering the impact of developments in correctional systems and societal perceptions of the balance between research burdens and potential benefits of research." Specifically, the Committee was asked to:

- Consider whether the ethical bases for research with prisoners differ from those for research with nonprisoners;
- Develop an ethical framework for the conduct of research with prisoners;
- Based on the ethical framework developed, identify considerations or safeguards necessary to ensure that research with prisoners is conducted ethically; and
- Identify issues and needs for future consideration and study.

Larry Gostin, the IOM Committee Chair, saw that "getting the balance right between scientific research and ethical treatment of prisoners is vital to a humane society." Committee members were fully versed on the potential for abuses in work with prisoners. They included researchers, ethicists, attorneys, prison officials, a former prisoner, IRB and regulatory professionals, and members with experience in more than one of these areas. The committee had its first meeting in March, 2005 and released its report, *Ethical Considerations for Research Involving Prisoners*, on July 12, 2006.

Data sources and methods used by the Committee included commissioned papers to help understand some issues; workshops with presentations from advocate groups, attorneys, prisoners, and others; telephone interviews; an e-mail survey of State Departments of Corrections to find out what type of research is being done and what type of protections are in place; a literature review; site visits to San Quentin and the California medical facility in Vacaville, both of which offered opportunities to interview prisoners; and a Prisoner Liaison Panel that included former prisoners, community organizations that work with prisoners, and other members who were familiar with both past abuses and what it means to be a prisoner today.

The speaker presented recommendations in five broad areas:

- Expand the definition of "prisoner" to expand the reach of human subjects protections;
- Ensure universal, consistent ethical protection (vs. the current "patchwork" of protections);
- Shift from a category-based to a risk-benefit approach to research review;
- Update the ethical framework to include collaborative responsibility; and
- Enhance systematic oversight of research with prisoners.

Redefining "Prisoner." The Committee found that only a small percentage of people who have their liberty restrained in some way by the criminal justice system are actually in prisons and jails. The population of prisoners has quadrupled since 1976; 7 million people could be called prisoners, of

whom only 2 million are in prisons and jails. The Committee felt that the same protections afforded those 2 million should be extended to the other 5 million people restrained by the system.

Dr. Visscher also observed that the population of prisoners today also differs from that of 1976 in that it includes more women, more minorities, a larger population that is aging, and more people with chronic diseases. She added that the Committee did not specifically consider children unless they were treated as adults, people who are prisoners under special provisions such as the U.S. Patriot Act, and people committed to mental institutions. This was not because the Committee did not view extra protections as needed, but rather because it could not address them all.

The expanded definition of "prisoner would include people on probation, parole, and in alternative settings such as work release and community programs.

> **IOM Recommendation 4.1:** ***Redefine "prisoners" to expand the reach of human subjects protections.*** *The Department of Health and Human Services and other relevant agencies that write, implement, or enforce regulations pertaining to research with prisoners should expand the definition of "prisoner" to include all settings, whether a correctional institution or a community setting, in which a person is held under conditions that restrict liberty as a result of the operation of the criminal justice system.*

Ensuring Universal, Consistent Ethical Protection. The Committee observed that most of the research currently being done with prisoners falls outside the purview of OHRP because it is not funded by HHS. Even among Federal agencies, a number of those that adopted the Common Rule did not adopt Subpart C in their Federal-Wide Assurance (FWA). The Department of Justice's Bureau of Prisons, for example, did its own regulations. The Food and Drug Administration (FDA) attempted to create its own regulations, but stopped when prisoners resisted, fearing lack of access to research.

> **IOM Recommendation 3.1:** ***Establish uniform guidelines for all human subjects research involving prisoners.*** *Congress should mandate a uniform set of guidelines for human research participant protection programs for all research involving prisoners.*

Currently, there is no public data base for all research involving prisoners. Such a data base would help to define the universe of studies, show what type of research is going on, capture the types of review that are occurring, help researchers network with each other to identify best practices in protection and identify other researchers engaged in topics of interest, encourage IRBs to share their protective practices, and enhance the application of findings to different populations.

> **Recommendation:** ***Maintain a public database of all research involving prisoners.*** *The Department of Health and Human Services, in cooperation with the Department of Justice, should systematically and comprehensively document all human subjects research with prisoners.* (Recommendation 2.1)

The speaker pointed out that transparency and accountability in prisoner research have been far from the norm. The Committee saw it as important for researchers to be very open about what they are doing inside prisons; transparency and accountability are hallmarks of good research generally and should be applied to research involving prisoners.

IOM Recommendation 6.7: ***Ensure transparency and accountability in the research enterprise.*** *Human research participant protections programs and prison administrations conducting human subject research should be open, transparent, and accountable.*

Applying a Risk-Benefit Framework to Research Review. The IOM Committee recommended a shift from the category-based approach to prisoner research used in the current Subpart C to a risk-benefit approach to research review, such as that used in Subpart D. Dr. Visscher observed that IRBs are used to looking at risks and benefits. This approach offers a much better framework for looking at research involving prisoners, since it allows IRBs to identify specific ethical issues that relate to a protocol and decide what protections need to be put in place.

IOM Recommendation 5.1*: Apply a risk-benefit framework to research review.* *The Department of Health and Human Services should revise regulations regarding research with prisoners from a model based on categories to a system based on weighing of risks and benefits for the individual human subject, similar to the approach currently used in Subpart D.*

Using a Collaborative Research Approach. Dr. Visscher observed that under an ethic of collaborative responsibility, investigators would be able to obtain input from prisoners and other stakeholders on the design and conduct of any research protocol involving prisoners. They should be able to consult with prisoner officials, prisoners, and others to gain an understanding of the setting in which they are considering doing research. Prisoners have told the IOM committee that they want to be given the opportunity to participate in research; given an opportunity, they believed they could help researchers develop strategies for studies that would work in their setting. They could help researchers understand how privacy could be assured, how confidentiality might be protected, and how they could most easily report problems to the IRB and ask any questions they might have before or after enrollment.

IOM Recommendation 5.2: ***Use a collaborative research approach.*** *Under an ethic of collaborative responsibility, investigators should find ways to obtain input from prisoners and other stakeholders on the design and conduct of any research protocol involving prisoners.*

Many prisoners do not have adequate medical care, and the prospect of having access to care can be inherently coercive. It is important to guard against undue influence from this motivating factor. In addition, it is likely that a facility that does not have adequate care will not be equipped to follow a protocol reliably or respond to adverse events appropriately should they occur.

IOM Recommendation 5.3: ***Ensure adequate standards of care.*** *Human research participant protection programs, together with the prison administration and prison health care professionals, are responsible for ensuring that research with prisoners occurs in an environment that is appropriate to the health and well-being of prisoners, including access to existing medical and mental health care that is adequate, protection from inmate attempts to coerce or manipulate participation or nonparticipation in research, and prompt access to decent health care services in case the research causes physical or mental harm.*

The prisoner population is growing and becoming more vulnerable. Research would be helpful in determining how to promote the wellbeing of people in the criminal justice system and help them re-enter society successfully. Prisoners have told the IOM Committee that they want research to help improve the system.

IOM Recommendation 5.4: ***Support critical areas of correctional research.*** *Government agencies should fund and researchers should conduct research to identify needed supports to facilitate prisoners' successful reentry into society, reduce recidivism, and inform policy makers about the most humane and effective strategies for the operation of correctional systems.*

Enhancing Systematic Oversight of Research Involving Prisoners. For high-risk studies, the Committee recommends the use of an independent Prison Research Subject Advocate (PRSA) who is not associated with the research to be the "eyes and ears" of the IRB. The PRSA would be able to tell the IRB how the research is being conducted and serve as an avenue to convey concerns. The Committee felt that more monitoring is needed to ensure that ethical concerns are appropriately addressed.

IOM Recommendation 6.3: ***Strengthen monitoring of research involving prisoners.*** *Institutional Review Boards that review and approve research involving prisoners should establish an on-site, ongoing monitoring function through a Prison Research Subject Advocate (PRSA).*

The Committee also recommended abolishing the existing certification process in order to avoid delays and unnecessary use of limited Federal resources. Dr. Visscher saw this as a "better use of everyone's time." The proposed changes would result in very few proposals going to OHRP for Federal review.

IOM Recommendation 6.4. ***Modify IRB considerations for independent ethical review of research protocols.*** *Institutional Review Boards (IRBs) should focus on the particular ethical issues that each protocol raises in the specific context of the correctional setting. IRBs would no longer be required to forward research proposals to OHRP for certification, except for those rare proposals that require federal-level review.*

Despite the above change, the Committee sees OHRP responsibilities as being enhanced. It would maintain a registry of research, make determinations for "research not otherwise approvable," enforce compliance, and serve as a national resource for IRBs to promote a consistent understanding and application of the regulations in different settings and with different types of prisoners.

IOM Recommendation 6.5: ***Enhance OHRP's capacity to provide systematic oversight of research involving prisoners.*** *The Department of Health and Human Services should strengthen the capacity of the Office for Human Research Protections to provide systematic oversight of research involving prisoners that is within its purview.*

The Committee saw no justification for having prisoner research covered by multiple sets of regulations and was particularly concerned to find that some research is occurring that is not addressed by any existing regulations. The IOM Committee saw the existing "patchwork" of protection as clearly unethical.

IOM Recommendation 6.6*: Establish systematic oversight of all research involving prisoners.* *Congress should establish a national system of oversight that is applied uniformly to all research involving prisoners.*

Believing that the principles of respect for person and for justice were paramount in research with prisoners, the Committee was concerned about the difficulty of prisoners making autonomous

decisions about whether or not to participate in a study. Although this is difficult, however, they were convinced that it is not impossible, and the researchers and IRBs should find ways to be assured that this can be done appropriately before approving a study in a particular setting.

> **IOM Recommendation 6.1:** ***Ensure voluntary informed consent****. Human research participant protection programs should ensure that voluntary informed consent is obtained from subjects in all research involving prisoners.*

The Committee also wanted to protect the privacy of prisoners, recognizing that this is a difficult task in a prison setting. While it is possible to have study design components that help ensure privacy, but IRB must be convinced that a strategy is in place that will work before doing the study in this setting. This is an area in which involving prisoners in study design is important and will help ensure a practicable solution.

> **IOM Recommendation:** ***Protect the privacy of prisoners engaged in research.*** *Human research participant protections programs should collaborate with prison officials, probation officers and other staff relevant to the correctional setting to protect the privacy of subjects in prisoner research.*

For more information, see the IOM Study Web site:

www.iom.edu/prisonerresearchethics

Dr. Visscher closed by stressing the potential of ethical research to "help us understand and promote the welfare of this large and growing segment of our society."

The book version of the study will be published in October.

DISCUSSION

The Chairman observed thanked the IOM Committee for its work. A dialogue followed between SACHRP members and the speaker.

Expanded Definition of Prisoner. The Chairman confirmed that the expanded definition of prisoner proposed by the Committee would include individuals who are on parole and individuals who were on electronic monitoring. He noted that the Subpart C Subcommittee had proposed additional protections for prisoners under the provisions of §46-111(b) but not in an amended Subpart C. Dr. Visscher responded that a person in the community in an electronic monitoring situation, for example, could participate in a study available to everybody in their community that would not have come under Subpart C because their participation has nothing to do with their status as a prisoner. However, if prisoners are enrolled because of their status as prisoner, the Committee concluded that they would have to fall under Subpart C protections.

Subgroups of Prisoners. Dr. Botkin probed the issue of subpopulations such as juveniles, which the Committee did not specifically address. He asked whether the committee suspected that significantly different issues might arise with some of these subpopulations within the prison system. If so, he asked whether it would be appropriate to try to address some of those particular issues prior to a more comprehensive attempt to revise regulations in this arena. Dr. Visscher said the three excluded groups – children, unless treated as adults, persons committed with mental illness, and political prisoners – would need very similar protections. She agreed that it might be a reasonable follow-on step to examine the

needs of these subgroups. However, Dr. Pope stressed that the need for a universal set of regulations stands separate from any need to explore these individual vulnerable populations individually.

Registry of Research. Dr. Genel asked whether the Committee was able to estimate the number of prisoners currently involved in research. Dr. Visscher said the Committee was unable to arrive at an estimate, but it appeared that the bulk of the research is social-behavioral in nature. Dr. Pope added that a major question is how much is going on through the private sector, and this is currently unknown.

Dr. Botkin asked whether, given the dearth of data on what research is occurring, the Committee has any specific knowledge of abuses of prisoners or any evidence that prisoners are being systematically denied the benefits of research. He wondered if more data needed to be collected before new regulations could be devised to address the abuses and issues that exist. Dr. Visscher agreed that the full scope of research is unknown and that it might be reasonable to do a database as a first step. Dr. Pope added, however, that the expansion of the prison population in itself suggests the need for strong protection.

Research Policies in Prisons. The Chairman asked whether there are prisons or prison systems that arbitrarily prohibit research involving prisoners. Dr. Visscher said that some of the survey respondents said they would not do biomedical research, but did not recall any that said they would do none at all. She also observed that some prison systems treat research done by internal investigators differently from that carried out by external investigators.

Adequate Standards of Care. The Chairman asked if the IOM had considered how best to determine whether or not a prison actually has adequate standards of health care. Dr. Visscher said it would be the responsibility of the researcher to determine what the level of care is in that setting. One important source of information would be to talk to the prisoners themselves. Documentation of how this determination was made should be included in the protocol submitted by the investigator to the IRB.

Speaking from the audience, Ms. Carr questioned whether it would make a difference if the proposed study would have the potential outcome of improving the standard or level of care in the setting. Dr. Visscher said that if no AEs were expected, a lower standard of care might be acceptable, but a medical study would require good medical care. Dr. Jones added that this should be worded carefully so it does not preclude social behavioral research where the standard of care is not relevant.

Risk-Benefit Approach. The Chairman asked whether the Committee's threshold for what it calls "low risks" is tied to minimal risk. Dr. Visscher confirmed that that was the intention. She added that the Committee felt the studies should benefit prisoners either individually or as a class. This allows some latitude in the concept of benefit.

Uniform Guidelines. The Chairman asked whether the Committee was aware of any sentiment in Congress to support this proposal and, if not, if the Committee had considered how OHRP and other Federal agencies might initiate such a mandate. Dr. Visscher had no comment on either issue. Dr. Schwetz said that the Assistant Secretary for Health (ASH) has been briefed on the fact that this report is now available and that it contains recommendations that are bigger than OHRP. HHS leadership will need to make the decision.

Dr. Visscher added that it would be an important step to encourage more agencies to adopt Subpart C. Dr. Prentice rejoined, however, that one of the reasons institutions have opted out of adopting Subpart C except for HHS-funded research is that it is restrictive and prohibitory. Many of these institutions do have what they view as equivalent protections.

Dr. Powell asked whether the universal protection the Committee recommends would be likely to offer prisoners the opportunity to participate in biomedical research. Dr. Visscher said the Committee agreed it was appropriate to offer prisoners the opportunity to participate in research that could be done in an ethical fashion. Dr. Powell emphasized the need for appropriate research done with prisoners as a part of understanding the epidemiology of communicable diseases that would be of concern as prisoners re-enter the community. Dr. Visscher agreed, giving the example of hepatitis as a disease common among prisoners.

Dr. Powe suggested that if the agency determines it will petition Congress to make such a change, it would be appropriate to consider extending the universal consistent set of protections to all human research subjects rather than just the isolated subset of prisoners. Dr. Weiner asked whether Dr. Pope was willing to be a liaison for the study to inform and advise any members of Congress or staff that would be interested in pursuing legislation. He indicated that he was interested, and some conversations have already occurred about who should receive briefings.

Dr. Powe asked which of the Committee's recommendations the speakers would view as most important. Dr. Visscher said the key recommendation would be that all prison research fall under one set of oversight, one set of regulations, and one oversight system. Dr. Pope agreed.

Becoming a Prisoner or Re-entering the Community. Dr. Powe asked for the Committee's insights regarding cases in which a person happens to become incarcerated after beginning a study or re-enters the community while participating in a study that began while the individual was a prisoner. Dr. Visscher said the Committee felt it was appropriate for people to continue in a study in which the individual is already enrolled after becoming a prisoner, especially if it confers benefits; however, the study would need to be re-reviewed by the IRB under the Subpart C rubric within 30 days of the person becoming incarcerated. A main purpose of the new review would be to make sure that adequate care is available to that person in the facility where he or she will be housed.

Dr. Genel probed the Committee's reasoning in barring enrollment in Phase 1 and Phase 2 trials for prisoners who are housed in the community, outside of the correctional institution. Dr. Visscher observed that such studies do not offer benefits to the individual. If the individuals are chosen because of their status as prisoners, the Committee felt that was not appropriate. However, if the individual chooses to participate as a community member, the individual is not barred from participation. The speaker further noted that in many community studies the fact that a person is a prisoner would not necessarily be known since there might not be a specific question that would elicit this information.

Advocate Role. Dr. Genel asked for clarification of how the research advocate would function outside of the traditional correctional institutional setting. Dr. Visscher explained that the prison research subject advocate is one of several protective mechanisms the Committee suggested. The IRB would need to assess the appropriateness of protective mechanisms for the specific situation, using a graduated approach to design the appropriate level of protection for the setting.

Collaborative Approach. Dr. Jones saw the Committee's recommendations in this area as part of a paradigm shift; the precedent set in regard to prisoners could potentially extend to other populations. At the same time, she wondered whether prisoners themselves might not sometimes view the standard of care issue quite differently and see it as appropriate to proceed in settings the Committee might view as potentially coercive. Dr. Visscher responded that it would still remain the responsibility of the researcher

to convince the IRB that the needed standard of care appropriate for the proposed study is available in that setting.

Dr. Pope stressed that each prison has its own culture; although many similarities exist, they are also distinctive. Because of this, there is a need for some collaboration in designing and conducting the research that is done in each individual prison so that a sense of the culture can be integrated into that research design.

Noting that the majority of prisoners are people of color, Dr. Powell asked whether the Committee considered cultural and racial diversity with respect to the collaborative representation of people in the IRBs that review protocols. Dr. Visscher said that the collaborative approach would be one way of involving more people of color in decision-making.

Next Steps regarding the IOM Report. Dr. Prentice suggested that SACHRP write a letter to Secretary Leavitt asking the Secretary to consider those recommendations contained in the IOM report that pertain to HHS and also asking that OHRP consider those recommendations that directly pertain to OHRP, taking into consideration the report of the Subpart C subcommittee as well. He also suggested highlighting the recommendation for universal protection of prisoners, perhaps also suggesting that the Secretary consider the possibility of seeking protections of all human research subjects. The Chairman also suggested that OHRP be asked to report back to SACHRP at its November meeting regarding its analysis of the IOM report, distinguishing between long-term and short-term steps.

Mr. Nelson asked Dr. Schwetz to comment on the relative degree of difficulty in executing the Committee's recommendation for a uniform set of regulations that applies to all prisoners to one that covers all human subjects. More generally, he asked for a "reality check" on what aspects of the regulations could be accomplished "in our lifetimes." Dr. Schwetz responded that the recommendations involving prisoners are more complex than those related to children. The recommended database is of a new type for which OHRP cannot yet estimate the degree of difficulty. The switch from a certification to a risk-based strategy is a significant one. OHRP has not yet compared the recommendations of the SACHRP subcommittee that studied Subpart C and those of the IOM Committee in any detail to see where they are complementary and where they may be in conflict. He observed that it was unlikely that OHRP would return in November with a specific answer as to how protections to could be extended to all human subjects.

As a starting point for expanding uniform standards, Dr. Jones suggested a "follow the money" approach in which Federal monies are withheld for prisons unless they ensure the standards are met.

Dr. Prentice clarified that the protections the IOM recommends extending would be those contained in a new Subpart C that has been rewritten with the Committee's guidance in mind. He added that it is not SACHRP's role to determine how this might happen, but simply to make a strong recommendation if that is SACHRP's decision.

ACTION

SACHRP unanimously approved the following motion:

> *SACHRP requests that the Secretary of HHS review the IOM recommendations that pertain to HHS and that the Secretary consider taking steps to extend protections not only to all prisoners who are subjects of research, but also to all human subjects of research.*

SACHRP recognizes that OHRP has been waiting for completion of the IOM report to implement the recommendations of SACHRP's Subpart C committee (as directed by the Secretary of HHS). SACHRP also asks that OHRP study the IOM Report and consider the recommendations that pertain to OHRP in relation to those previously brought forward by the Subpart C subcommittee. SACHRP requests a progress report from OHRP on its conclusions at its next meeting, including both short-term and long-term strategies for addressing recommendations.

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Panel on Research Involving Individuals with Impaired Decision-making Capacity
David Strauss, M.D., Moderator; Charles McKay, Ph.D.; David Shore, M.D.; Myra Christopher; and Laurie Flynn

Dr. Prentice introduced the panel, noting that its charge emerged from the discussion of vulnerable populations that has been occurring in the Subpart A Subcommittee. Panel members were charged with providing a review of prior national efforts to address the rights and welfare of this population as research subjects and with discussing whether guidance or additional regulations are needed for research involving this vulnerable population.

Decisional Impairment and Vulnerability
Remarks by David Strauss, M.D.

Dr. Strauss began by stressing that each presenter is expressing his or her own views; there has been no prior attempt to achieve consensus.

Citing the Belmont Report, Dr. Strauss observed that some persons are unable to function autonomously; they cannot undertake activities freely and with awareness of possible adverse consequences. Such people may sometimes have to be excluded from research participation for this reason. For such individuals, the IRB is more likely to retain a greater share of the necessary risk-benefit analysis. The ethical obligation is to ensure protections that will safeguard persons who are highly vulnerable because of their impaired decision making, but at the same time to recognize the importance of certain essential kinds of research to this population – for example, biomedical and neuroscience research. The regulations are vague on what types of safeguards might be required, stressed only that "additional safeguards" must be included. It is not clear what procedures should be followed, for example, to ensure appropriate informed consent.

In order to consent, subjects must have sufficient *information* to make the choice; *understanding* of that information, meaning both a factual level of understanding and having the rational ability to manipulate that information and use it to make a choice; and a free exercise of *choice*, or "voluntariness."

Decisional impairment may be either *situational* (as when a person has an impairment related to a stroke) or *related to a disorder*. It may also be either *global* (for example, a person who has taken an overdose of sedatives and is stuporous) or *specific* (for example, a person with paranoid psychosis, who may have focused problems with rationally assessing information in certain areas. Decisional impairment may also be classified *static* and permanent (for example, someone with severe mental retardation), *progressive* (for example, a person with Alzheimer's disease), or *episodic* (in which a person loses decision making for a period of time and then returns to normal decision-making

capacity (for example, a person with bipolar disorder who is experiencing a manic episode). Finally, the impairment may be either *persistent* (for example, a person with autism) or *acute* and reversible.

Dr. Strauss also stressed that the capacity to consent in task specific. For example, a person may have enough capacity to designate a person who is trusted to make a certain decision for him or her. Some people may be able to consent to low complexity and low risk research, but lack the ability to sufficiently understand and choose regarding higher risk research. This should be envisioned in terms of a continuum. Individuals who do have impaired or diminished decision-making abilities may still not be impaired to extent they must be excluded. The challenge before SACHRP is to recognize the ethical obligations that arise; acknowledge the complexity of the concept of decisional impairment, as well as the complexity of the populations and settings in which it is common; and create an appropriate regulatory framework through which ideals can be translated into meaningful practice.

Overview of the History of Proposed Regulations for the Institutionalized Mentally Disabled. Remarks by Charles R. MacKay, Ph.D.

Dr. MacKay reminded SACHRP of how far the notion of the protection of human subjects has come since the 1960s, when several seminal papers were written on policy. He noted that even when Subpart A was published in 1981; a long preamble was attached that carefully defends the requirement that subjects give informed consent. He suggested that the regulations forced discourse on the issue.

Issues related to mental health and the institutionalized community in the 1970s influenced the debates of the National Commission, since there were a number of emerging forms of treatment that were viewed fearfully, such as psychotropic drugs and psychosurgery. Issues involving the mental health community were energetically debated.

Dr. MacKay recalled that in late 1978 FDA published a proposed regulation that would have extended its authority over research involving institutionalized populations without any definitions to distinguish different categories of individuals, such as persons with mental disabilities. This forced a debate, and a decision was made at the highest levels that FDA and the agency now called HHS would develop th uniform set of recommendations that is now Subpart A.

At that time, there was a good deal of confusion. Courts and State laws aimed at defending the rights of institutionalized populations came into play. There were uncertainties around how minimal risk should be understood in the context of institutionalization and illness. The report of the Commission was problematic in many respects:

- What "gatekeeper" is authorized to give access to patients receiving clinical services?
- IRBs were authorized to use a consent auditor to review the consent process, but they lacked the resources, authority, and power they needed to exercise this option.
- A role was envisioned for an advocate, a supportive person who would help the mentally or cognitively impaired person reach a decision. However, it was not clear how to ensure this person really had the subject's best interest at heart.
- There was a potential for confusion between the recommendations of the commission and the existing laws regarding the roles of the "legally authorized representative" and the "guardian." These two very different roles were conflated in the report.
- The concept of a "court of competent jurisdiction" was not workable.

"Getting to yes" for the final version of Subpart A was not easy, and the process was affected by many stakeholders. One of the bargaining chips in achieving an approvable regulation was the understanding that the Department would be less aggressive in finalizing protections for persons with mental disabilities. The language included in Subpart A regarding vulnerable subjects seemed to offer a level of protection, but at the same time open a way to do research that involved subjects with mental disabilities, whether or not they were in institutions.

Impaired Decision-Making Capacity and Recent Ethics Panel Recommendations: Additional Safeguards and Restrictions on Translational Research
Remarks by David Shore, M.D.

Dr. Shore stressed the problem of balancing the need to provide safeguards for a vulnerable population while avoiding steps that might seriously impede research on the causes of severe cognitive impairments.

Recent Efforts to Address Research involving Individuals with Impaired Decision-making Capacity

- National Bioethics Advisory Commission (1998): *Research Involving Persons with Mental Disorders that may Affect Decision-Making Capacity*
- National Institutes of Health (1999): "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider"
- US Department of Health and Human Services (HHS) Working Group: "Analysis and Proposed Actions Regarding the NBAC Report"
- National Human Research Protections Advisory Committee (2002): "Report from NHRPAC on Informed Consent and the Decisionally Impaired"

He highlighted a number of key reports (see text box) that have sought to address related issues in the last ten years. In 1997, NIH and OHRP (then known as the Office for Protection from Research Risks) brought experts together to consider what additional safeguards could be implemented without a change in the current regulations for people with questionable capacity to consent. A 1998 report by the National Bioethics Advisory Commission (NBAC) addressed research abuses and specifically the use of surrogates to allow the participation of people who did not have capacity into research. However, there were concerns that some of the report's 21 recommendations could be very problematic for research. An HHS committee completed a thoughtful and detailed analysis of these recommendations that informed a report by the National Human Research Protections Advisory Committee (NHRPAC).

Objections to the NBAC's recommendations included the apparent creation of a new layer of bureaucracy in this national ethics review process (called a Special Standing Panel) and the focus on people with mental illness as a group (most people with mental illness do not have any impaired capacity to provide informed consent to research). Recommendation 2, which addresses the possibility of prospective authorization to participate in research, suggests NBAC concerns about research involving people with mental disorders. While prospective authorization would theoretically make it possible for a person who knows that Alzheimer's disease runs in his family to consent, while still healthy, to participate in a research study when he or she is affected by the disease, the consent must be based on the explanation of a particular study. Dr. Shore noted that it is not possible to know what types of research might be occurring in the future, and commented that if he were consenting to such research he would

prefer to be in the newest, most innovative research available at the time – not a study that could be explained 15 years earlier.

> **NBAC Recommendation 2:** Relevant protocols not otherwise approvable by IRBs (greater than minimal risk, no direct medical benefit) are to be forwarded to a SSP convened by the HHS Secretary. The SSP can approve a protocol if it offers the possibility of substantial benefit to the population under study, risks are reasonable in relation to possible benefit, and the study could not be conducted without the proposed population. The SSP could also issue guidelines covering a particular class or category of research. SSP members would represent diverse interests, and approvals and guidelines made public.
>
> **NBAC Recommendation 12:** An IRB may approve relevant research protocols involving greater than minimal risk and without the prospect of direct medical benefit if there is:
> - Informed consent by the subject, *or*
> - Prospective authorization and or
> - The permission of both the LAR and the Special Standing Panel (SSP).

Under Recommendation 12, studies that involve more than minimal risk without direct benefit for people who lack consent capacity would have to go to an SSP. Dr. Shore reported that during the 1990s when this approach was being used, it often took over 3 years to get an opinion from these panels; people knew that by the time the study was likely to be approved, it might no longer be relevant.

The 1999 study by NIH recommended a number of specific precautions, such as the use of independent monitors, use of surrogate decision making involving substituted judgment, assent of subjects whenever possible, and the use of advanced directives. Rather than categorizing research by risk levels, it proposed that a "sliding scale of risks, benefits, and capacity to consent" guide IRB's decisions.

The NHRPAC report produced a few succinct proposals that closely mirror the Subpart D recommendations for research involving children. One proposal of concern to Dr. Shore states that, "if there is no direct benefit, then research with more than a minor increase over minimal risk *cannot* be approved by the IRB." Dr. Shore said that the NHRPAC approach would make it relatively easy to approve direct benefit research involving a "me too" drug that produces relatively minimal actual effect but has some problematic side effects, but it would prohibit studies that are likely to uncover the underlying causes of these disorders. Dr. Shore observed that in reference to progressive, degenerative, or neurodevelopmental disorders, the likelihood of finding a treatment that will reverse 15 years of deterioration in brain functioning is fairly remote; it is much more likely that researchers will discover the underlying pathophysiology of these disorders, and based on that be able to design attempts to prevent the development of the illness. His concern is that policies that make it more difficult to discover the underlying causes of these disorders may unintentionally impede the search for this type of preventive intervention.

The speaker emphasized that people with schizophrenia and related disorders decide to participate in research for much the same reasons that everyone else does. Mental disorders do not mean that a person loses all sense of altruism. A person with schizophrenia has the same interest in helping other members of his and her family as others. He expressed the hope that the presence of a cognitive impairment will not block the research that could help prevent that cognitive impairment, and that as additional safeguards are considered, that there will be flexibility and a consideration of the possible consequences of restrictions of research.

A Family Perspective
Remarks by Laurie Flynn

Laurie Flynn is currently the Director of the Carmel Hill Center at Columbia University, where she works to improve services for youth with serious mental disorders. She developed the National Alliance for the Mentally Ill (NAMI), one of the largest grassroots advocacy organizations for individuals with mental illness. To place her remarks in context, she highlighted her family history of depression and suicide and her daughter's struggle with schizo-affective disorder. Her daughter has benefited from research, but still has a serious and persistent mental illness (SPMI).

Ms. Flynn characterized SPMIs as devastating illnesses that afflict 5 to 7 million people and frequently last a lifetime. They are misunderstood and stigmatized illnesses. People with SPMIs have a higher risk of suicide and are more likely to have other health problems. On average they die 10 to 15 years sooner than age and sex- matched cohorts, not from their mental illness, but from other deteriorations in their physical health.

Today, as a result of deinstitutionalization, the vast majority of people with such illnesses are not in hospitals. It is estimated that fewer than 65,000 patients are in state hospitals today. The emphasis is on community care and a focus on giving people back the skills and supports, the education, and the opportunity they need to go forward. The focus is on recovery, meaning a recovery of function and a return to as much of a normal and fulfilling life as one can achieve.

Research discoveries have helped people recovery. It is now clear that SPMIs have biological and genetic underpinnings. Research is learning about the biochemical and biological processes inside the brain. More research is needed to understand the underlying core dysfunctions involved, and most families and patients are strongly supportive of that research. Further, most of these patients are cared for in the public sector, making their treatment a costly challenge.

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Ms. Flynn emphasized that severe symptoms are not necessarily constant. or permanent. Decisional capacity varies with individuals, with treatment, and with time. Any regulation that would seem to imply that a mental illness diagnosis equals impaired capacity would be incorrect, inaccurate, and stigmatizing, not to mention discouraging to people who are recovering. She stressed that policies that curtail research with decisionally impaired individuals will ultimately harm them.

The speaker commented specifically on the needs of IRBs to enable them to make good decisions involving people with impaired decision making capacity. She pointed on the need for more family members of people with serious and persistent mental illnesses, patients, and community clinicians serving on IRBs. She stressed the need for such voices everywhere that decisions about research involving these individuals are considered. Also, IRBs need specific training to enable them to address this topic, and some specialized IRBs may be needed that have the expertise necessary to understand and address important subtleties. She also felt that researchers needed more guidance on a variety of subjects, including the informed consent process. She stressed the importance of a continuing dialogue with vulnerable individuals, especially those whose capacity could fluctuate.

Ms. Flynn favored an approach in which protections for impaired patients are added as the risks rise, particularly if the research does not provide direct benefit. She saw a need for guidance and concrete help to IRBs and to investigators, as well as to vulnerable populations, individual patients, and families who may be involved in research.

Protecting Research Subjects with Diminished Capacity
Remarks by Myra Christopher

Ms. Myer, who is the President and CEO of the Center for Practical Bioethics, focused her remarks on recommendations concerning the protection of human subjects with diminished capacity that resulted from a national round table that was convened by the Center earlier this year. Participants were a diverse group that included philosophers and physicians, scientists, historians, attorneys, state legislators, consumers, and a family member of a person with a serious mental illness. The roundtable is one in a series that seeks to provide information for policy makers and citizens that will result in improved public health policy.

There was a quite strong consensus among participants that a Subpart E should be added to 45 CFR 46. Participants proposed that it be called, "Additional Protections for Research Subjects with Diminished Cognitive Capacity." They recommended that Subpart E be modeled after and consistent with Subpart D. To the extent possible, they felt it should incorporate NHRPAC's recommendations, including adopting a three-level classification according to anticipated levels of risk.

The roundtable also had a number of specific recommendations. First, with regard to confirming incapacity, the group advised the inclusion of a definition broad enough to apply to those whose capacity is diminished for different reasons. Examples, case studies, and scenarios are needed to explain the definition. Members wanted to avoid requiring specific procedures for requiring or determining incapacity. However, they wanted to be sure that the procedures that had been used were documented and that justification was given for such a determination. They also wanted to require that capacity be reassessed often. The speaker stressed that in this population, the capacity to consent may fluctuate.

Because levels of risk are difficult to define, the panel urged the use of definitions, examples, and case studies to help people make appropriate determinations. They also urged public input on the definition of these terms.

With regard to permitting and obtaining surrogate or proxy decision making, the panel proposed that a prioritized list of individuals who may serve as legally authorized representatives be established and that the states be encouraged to adopt such a list. The speaker observed that many states have adopted so-called “next of kin statutes” with regard to decision making for this population. The panel also wanted to require an advocate for each participant who would stay engaged with the individual throughout the process (not just for consent). With regard to confirming the subject's assent or dissent, in keeping with Subpart D, panelists proposed that subjects with diminished capacity either assent or at least not dissent from participation, regardless whether a surrogate or proxy has given permission to do so on their behalf. Lastly, any prior evidence of the subject's willingness to participate, including advanced directives regarding research, should be acceptable. Since these are expected to be rare, conversations with family members should also be respected.

Adults with serious mental illnesses who have the capacity to do so should be allowed to participate in the approval and review of research protocols. In the case of protocols with greater than minimal risk that are unlikely to offer a direct benefit, special review by HHS at the Secretary's level should be required. Studies that pose greater than minimal risk should have data safety monitoring boards and other mechanisms in place to halt studies if adverse events dictate.

Lastly, the panel recommends that institutions that conduct Federally funded research of this kind participate in the human research participation protection program through their Federal-Wide Assurances.

Closing Reflections
Remarks by David Strauss, M.D.

Dr. Strauss called attention to the considerable degree of consensus among speakers and summarized their remarks. In addition, he noted that there is a population of patients without capacity to consent that includes people who unconscious or otherwise completely unable to provide consent because of acute insults. There is currently very little regulatory guidance related to these individuals as research subjects. Neurologists who work with patients who have experienced acute strokes, for example, are frustrated by how difficult it is to even create models for research interventions in this area. He closed with the observation that regulations must keep pace with advances in neuroscience and clinical neuroscience.

DISCUSSION WITH PANELISTS

Advocate vs. Consent Auditor. Dr. Tilden asked for clarification on the role of the advocate and the consent auditor as envisioned by the Commission and the degree of independence from the research project needed to play the role of advocate. Dr. MacKay said that at the time the Commission prepared its report, it envisioned that a member of the institution supporting the board or a member of the IRB itself might play the role of consent auditor. However, some objected that an individual funded by the institution would have an inherent conflict of interest. The consent auditor would be involved where there were questions about the ability of the individual to continue to consent and understand the research could be stopped. The advocate was intended to observe and report, consider procedures and their implications, and have the right to withdraw the individual from the study if need be.

Ms. Christopher commented that the panel convened by her organization thought these roles could be played by only one person. Families or the person named as having durable power of attorney should be trusted to make such decisions. Ms. Flynn agreed, stressing the need for involvement of friends and family members. She was concerned about the notion of having an individual guardian *ad litem;* she saw this as patronizing.

Dr. Shore, however, thought there would be two different roles in some cases. The legally authorized representative could address questions about consent capacity, but a consent monitor would play the distinctive role of representing the IRB and making sure the person really understands the implications of the protocol. Dr. Strauss also found the "one size fits all" approach problematic.

Dr. Shore added that the process of getting legal guardianship can be much more traumatic for the individual and family than the proposed research. Ms. Christopher strongly agreed.

Assessment of Capacity. Dr. Botkin asked who should make the assessment of capacity. Dr. Strauss felt a clinical assessment would be required. Dr. Shore said many types of evaluation tools exist, and different study designs may require different approaches to determine whether a given person understands the key elements. Ms. Christopher said there is no litmus test. Dr. MacKay stressed the difference between assessing capacity and assessing comprehension. He felt that assessing capacity

should not be left in the investigator's hands, since the researcher might have mixed motives. He also said there were many tools to assess capacity.

Ms. Flynn said that focus groups of family members on this issue sponsored by NAMI found that the greatest concerns were making sure that family members and participants understood that the research was not necessarily treatment, and that individuals realized they had to stop participation.

Next Steps. Dr. Jones asked about the timing for addressing the issue and the next steps needed. Dr. Strauss observed that existing protections are vague and open ended; also, decisionally paired individuals are "lumped in" with other vulnerable populations. People with impaired decision making ability are not the same as either prisoners or children. He suggested that there is a lack of guidance on the type of critical issues just discussed.

Dr. MacKay pointed to the many legal obstacles that must be taken into consideration in moving forward, given the many differences in state law and pertinent legal requirements.

Dr. Powe observed that researchers who are not specifically studying this population seem to exclude them. He saw this as a problem that should be considered as further regulations are contemplated. Ms. Christopher argued that the "murkiness around the issue" is what makes researchers uncomfortable, and if the boundaries were made more precise, they would be less worried about involving this population as subjects.

Dr. Prentice asked whether panel members thought SACHRP's next step should be to do nothing, have one or more additional panels, or convene a subcommittee to explore the issues. Panelists responded:

- Dr. MacKay saw a need to collect information on the current status, including what Federally funded research exists involving this population and what difficulties are encountered. Surveys of the IRBs involved in funded research might also be useful.

- Dr. Strauss observed that currently the field is diverse in its approach to these issues, and absent OHRP guidance and recommendations there will be little improvement.

- Ms. Flynn said doing nothing would be unacceptable; the field is waiting. She suggested that any subcommittee have very specific goals that will make a difference. She saw a critical need for models and guidance, but not necessarily regulation. Dr. Shore agreed with Ms. Flynn.

- Ms. Christopher stressed the need for guidance in whatever form.

DISCUSSION

Dr. Jones moved to convene a subcommittee charged to consider short-term guidance to enable research in this area. The motion was seconded. In the ensuing discussion, the Chairman suggested a charge be developed based on consultation with experts rather than limiting the subcommittee's efforts at this time. The motion was amended. Members also agreed that it should be given an open hand rather than asked to draft a Subpart E.

Dr. Weiner commented that it would be vital to make sure that in particular discussions there be adequate representation for whatever category of impairment is being discussed.

Dr. Botkin stressed the importance of collecting data to better understand the nature of the problem. Members recognized this would be difficult, but suggested that subcommittee members might reach out to NIH to request available data.

ACTION

SACHRP members approved the following motion with one abstention:

SACHRP recommends that OHRP form a subcommittee to consider what is needed to enable research involving individuals with impaired decision-making capacity and that it develop an appropriate charge to guide their work.

PUBLIC COMMENT

Ms. Putney was pleased that the subcommittee was formed, noting that this is a chaotic sphere in which some IRBs seem happy to exploit silence of state law.

In regard to prisoners as subjects, she pointed to the problem of gangs and the larger issues of power relationships in prison. She wondered if prison gang leaders might represent a problem in terms of coercion and undue influence.

Dr. Prentice said he had not yet read the IOM report thoroughly, but he noted that representatives had the expertise to consider such issues as the current gang climate.

Secretary's Advisory Committee on Human Research Protections
Meeting July 31-August 1, 2006
North Bethesda, MD

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: APPROVED: NOVEMBER 2, 2006

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