Secretary's Advisory Committee on Human Research Protections
November 2 and 3, 2006 – Arlington, Virginia

Minutes

THURSDAY, NOVEMBER 2

Welcome
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. 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.

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

Calling it a "sad day" for SACHRP, Dr. Agwunobi observed that Dr. Prentice is ending his term as SACHRP Chair. He said Dr. Prentice's leadership and his skill in nurturing trusting relationships has enabled SACHRP to take on issues that eluded its predecessor committee. While Dr. Schwetz has asked that the Chair be allowed to continue in this position, the administration has a philosophy that chairmanships should be rotated. Dr. Agwunobi expressed the hope that Dr. Prentice would be willing to serve on a subcommittee.

SACHRP has taken on key issues in recent meetings, including considering human research protection needed for those who are incarcerated or decisionally impaired. He stressed the importance of expert advice on how to understand the unique needs of special populations. He applauded the committee's work and informed members that Dr. Schwetz will soon brief him on the work of the Institute of Medicine (IOM) committee on protection for prisoners, as well as SACHRP's previous work in this area. He assured members that he intends to remain actively and personally involved in the committee's work and to translate that work into Department-level policy.

The Assistant Secretary then acknowledged the contributions of Dr. Nancy Jones and Dr. Celia Fisher, both of whom are also leaving SACHRP. He read parts of letters from the Secretary of HHS, Michael O. Leavitt, to Dr. Jones and Dr. Fisher expressing appreciation for their contributions. He presented a certificate of appreciation to each member.

Dr. Agwunobi then read portions of his own letter of appreciation and gratitude to Dr. Prentice. He especially noted Dr. Prentice's diplomacy, patience, quiet humor, support, and good will. He complimented the Chair on his ability to "distill complex issues and diverse opinions into coherent assessments," a skill that has enabled SACHRP to "carry out its mission with great public success." A second letter from the HHS Secretary was presented to Dr. Prentice but not read.

Opening Remarks
Ernest Prentice, Ph.D.

The Chairman said it had been a privilege to serve as Chair and that the work, as well as the human interactions associated with it, had been rewarding. He thanked SACHRP members and government members for their contributions.

Dr. Prentice reminded attendees of SACHRP's Charter, which comprises protection of human research populations, especially vulnerable populations such as children and prisoners. 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 represent various Federal agencies and 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, especially Executive Secretary Cathy Slatinshek and Kelley Booher.

The Chairman then reviewed the agenda for the day.

The Chairman reviewed accomplishments of SACHRP during his tenure. These include:

- Developing recommendations on the interpretation and application of Subpart D.
- Developing recommendations on the interpretation and application of Subpart C. To provide a foundation for long-term remedies for Subpart C, OHRP contracted with IOM to complete a study on the ethics of research involving prisoners.
- Developing recommendations on interpretation and application of Subpart A (still in progress).
- Developing recommendations on the harmonization of HIPAA and the Common Rule, currently under review.
- Recommending a workshop on alternative models of IRB review, which was held last year. Following the workshop, SACHRP encouraged a follow-up conference on the same subject with wider attendance, to be held shortly. Both received interagency sponsorship.
- Recommending the development of coordinated guidance on reporting of Adverse Events (AEs). OHRP has now produced Draft Guidance on Adverse Event Reporting, and the final version is expected shortly.
- Encouraging OHRP to develop guidance on the definition of research, which is now in draft form.
- Recommending the appointment of a Subcommittee on Research with the Decisionally Impaired, now being formed.
- Holding a panel to address the role of Institutional Officials in human subject protection, which fostered an ongoing initiative by Dr. Schwetz to promote their involvement.
- Endorsing the concept of accreditation.

The Chair stressed that the credit for these achievements belongs to members of SACHRP and its subcommittees.

Minutes for the previous meeting (July 31-August 1, 2006) were approved unanimously. Dr. Prentice then reviewed the agenda for the day.

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

Dr. Schwetz provided updates on activities of concern to SACHRP.

OHRP Activities. In regard to the national conference on alternative IRB models to be held November 20-21, Dr. Schwetz informed SACHRP that over 300 people have already registered and the conference is 2 weeks away. It is likely that over 400 people will attend. Sponsors hope that attendees will include persons who are influential in determining what forms of IRB review are used in their institutions, such as IOs, attorneys, and Deans of Research. Dr. Schwetz asked those present to encourage such decision makers to attend. The hope is that as a result of this conference, they will be better informed and more innovative as they consider IRB models.

OHRP staff have been evaluating recommendations from the IOM report, *Ethical Considerations for Research Involving Prisoners*, released on July 12, 2006 (www.iom.edu/prisonerresearchethics). Some of these recommendations apply to OHRP, while others are directed to HHS as a whole or to the U.S. Congress. OHRP is considering which recommendations would require rulemaking and which may be accomplished through guidance. The Director and staff will brief Dr. Agwunobi on these recommendations and on OHRP's suggestions for follow up.

The Subcommittee on Research Involving Children has completed its work, and about 40 recommendations are about to be sent to the Secretary for review. As with recommendations from IOM and those from a previous SACHRP subcommittee on research involving prisoners, some recommendations can be accomplished through guidance and some require other mechanisms of implementation. OHRP expects to develop a package of guidance reflecting these recommendations.

Dr. Schwetz reported that OHRP is now at the final stages in making revisions to its draft guidance on adverse events. He hopes to have final guidance out in 2006.

To inform those engaging in international research that involves human subjects, OHRP has compiled guidance and regulations from 76 different countries and organizations. This information is now available to anyone on the OHRP Web site. Also available on the Web site is a new set of answers to Frequently Asked Questions that addresses investigator responsibilities.

The Director also reported that he has experienced success in his efforts to reach out to institutional officials and signatory officials of the Federal-Wide Assurance. He began by adding meetings with IOs to other OHRP meetings and gatherings and has been rewarded by having institutions and regions invite him to attend meetings with IOs. The IOs are interested in learning how they can do their jobs better, and OHRP is learning how it can be of more help to IOs.

Special Government Employees. Dr. Schwetz said that with the departure of the Chair and two other SACHRP members, he has found a different meaning in the term used to designate advisory committee members: special government employees. He acknowledged Dr. Fisher's major contribution as Co-Chair of the Subcommittee on Research Involving Children, the valuable products that reflect her accomplishments, and her hard work making the subcommittee as productive as possible. He also thanked Dr. Jones for her engagement on all issues, for being a "voice of reason," and for helping to either keep discussions in bounds or expand them when necessary.

The Chair suggested that Dr. Prentice could be viewed as a "Very Special" Government Employee, perhaps analogous to fine cognac. He said that while Dr. Prentice had an agenda of his own that

reflected his 25 years of experience in the IRB community, he worked closely with the Director and others to develop the SACHRP agenda rather than imposing his priorities. He provided excellent advice and strong leadership that helped make subcommittees both productive and relevant. As a result, SACHRP now has a reputation that is instrumental in encouraging people to serve on it. Dr. Prentice has contributed an unusual amount of time and energy to his work as SACHRP Chair. The Director said that SACHRP's work under Dr. Prentice has had a positive impact on the IRB community and on human subject protection. He thanked him for his contribution.

Dr. Schwetz then presented Dr. Prentice an award given by OHRP to acknowledge significant contributions to the protection of human subjects. The award was first given to members of the National Commission when the 25th anniversary of the Belmont Report was celebrated and has not been given since. Dr. Prentice said he was deeply honored by the award and emphasized the critical role played by each SACHRP member, subcommittee members, and OHRP staff in SACHRP's success. He asked OHRP staff to stand and be recognized.

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

Mr. Nelson reviewed the charge to the subcommittee, its goals, and its membership. He stressed that its three goals - to enhance protection of human subjects, to reduce regulatory burdens that do not contribute to the protection of human subjects, and to promote scientifically and ethically valid research - were not necessarily incompatible ones.

Co-chairs said they would present what they hoped would be final recommendations on continuing and expedited review, followed by a proposed analytic framework for determining whether research can be considered "minimal risk." They will then seek SACHRP guidance on future topics.

The Co-Chairs acknowledged the contributions of Lorna Rhodes, who has resigned from the subcommittee.

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, six 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

Mr. Nelson reviewed Subpart A regulations relevant to continuing review. He noted that only one section addresses the continuing review process with any detail and says, in its entirety: "An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research" (§45 CFR 46.198[e] and §21 CFR 56 109[f]). This brief provision has been applied in variable ways across the country and across the world, and updated guidance would be helpful in the view of the subcommittee. The working assumptions of subcommittee members are that continuing review plays a central, often undervalued role in the IRB process and that practices that do not demonstrably enhance the safe and ethical conduct of research diminish overall human subject protections.

Remaining issues of concern to SACHRP include the question, "how should temporary lapses in approval be handled?" The following recommendation was approved "in principle" by SACHRP on July 31, 2006, but changes have been made to address specific concerns.

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 the IRB finds that there are no substantive concerns that impact human subject protections, suspension of all research activity is not required when the expiration date passes, provided that IRB review is completed within 30 days past the expiration date.*

Underlined passages respond to SACHRP input.

DISCUSSION

What are substantive concerns? The Chair asked for a definition of "substantive concerns." Mr. Nelson said that such activities would include consent form updates, bookkeeping requirements, or clarifications that do not have meaningful impact on human subject safety and that the IRB believes can be readily addressed. For example, a co-investigator has left and references to the individual need to be removed from the application and the consent form. Mr. Nelson added that "substantive" is clearly a subjective term. Members had several suggestions for operationalizating this term:

- Dr. Fisher suggested specifying that there has been no substantial deviation from what the IRB has approved or that the risk/benefit balance has not changed. Mr. Nelson responded, however, that another type of concern such as an adverse event would not be captured in the narrower language.

- Dr. Prentice suggested the following wording: "…no substantive concerns in terms of the risk/benefit relationship or the informed consent that impact human subject protection." Dr. Jones felt this still might be too narrow and suggested that the term "such as" should be introduced. Dr. Botkin suggested opening it up as follows: "…no substantive concerns in terms of the risk/benefit relationship, informed consent, or other key protections."

- Dr. Tilden wanted to write a more general recommendation that simply advised OHRP to modify its guidance on continuing review to allow IRBs not to suspend all research activities and asked OHPR to consider developing guidance or criteria for when suspensions are appropriate. However, Mr. Nelson felt it would be advisable to "give OHRP as much of a clue as we can" regarding the intended direction.

- Dr. Fisher sought specific criteria defining "substantive concerns" so that it would be clear what threshold would be necessary for a concern to rise to this level. Dr. Prentice did not see a way to further define this threshold without being overly prescriptive. Dr. Gyi added that the recommendation simply addresses the need to avoid lag time in certain instances; it is a relatively minor issue. Mr. Nelson pointed out that no substantive change to the continuing review process is envisioned.

Dr. Genel preferred a more positive phrasing of the recommendation.

The revised recommendation was as follows:

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 the IRB finds that there are no substantive concerns in terms of the risk-benefit relationship, informed consent, or other key protections, suspension of all research activity is not required when the expiration date passes, provided that IRB review is completed within 30 days past the expiration date.*

ACTION

The recommendation was accepted as stated with one abstention and no members opposed.

Expedited Review

Mr. Nelson provided a brief introduction to set the recommendations in context. HHS and FDA regulations provide for an expedited review procedure under which the IRB Chairperson (or one or more experienced IRB members designated by the Chairperson) may approve research in categories appearing on a list published in the Federal Register and found by the reviewer to involve no more than minimal risk. Eligible research also includes minor changes in previously approved research that are needed during the period for which approval is authorized (one year or less).

Co-Chairs stressed that expedited review should not be confused with "review lite"; the rigor is the same as full review. Only the number of reviewers is different. In reviewing the research, the reviewer or reviewers may exercise all of the authorities of the IRB, except that the reviewers may not disapprove the research. Expedited review procedures may be applied only to minimal risk research. As with review by the convened IRB, expedited review must fulfill all the requirements for approval found at §46.111 and Subparts B, C and D, if applicable. The Co-Chairs reviewed these criteria for approvable research and the specific categories of eligible research listed in the recommendations.

Working assumptions for the subcommittee are that expedited review is a valuable mechanism that allows IRBs to triage studies to give them an appropriate level of review. It affords effective oversight of minimal risk research while permitting the majority of IRB members to focus their efforts on protecting subjects' rights and welfare in research with potentially serious risks. To the extent that expedited review can be used for minimal risk research, the time and resources of IRBs can be concentrated on protecting subjects facing the greatest levels of risk.

Categories of Research Eligible for Expedited Review. The remaining recommendation stems from the subcommittee's exploration of the following question: does the 1998 list of "Categories of research that may be reviewed by the IRB through an expedited review procedure" need updating or revision? Co-Chairs reported that social and behavioral science investigators and IRBs have difficulty fitting their research into the current regulatory structure and have indicated a need for greater specificity in identifying research that may be appropriate for expedited review.

The subcommittee considered several options for addressing this need, including reordering the 1998 list, relabeling the 1998 list, and revising the 1998 list to highlight and extend topical areas of social and behavioral research, as well as methodologies commonly used in that research. The subcommittee

chose the final approach. SACHRP had suggested several changes to the proposed recommendation that the subcommittee gave due consideration, bringing forward the following revision:

Recommendation. To revise category (7) research as follows:

> *(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 (including, but not limited to, survey, interview, oral history, participant observation, ethnographic, focus group, program evaluation, human factors evaluation, or quality assurance methods.*

A previous version of this recommendation was tabled by SACHRP on 7/31/06.

DISCUSSION

Dr. Fisher supported the recommendation, but noted that the problem social and behavioral researchers encounter is not so much with the procedures, but with an overestimation of the harm that could be associated with those procedures. The subcommittee that developed recommendations pertinent to Subpart D sought to address this problem by suggesting exemplars of particular risk levels – for example, it is typical for a physician to ask older children about sex and drug use. Dr. Prentice, however, felt this concern more properly belonged to the next topic. Mr. Nelson agreed with Dr. Prentice, but he also agreed with Dr. Fisher that overestimation of the risks associated with social and behavioral research is a concern.

Dr. Botkin wondered whether specific examples should be referenced, but Dr. Gyi was concerned that examples would move too far toward specification of particular concerns. The subcommittee sought to create a list that would be general and appropriately conclusive. He noted that persons involved in putting together the original list have said that they expected it to be reviewed on a yearly basis, with some thoughtful consideration given to what should be removed from the list, remain on the list, or be added.

ACTION

SACHRP approved this recommendation unanimously.

Periodic Review of Categories of Expeditable Research by OHRP. Recognizing that the current list of categories has not been revised since 1998, Dr. Prentice suggested a recommendation that OHRP should review the categories at some stated interval.

DISCUSSION

Dr. Tilden pointed out that FDA has adopted the same list of expeditable research categories and should therefore be referenced in the recommendation.

Dr. Romero suggested that every five years would be an appropriate interval. Dr. Schneider agreed. Dr. Bodkin wanted to be sure that the recommendation does not preclude a more frequent interval as needed, so the words “at least” should be included before “five years.” Dr. Schwetz also liked the suggestion, noting that the review process would involve interagency coordination.

Recommendation: Periodic Review of Expeditable Research Categories.

OHRP will review categories at least every five years, harmonizing the list with FDA guidance.

ACTION

SACHRP approved this recommendation unanimously.

Revising the 1998 List of Expedited Review Categories. IRBs have indicated that time in convened meetings is expended on *pro forma* reviews of research that is clearly minimal risk, but for which there is no specific category in the current expedited review list. The subcommittee considered mechanisms that would permit IRBs to review such research using expedited procedures and save limited meeting time for proposals that present greater risk.

Creation of a new category 10 would have allowed a convened IRB to define additional categories of minimal risk research that are not already included on the list so that they could be reviewed and approved using expedited procedures, based on the particular nature and context of research routinely reviewed by the IRB. This recommendation was tabled by SACHRP on 7/31/06. Neither SACHRP nor the Subcommittee on Subpart A (upon revisiting this subject) could reach consensus on the need for or advisability of this additional category. The recommendation was therefore withdrawn

Applying the Definition of Minimal Risk

Dr. Gyi acknowledged the contributions of Dr. Strauss and other members of the Subcommittee to his presentation. He began by reviewing the "Risk Escalation Principle of Protection," which holds that as the risk of the research rises above the threshold of "minimal risk," restrictions and additional protections are required, particularly for vulnerable subjects.

Existing Definitions of MR. Dr. Gyi reviewed references to minimal risk throughout the regulation and highlighted their implications for IRB review.

> **Definition of Minimal Risk in Subpart A:** *Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

Dr. Gyi noted that interpretation of standards has varied great deal. HHS and FDA have both provided guidance on how to interpret the concept:

> **HHS Clarification on the Definition of Minimal Risk:** "*HHS in the proposed regulations used the terminology 'healthy individuals.' In light of the public comments on this, however, HHS has reworded the final regulation to reflect its intention that the risks of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research" (1981).*
>
> **FDA Clarification on the Definition of Minimal Risk:** "*This definition takes into account the fact that the risks in the daily life of a patient are not the same as those of a healthy individual, and uses the risks in daily life as the standards for minimal risk."*

Dr. Gyi held that while the two agencies were in apparent agreement in the preamble, the two clarifications do appear somewhat inconsistent with each other. He then noted that the explanation of the standard contained in Subpart C focuses on the risks encountered by healthy persons rather than by patients. The National Commission, similarly, used the standard of a healthy child for comparison.

> **Definition of Minimal Risk in Subpart C (Research Involving Prisoners).** "*Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.*
>
> **The National Commission's Definition of Minimal Risk (Research Involving Children).** *Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of healthy children.*

There is no definition of minimal risk in either Subpart B or Subpart D; in the absence of guidance to the contrary, this would mean that the definition used in Subpart A would apply here as well. However, the SACHRP subcommittee on Subpart D followed the National Commission in proposing a standard based on healthy children:

> **SACHRP'S Recommended Interpretation of Minimal Risk for Subpart D**: *The definition of "minimal risk" at 45 CFR 46.102(i) when applied to Subpart D should be interpreted as those risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests.*

The above definition was approved by SACHRP.

OHRP'S Clarification of Minimal Risk: In a communication to the SACHRP Chair, OHRP staff member Dr. Carome states that OHRP has never issued official guidance regarding the definition of minimal risk on its Web site. However, when asked, OHRP recommends the use of the "healthy person" standard when applying the provisions of Subpart A of 45 CFR 46.

Dr. Gyi stressed that the interpretation and application of the concept of minimal risk because an assessment of risk that is incomplete or incorrectly characterized may result in the approval of research or methods of obtaining consent that do not serve the interests of human research protections, data integrity, or application of the results to the target population. Interpretation should not be left to the "gut feeling" of IRBs. To meet this need, the subcommittee is engaged in the development of a structured analytic framework through which IRBs and researchers can conceptualize and apply the definition of minimal risk.

Types of Standards. The discussion around minimal risk generally centers on two types of standards. The first may be called the uniform, absolute, or fixed standard. This threshold provides a fixed threshold or limit against which the risks of the research may be compared. The subcommittee envisions a standard based on the background of risks to which we are all exposed. A threshold based on the risks of "daily life" may be expressed as a mean value in a distribution of risk encountered by "the general population." Dr. Gyi stressed, however, that the minimal risk threshold is a range rather than a precise figure. It is an estimate, not a specific point that can be derived and shown on a graph.

In contrast, a relative standard may base the estimate of risks of daily life on the experience of the research subjects, the subpopulation from which the subjects are recruited, or a specific locale in which the research is conducted. For example, the "routine" medical tests and examinations for a

typical oncology patient entail considerably more harm and discomfort than routine medical tests and examinations a healthy individual experiences. If the threshold is based on the daily life of research subjects, this can inappropriately put subject at greater risk. The risks posed by a particular study may be held to be greater in one setting with one set of subjects that in another. In other words, the estimate of minimal risk can change based on the daily life of the research sample. Because such a "relative standard" would increase the level of risk permitted as "minimal" for already vulnerable subjects, it is widely considered to be unacceptable. By and large, this standard is not used for these reasons.

Clarifications and Caveats. The subcommittee rejects the relative standard, but it also rejects the usual understanding of "uniform standard." Dr. Gyi presented following clarifications and caveats related to the process of assessing minimal risk proposed by the subcommittee.

- The harms and discomforts of the research *in a healthy population* are not relevant (this is not part of the analysis). Rather, reference is to the distribution of risks encountered in the general population.

- The comparison is between probability and magnitude of harm in the research vs. the probability and magnitude of harm in daily life.

- The *type* of harm does not have to be one which is part of daily life.

Dr. Gyi also presented a clarification of what is meant by the "probability and magnitude of harm or discomfort anticipated in the research," which must be compared to the probability and magnitude of harm in daily life to derive the minimal risk estimate. In the view of subcommittee members, the following interpretation holds:

- "In the research" means the harm or discomfort as expected to affect those subjects who will be enrolled in the research.

- "In the research" means *in the approved research* and considers all steps taken which will serve to minimize harms and discomforts.

- It is incomplete or incorrect to speak of research *procedures* as being minimal risk or more than minimal risk.

DISCUSSION

Dr. Gyi clarified that the subcommittee does not envision the "mean" value of the distribution of risks in the population in strictly mathematical or statistical terms. Dr. Fisher suggested that a different word from "mean" is needed in this case, since there is no precise means of calculating the degree of harm or the level of risk in the general population. She also objected to the word "estimate." Instead, she saw minimal risk as a judgment of the distribution of risk that takes into account the variability in the general population. Mr. Nelson agreed.

Dr. Powe agreed that minimal risk is based on judgment, but proposed that this judgment must not ignore available evidence, including quantitative data. Dr. Fisher said, however, that such data were rare and that it would be a mistake to link judgment to data.

Dr. Gyi further explained that the subcommittee does not propose limiting the general population to persons living in healthy, safe environments, but envisions a blanket comparison that applies across the board to the general population as a whole ("everyone in the world").

The reference to "approved research" seemed illogical to Dr. Fisher, since the assessment of the research in relation to minimal risk must be made prior to approval. Better language might be "to be approved." Dr. Gyi agreed.

Dr. Genel asked why a distinction was being made between research procedures and the research itself. Dr. Jones responded that the risk posed by a procedure would have to be evaluated in the context of the specific study and its population; for example, a blood draw from a hemophiliac would be a different risk level from a blood draw from others. Dr. Gyi added a second example: a simple venipuncture might be a very safe activity in the hands of a trained phlebotomist, but a risky one if done by a person without the proper training. The IRB must assess and quantify risks as they affect the subjects who would participate in the study and do so in the context of the entire study design.

Continued Presentation, MR Estimation. Aspects of the study design may increase or lessen the estimate of study risk for the proposed sample. To estimate the probability and magnitude of the anticipated risk of the study, the IRB must:

- Define and evaluate the study's harms, discomforts, burdens;
- Assess and quantify these risks as they affect the sample of subjects to be enrolled in the study; and
- Consider aspects of the study design that will serve to minimize study risk.

Co-Chairs then discussed the process of comparing the estimate to the daily life standard.

- The threshold value for minimal risk research is set or fixed to an estimate of probability and magnitude of harm and discomfort for the general population.
- This estimate of the harm and discomfort ordinarily encountered in daily life does *not* refer to the daily life (or routine medical or psychological examinations) of the research subjects in the study under review.

DISCUSSION

Dr. Fisher asked why the Subpart A subcommittee was not building on deliberations of Subpart D committee and wondered what parts of the Subpart D committee's deliberations would not be appropriate. She also found the criterion or index for minimal risk unclear. Dr. Gyi explained that the subcommittee is proposing a uniform standard; however, the point of comparison is the general population rather than specifically the healthy population. He further noted that individual and group characteristics make some subjects more or less vulnerable to research risk. Also, aspects of the study design may increase or lessen the estimate of study risk for the proposed sample. Examples include provisions for subject recruitment and selection, the expertise of study personnel, criteria for exclusion of subjects or early drop-outs and provisions related to confidentiality. Dr. Prentice suggested that the index will become more apparent in the context of the case studies.

Analytic Framework Proposed by the Subcommittee. The Co-Chair reviewed points to consider in determining whether or not research should be considered minimal risk. These include:

1. Estimate the probability and magnitude of harm or discomfort as they are anticipated to affect the subjects to be enrolled in the proposed research.

2. The estimate of risk will vary based on the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.

3. It is best to conceptualize the estimate of risk as a range, rather than as a precise value. IRB reviewers should consider the inherent uncertainty of this estimate (e.g. the confidence interval of the estimate) and be mindful of the consequences of an incorrect judgment.

4. This estimate will be compared against a threshold value—the "minimal risk" estimate.

5. Minimal risk is the probability and magnitude of harm or discomfort ordinarily encountered in daily life (or during the performance of routine physical or psychological examinations). This notion of minimal risk represents a fixed or standard threshold against which the risk of research is judged. The proposed standard, Dr. Gyi emphasized, is not a relative or shifting one.

6. The probability and magnitude of harm and discomfort in daily life is an abstract idea that is meant to describe a mean of background risks that are part of the routine experience of life for "the average person," a member of the "general population."

7. The threshold is not based on the "daily life" of the research subject or the specific population from which the subject is drawn. However, this does not mean that the subject's daily life is completely irrelevant.

8. For the purposes of this definition, the risks of daily life under special conditions, environments or cultures are never considered in the estimate of the risks of "daily life" when such considerations would serve to raise the minimal risk threshold.

9. The threshold is also not based on the risks of the research as they would impact "the average person," a member of the "general population."

10. The minimal risk threshold, like the estimate of study risk, is best conceptualized as a range.

11. The estimate of the risk of harm to the study population introduced by the research is measured against this minimal risk threshold.

Case Examples to Illustrate the Application of Proposed Analytical Framework. Dr. Gyi showed how these points would influence deliberations in several different cases.

Minimal Risk – Case 1. *Researchers interested in end-of-life decision-making propose to use an hour-long semi-structured interview to gather data from subjects who are recruited in a hospital cancer treatment center. The estimate of harm and discomfort of such a research intervention will depend on many factors, including who the researcher will interview, when during the course of a patient's illness the interview is conducted, the qualifications of the interviewer, and others.*

Dr. Gyi noted that:

- The same semi-structured interview might be judged to cause significantly more distress in newly diagnosed patients with cancer or if administered to acutely bereaved family members than in a sample of patients who are previously diagnosed and are participants in a support group for terminally ill patients.

- The same diagnostic interview in the hands of a clinician experienced in working with the terminally ill can be expected to cause less harm or distress than in the hands of unskilled interviewer; in skilled hands it could, in fact, be therapeutic.

- The same end-of-life decision-making survey would be judged to introduce different risks in the group of (a) acutely bereaved family members, (b) newly diagnosed patients with terminal illness, and (c) patients in a support group for the terminally ill.

To determine the risk level of the proposed study, the estimate of risks introduced by the research interview is compared with the estimate of harms and discomforts of daily life. In this case, the interview in newly diagnosed cancer patients or recently bereaved family members is seen as introducing more harm or discomfort than "the average person" might experience in daily life, or during the performance of routine physical or psychological assessments. Therefore, as proposed and in these populations, this study might be considered greater than minimal risk. However, in the group of patients who have spent considerable time in considering end-of-life concerns in a support group (c), the research is judged to introduce less harm or discomfort, given the subjects' experience. For them, the harm or discomfort might be considered no greater than that of daily life for "the average person." Therefore, it would be concerned no greater than minimal risk.

DISCUSSION OF CASE 1

Dr. Gyi clarified that the threshold for minimal risk is static; instead, it is the changes in the population and procedures that cause the level of risk to decrease or increase. Dr. Tilden suggested, however, that the survey might also be found to be beneficial for groups (a) and (b) under certain circumstances – for example, if a survey were included that allowed them to express their anxieties about cancer. Dr. Fisher thought, however, that the question of benefit confounded the issue and should be left out of the decision making process until the level of risk has been determined independently.

Minimal Risk – Case 2. *A cross-sectional study of memory and attention in cocaine dependent subjects and in healthy subjects with no substance use history involves a 3-hour battery of commonly employed neuropsychological examinations.*

The estimate of study risk for research subjects with no substance use history falls at or below the minimal risk threshold. For cocaine dependent subjects, however, risks related to confidentiality in the study as proposed are judged to introduce significantly higher risks, including stigmatization and legal liability. The fact that risk of legal liability is part of the daily life of substance abusers is relevant in the analysis of minimal risk.

However, if the study proposal were to include special protections regarding confidentiality – for example, obtaining a Federal certificate of confidentiality – and if the researchers proposed to segregate and restrict access to datasets to the research group, also agreeing to pay the subjects by an untraceable

means (if payment is involved), then the study would likely be considered below the minimal risk threshold.

DISCUSSION

Looking at a graph that showed minimal risk as a blurred line, the Chairman questioned whether there was any meaning in the phrase, "at or below" minimal risk. He wondered how any risks could fall below the risk of daily life unless the person were dead. He asked the subcommittee to give further consideration to how to depict the topic graphically.

Dr. Tilden asked whether the subcommittee intended to make a distinction between *minimal risk* and *minimizing risks* – two distinct concepts. He felt that in this case, even though the procedure is not particularly harmful, the risks to the individuals should still be minimized. He thought blurring these issues could lead to confusion. Dr. Fisher agreed.

Dr. Fisher raised the question, "at what point is the minimal risk assessment made?" She asked whether it was held to be made looking at risks without extra protections (such as the procedures described to protect confidentiality) or whether it was held to be made looking at the entire research protocol. She suggested making this distinction clear, adding that the minimal risk decision comes into play after procedures to minimize risk have been considered.

Minimal Risk – Case 3. *A study of immune response to treatment in adults with leukemia involves a series of three bone marrow biopsies over a five-day period. All subjects have had several prior bone marrow biopsies for treatment purposes.*

While patients with leukemia may have experience with the bone marrow biopsy, this experience this is not seen as lowering the main risks associated with the procedure. The risks of the research, for them, are still considered greater than the risk ordinarily encountered in daily life for "average person" in "the general population." The biopsy does not cause less pain for this population or have a lower risk of infection, despite the fact that such biopsies are included in the subjects' daily lives.

Minimal Risk – Case 4. *A study of cardiac physiology involves noninvasive cardiac monitoring during a maximal exercise stress test. The study sample includes "older subjects," age 65-80, all of whom have risk factors for cardiovascular disease, and medically healthy trained athletes, age 18-30. Subjects are screened for eligibility with a standard physical exam and medical history. The research procedures are monitored by a trained research assistant.*

The harms of the exercise stress test must be identified and estimated for the proposed subject samples. In this case, the risks of the study are likely to be significantly different in the two groups. If the study were to involve only younger trained athletes prescreened for cardiac problems, the exercise stress test might be judged to introduce risks that are no greater than the risks of daily life. In the older group, the group that is more likely to have cardiac problems that are not identified by history or routine physical exam, the exercise stress test is judged as introducing risks that the improbability and magnitude is greater than the risks of daily life.

DISCUSSION

Other Risks. Dr. Kirchner suggested that there is a significant risk of false positives that should be taken into account. For example, for a woman in her 40s who is healthy, the test might have a 40

percent false positive rate that would require follow-up. The test is actually more reliable, he said, in the older group.

Mr. Nelson noted that the case study should specify whether or not the procedure is being done as part of a research study for cardiac physiology and whether anyone will do a clinical follow-up based on the results. The IRB would have to consider whether or not there are provisions for follow-up to address any issues that might be revealed by the test.

Relevance of Data. Dr. Botkin pointed out that there are data on the level of risk associated with an older individual undergoing a cardiac stress test. The investigator should be prepared to present these data. He asked whether it would make a difference if, for example, the investigator said he or she had done this study at other sites and the adverse event was 1 in 5000.

Type of Stress Test. Dr. Prentice noted that a maximal stress test cannot be expedited. He suggested that the case would be more realistic and useful if submaximal exercise tests were used. Further, he added that average healthy individuals do not engage in maximal exercise in which they try to bring the heart rate to the highest level possible.

Component Analysis. Dr. Fisher suggested that the discussion of component analysis that took place in developing recommendations for Subpart D would also be useful in the context of the discussion of minimal risk. She added that it is helpful to consider which procedures are intended to confer direct benefit and which are simply part of the research.

Vulnerable Subpopulations. Dr. Powe raised the question of how to handle young subjects who have relevant risk factors and whether their presence would raise the estimated risk. Mr. Nelson suggested that this concern should be addressed in the criteria for inclusion in the study. Mr. Cortesi commented that statistically, a certain percentage of people will meet eligibility requirements for the test, but still have risk factors. Mr. Nelson responded that the blurry line in the graphic presented is an error bar that captures the distribution among study participants. Dr. Tilden felt that a clear presentation of such statistical risks should be part of the consent process.

Dr. Botkin gave the example of a study that involved a single needle stick for children. He questioned whether the presence of a significant number of needle phobic children would mean that the study should be considered more than minimal risk or whether the situation would simply be addressed by "backing off" if a parent objected. Dr. Prentice felt that the magnitude of potential harm would depend on the percentage of participants judged to have needle phobia. Mr. Nelson said the subcommittee felt it should stop short of delineating a specific percentage in such instances; instead, the subcommittee's intent was to present a framework for decision making.

Minimal Risk – Case 5. *A U.S. research team aims to examine barriers to local access to foreign relief assistance needed as a result of community, social, and political crises. The study is to be conducted in several remote villages in a country in South Asia devastated by both the Tsunami of 2005 and persistent violent civil unrest. Focus groups and individual interviews will be used to gather data on individual and family access to relief assistance. Individual interactions with community leaders and relief organizations will be described.*

While focus groups are ordinarily considered minimal risk procedures, knowledge of the local context is critical to the proper assessment of subject risk. For example, group composition (e.g. including both men and woman) may itself cause considerable discomfort or breach local custom. Discussion of attitudes or complaints regarding the local authorities may be experienced as uncomfortable.

Disclosure of this information within the focus group or unintended disclosure outside the group may place individuals at considerable risk for personal harm.

The facts that these communities have been devastated by natural disaster and civil unrest and that their "daily life" confers considerable risk from hunger, illness, and violence do not alter the minimal risk threshold. These circumstances do not represent a reasonable background level of risk on which to base the minimal risk estimate. This study is greater than minimal risk.

DISCUSSION

Dr. Schneider asked who should be held responsible for determining risks within the context of the specific culture. Dr. Gyi held that the IRB should understand the context. However, Dr. Fisher noted that SACHRP members have previously placed the responsibility and burden for presenting such information on the investigator, with the understanding that the IRB may still seek information on cross-cultural differences. Dr. Gyi agreed and suggested that in fact the responsibility should be seen as shared between the investigator and the IRB. Dr. Jones added the caveat that the field is still too immature to assess the risks in specific populations.

Additional Questions for Discussion. Co-Chairs invited comment on the following questions:

- Will guidance like this be helpful?
- Do we need guidance on the concept or definition of risk?
- Can research which is minimal risk nonetheless be so ethically or procedurally complex that expedited review (and other regulatory provisions allowed for MR research) may be inappropriate?

DISCUSSION

Case Mix. Dr. Powe found the cases presented thought provoking, but suggested that it would be more instructive to include more clear-cut cases in which the risk was held to be minimal risk. Dr. Genel agreed. Dr. Gyi suggested giving cases in which the risk initially fell above the threshold but was mitigated through the use of safeguards. Others agreed that that would be useful

Risk. Dr. Prentice encouraged the subcommittee to encompass the concept and definition of risk in its deliberations.

Addressing the Problems. Dr. Botkin asked for clarification of the problem the guidance would be designed to solve: are IRBs overestimating or underestimating risk? Mr. Nelson answered that this is indeed common, and the use of the relative standard sometimes creates a "slippery slope." He noted that studies have been conducted in which different IRBs have given different estimates of risk on the same study.

Dr. Fisher summarized her understanding of the subcommittee's main points as follows:

- The ceiling for minimal risk are those risks in the general population;

- There are some populations for which procedures that are minimal risk for the general population are greater than minimal risk for other populations; because of this, it is necessary to look at the background or contextual nature of the research.

- The determination of minimal risk should come after an evaluation of research protections within the research pattern itself.

These recommendations address key points of confusion in the field: whether to apply uniform or variable standards, whether or not to consider the risks of the specific population in making their determination, and at what point the judgment about minimal risk is made. The subcommittee's statement about international risk is also helpful. Therefore, she encouraged the subcommittee to move forward.

Complex Research. Dr. Gyi posed the question, "can research that is minimal risk be so ethically or procedurally complex that expedited review and other regulatory provisions allowed for minimal risk research may be inappropriate?" Dr. Prentice thought the answer was obvious and unworthy of debate.

Topics for Future Consideration by Subpart A Subcommittee

Mr. Nelson asked for "marching orders" from SACHRP. He reminded them of various topics that had been suggested for consideration at the subcommittee's first meeting and presented to SACHRP previously. The subcommittee considers its deliberations on continuing review and expedited review complete. The consideration of minimal risk is still underway. Assurances and cooperative reviews are not ripe for consideration since OHRP is pursuing other avenues for clarification. OHRP is developing a definition of research to help IRBs determine whether or not an activity is subject to the Common Rule; this would also not be appropriate for consideration by the subcommittee.

One important area that remains to be addressed is informed consent. It is questionable whether lengthy and frequently unread documents actually protect subjects. Dr. Botkin agreed that this is a critical task and suggested it should be made a priority. Dr. Prentice also felt the area was critical, and agreed with Dr. Botkin that it might be worthy of a subcommittee of its own. Dr. Genel concurred.

Dr. Prentice raised the concern of what constitutes an exemption. Technically, this means exemption from the requirements of 45 CFR 46. OHRP has taken the position that investigators should not be able to decide for themselves whether or not their own research should be considered exempt, because it is likely that the majority of research would then be exempt. However, Dr. Prentice suggested that even exempt research should undergo an assessment to ensure that it conforms to appropriate ethical standards. A mechanism to accomplish this is required for accreditation. Mr. Nelson rejoined that in many cases by the time an IRB reviews a study to determine its status, it has in effect conducted an expedited review.

Mr. Nelson suggested that membership criteria might need to be revisited, since those in the regulations are now 30 years old and there have been changes. For example, review boards are larger now, so the number of persons needed to represent a group might need to be increased. There are also specific issues, such as who qualifies as a scientist or nonscientist. Dr. Genel agreed that this would be a useful area.

Dr. Prentice also suggested examining how the performance and effectiveness of IRB members should be evaluated. He noted that this is a problematic topic in that IRB members are volunteers. Dr. Gyi asked for more specific guidance on what should be addressed in the area, since the topic is so broad; however, Dr. Prentice preferred an open exploration of associated issues. Dr. Genel proposed that the subcommittee also look at training issues.

Dr. Powe suggested that the discussion of membership would inevitably lead to discussions of the volume of applications, resources spent by committee members, and compensation. Mr. Nelson agreed that these areas should be addressed.

Dr. Lux asked the subcommittee also consider examining the role of Data Safety and Monitoring Boards (DSMB), their composition, and their relationship to IRBs. However, Mr. Nelson saw this question as tied to issues being addressed by the Federal Adverse Events Task Force.

For the present, the subcommittee will proceed to address the issues of minimal risk and IRB membership. The idea of whether SACHRP should recommend a subcommittee to address informed consent may be addressed at a future meeting.

PUBLIC COMMENT

The Chairman invited public comment.

Dr. Gary Chadwick asked SACHRP to recommend that the Secretary of HHS begin the regulatory process to add investigator responsibilities to regulations on the protection of human subjects. He saw this as a common sense action needed to address a gap in current regulatory protections. This would be done by adding a new subpart under 45 CFR. He compared the current situation to a hypothetical one in which the Federal Aviation Administration (FAA) regulated only airport towers and companies, with no training requirements or regulations related to pilots. He characterized formal training for investigators in research ethics, responsible conduct, and basic research techniques as "spotty at best." Too many, he said, see regulations intended to protect human subjects as "IRB regulations" and do not universally take responsibility for protecting human subjects in their research. Yet, only investigators can truly accomplish this. They should be given an unambiguous message that, "if you are going to do research, do it right or don't do it at all." Such a message will become increasingly important as central IRBs play a greater role in oversight.

Dr. Chadwich proposed amending the regulations to add three new sections that specifically address investigator responsibilities. The sections would address:

- *Responsibilities of investigators when experimenting with human subjects.* This section would include commitments such as conducting research according to sound research design and applicable laws and regulations, as well as general responsibilities such as conforming to generally accepted scientific principles, providing the IRB with sufficient information to make the determinations required in §46.111, complying with approved study plan, and monitoring the study and each subject for safety.

- *Qualification standards for investigators.* Investigators should be trained in research techniques and in ethical principles, including the responsible conduct of research and how to identify and manage conflicts of interest. Dr. Chadwick felt that investigators should be required to provide evidence of their qualifications through up-to-date CVs and other relevant information.

- *Investigator records, reports, and documentation.* This section should make it clear that the investigator is responsible for the completeness, legibility, and timeliness of all data recorded and reported in research. Investigators should also be required to maintain documents that permit the evaluation o f the research and the quality of data produced.

As a model, he pointed to the International Conference on Harmonization of Pharmaceutical Products, a multi-national guideline that standardizes research requirements and has gained international acceptance as the right thing for investigators to do. Dr. Chadwick also drafted sample wording in a document passed out for review at the meeting.

Dr. John Mather, Vice President for Research at Chesapeake Research Review and a counselor and site visitor for the Association for the Accreditation of Human Research Protection Programs (AAHRPP), next addressed SACHRP. He said it was encouraging to hear of Dr. Schwetz's emphasis on the role of the IO. He said it was important to address the question, "what does it really mean in a corporate sense to be engaged in research?" He observed that IOs in many institutions do not understand their oversight responsibilities. He also highlighted a common misunderstanding that once research is exempted from IRB review, the institution is absolved of responsibility. It is also critical to address the meaning of responsible conduct of research in the context of the institution. Simplification and harmonization are both important as these areas are addressed.

Discussion of Investigator Responsibilities. Dr. Prentice focused SACHRP's attention on Dr. Chadwick's recommendation that regulations be added to address investigator responsibilities to protect human subjects. In response to a question from a SACHRP member, he clarified that regulations do not specify any responsibilities, apart from a brief mention of requirements related to informed consent. Some recent guidance from OHRP does address investigator responsibilities, but it is Dr. Chadwick's belief that responsibilities should be defined in the regulations. FDA regulations do define them more specifically.

Noting that this proposal was previously discussed by the Subpart A subcommittee, Dr. Jones cautioned that careful attention should be given to the cultural demands placed on researchers. She said that codifying the responsibilities of investigators would require a paradigm shift from the assumption that researchers are professionals who are worthy of trust. Further, she questioned how these new regulations could be enforced through the mechanism of the FWA. She therefore proposed that SACHRP consider the topic within a larger framework. Specifically, she suggested that SACHRP explore the questions of how best to enable investigators to assume the responsibility that is implicit in the social contract they have made to do research. She felt that codifying these responsibilities should be the "last option" considered.

The Chair asked Dr. Jones to clarify the problem in making implicit responsibilities explicit. He also wondered why regulations are needed if everyone is already doing the right thing. He also did not understand why there might be negative ramifications if these expectations were codified. Dr. Jones explained that she thought next steps should be carefully considered; she suggested a panel of investigators who would address SACHRP on regulatory issues. She was concerned that given the culture of science, regulations would reinforce an adversarial relationship between the IRB and investigators. Instead, she wanted to examine the institutional, educational, and professional resources available to help investigators make a paradigm shift to see themselves as the first line of defense for human subjects.

Future Panel on Investigator Responsibilities. Dr. Genel supported the idea of a panel at a future SACHRP meeting as a next step and suggested the Association of Patient Oriented Research as one source of potential panelists. Dr. Genel also observed that the Council on Ethical and Judicial Affairs of the American Medical Association has produced some pertinent materials on investigators responsibilities.

Dr. Powe agreed with Dr. Jones about the potential negative ramifications of rulemaking on the subject. He added that standards are needed for all scientific research, not just human subjects research. Dr. Powe also felt that further discussion in SACHRP would be helpful, though it might not result in formal recommendations.

Dr. Tilden observed that FDA has codified investigator and sponsor responsibilities in 21 CFR 312; ironically, he said, investigator responsibilities in privately funded research are more clearly articulated than those in Federally funded research. Institutions are required to have policies regarding investigator responsibilities to achieve accreditation, and it might be possible to include similar requirements for institutions seeking FWAs rather than follow the regulatory route.

Dr. Powell supported the idea of further discussion with investigators, including a discussion of how physicians who do studies for industry are certified to perform this work. He added that the American Academy of Pharmaceutical Physicians and Investigators trains physicians to do research.

Dr. Prentice was not opposed to having panels and gathering more information on the topic, though he did not believe that rulemaking would fix whatever problems may exist. He stressed the obligation of institutions to ensure adequate human subject protection through education and through the development of a culture that fosters human subject protection and, at the same time, facilitates good science. However, he did not understand why investigators would object to having their responsibilities specified in regulations. This would not result in new responsibilities, since ethical investigators would already be in compliance. Noting the diversity of viewpoints within SACHRP, however, he suggested a panel as the next step.

Importance of the Problem. Dr. Botkin observed that regulatory oversight to date has placed insufficient emphasis on investigator responsibilities. However, he sought more clarity on whether a practical problem exists that needs to be solved through these guidelines. He wondered if investigators are engaging in risky or inappropriate activities and, if so, to what extent the IRB system has been ineffective in addressing the problem.

Dr. Romero agreed with Dr. Prentice on the importance of keeping the issue open. As a member of a population that has suffered as a result of poorly trained investigators and institutions that failed to uphold their responsibilities (American Indians and Alaska Natives), Dr. Romero saw regulations as a timely approach to holding investigators to standards. As IRB Chair, each year she encounters five to seven cases in which investigators have offended communities through inappropriate procedures that caused real damage. Investigators, she stressed, must be held responsible.

FRIDAY, NOVEMBER 2

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

The Chairman provided an overview of events for the day. He then introduced a presentation regarding progress toward establishing a SACHRP subcommittee on protection for persons with some form of cognitive impairment. Dr. Strauss, who will Co-Chair the subcommittee, provided this update.

Report of Subcommittee on Research Involving Individuals with Impaired Decision-making Capacity
David Strauss, M.D., Co-Chair

Dr. Strauss began by recalling his introduction to the complexity of the issues surrounding research with persons who have impaired decision-making capacity. He was an attending psychiatrist on a schizophrenia research unit. He proudly told a visiting State legislator that subjects with impaired decision-making were never included in any of their research studies. The legislator responded with the question, "But isn't that exactly why we funded this operation, for you to help those most in need of help?" Dr. Strauss pointed to the ongoing need to strike a balance between protecting the rights and welfare of this population and the need to address its critical clinical and research needs.

Dr. Strauss presented the charge of the new SACHRP Subcommittee on Research Involving Individuals with Impaired Decision-making Capacity:

> *The Subcommittee will develop recommendations for consideration by SACHRP about whether guidance and/or additional regulations are needed for research involving individuals with impaired decision-making capacity.*
>
> *In making its assessment, the Subcommittee will review the relevant provisions of subpart A, 45 CFR part 46, including the provisions at 45 CFR 46.111(b) (and 21 CFR 56.111[b] for FDA), and will seek additional information to formulate its decision as it deems necessary.*
>
> *The Subcommittee will develop either one or both of the following products, depending on its conclusions: (1) recommendations on the interpretation of specific Subpart A provisions that will enhance protections for this population; and (2) recommendations for a new subpart under 45 CFR part 46 (and FDA's human subject protection regulations) that would provide additional regulatory protections for this population.*

He noted that there is no specificity in the Common Rule regarding what "additional safeguards" are needed to protect persons with impaired decision-making ability or how they should be provided. There is also no working definition for mental disability. He envisioned the committee addressing these issues, as well as how reviews should be structured to ensure adequate protection for this population and how consent should be handled. He noted that many of the most notorious cases in experimentation on humans do involve such populations. States have generally failed to provide constructive guidance for researchers and IRBs on who may be included in research and what types of research are permissible for persons who lack the capacity to consent. This is clearly an area in which particularly thoughtful guidance is needed, as well as possible additions to the regulations.

The subcommittee will have the benefit of increasingly systematic research on IRBs are applying the regulations in the absence of specific direction. For example, Dr. Gary Chadwick, a member of the Subpart A subcommittee, is involved in a project examining how the process of surrogate consent is being applied.

Dr. Strauss noted that there are many classes of individuals who may have impaired decision-making abilities, some of whom can still consent to research. Impairments may be of many different types; for example, they may be global or specific, and situational or disorder-related. (See Dr. Strauss's presentation in the minutes of the SACHRP meeting on July 31- August 1 for more detail.) It is also important to recognize that new and more successful treatments for many brain disorders are now

available, and the ability to do research on impaired subjects is increasingly important to continue this groundbreaking work.

Challenges for the subcommittee include:

- Learning from history,
- Considering all perspectives,
- Defining the vulnerable group(s),
- Understanding impaired decision-making capacity,
- Evaluating the risks and benefits of regulatory change or guidance, and
- Translating ideals into meaningful practice.

OHRP has assembled a long list of possible members, and there is considerable interest in the subcommittee. Final decisions will be made in the coming weeks and invitations issued.
The following are among the qualifications for membership being considered:

- Clinical and scientific expertise related to disorders that affect the central nervous system, critical care medicine, and health care literacy.

- Patient and family advocacy. Multiple voices and perspectives should be taken into account.

- Expertise in empirical aspects of research ethics (a growing field).

- Familiarity with the law and current thought on issues like surrogate consent.

- Expertise in research oversight and human subject protections.

Dr. Strauss stressed the importance of not only capturing concepts and principles, but also ensuring they can be realized in practice. Recommendations must work from the perspective of those responsible for oversight.

DISCUSSION

Dr. Strauss responded to the following questions from SACHRP members.

To what extent are IRBs that are reviewing research for decisionally impaired subjects applying appropriate additional protections? If they have been doing this, what are the common methods used to apply these protections? Dr. Strauss said he had not done systematic investigations on the subject; however, he believed that research facilities that work with these populations typically do provide additional protections in the consent process. Many require independent assessment of the capacity to consent. Recently, many institutions have begun using other tools to assess capacity, such as questionnaires. In his own institution, reasonable protections shift to reflect the perceived vulnerability of the subject.

Subpart E was drafted to reflect the categories used in Subpart D. What does your IRB think about tying risk limitations to vulnerability? The categorical approach is overly restrictive and ultimately unhelpful, since vulnerability occurs along a spectrum. As a result, such an approach can overprotect some groups and under protect others.

Will the committee be addressing such elements of decision-making capacity as memory impairments or excessive dependence on caregivers? Dr. Strauss emphasized that the subcommittee will take its charge from SACHRP and that it intends to "cast a wide net" in its deliberations.

How long do you think it will take to develop a series of recommendations that will fulfill the subcommittee's charge? Dr. Strauss said he could not predict the time required until the subcommittee has met and SACHRP has given further direction on specific focus areas.

What do you see as the advantages and disadvantages of providing additional guidance as opposed to new rulemaking? A Subpart E that looks like Subpart D could be overly restrictive; it is important not to develop a Subpart that focuses tightly on a specific category of research subjects. Also, in making this determination, more information is needed on what has gone wrong in previous attempts to address these issues.

In setting priorities, to what extent do you look at what kinds of research are emphasized today, as opposed to looking broadly at issues related to different forms of impairment (regardless of the extent to which research is addressing those types of impairment)? To some extent, assessment of capacity is always required during the consent process. It is possible to think about guidance related to informed consent that applies in all cases but changes in intensity based on the nature of the conditions and what is learned in the initial assessment. Rather than writing guidance or a subpart that is directly related to particular disorders or categories of illness, it may be best to envision a spectrum of decision making and sensitize IRBs to the issues and principles involved.

Will the subcommittee consider ways of enhancing decision-making by providing supports for certain categories of individuals? This could take the form of a sophisticated tool or simply a better consent form. For example, Dr. Strauss's IRB uses a cover sheet that serves as a guide to the longer form and helps orient the subject. Even small enhancements may be helpful.

What is your sense of the current situation? Are risks too high or are IRBs excessively restrictive? Or are both true? It is probably both. The loudest complaints come from researchers who feel that important work they want to do cannot be done because IRBs are overly restrictive. In academic communities, many people feel that some research is not occurring because of inadequate guidance. Another group of people does feel that risks to subjects are too high.

Do you have data on how many subjects sign the form after reading only the cover sheet? I don't think this is happening. It really is a guide, and investigators are required to go through the whole form.

The Subpart A Subcommittee will probably address some overlapping areas. How do you see the two interacting? Dr. Strauss is also a member of the Subpart A subcommittee and sees the two subcommittees working together on such issues as IRB membership. Mr. Nelson added that overly prescriptive recommendations that mandate representation in numerous categories can result in extremely large IRBs.

The Chair invited comments from *ex officio* members. Dr. Shore of the National Institute of Mental Health (NIMH) said that he feels strongly that a new set of regulations could have adverse consequences for the research that is most needed at present. Dr. Barratt from NIH added that Dr. Shore will be helping to lead an NIH-wide consideration of these issues. A subcommittee will be developing a document that captures points to consider in issues in which subjects' capacity for decision-making is questionable.

Panel on Research Involving Individuals with Impaired Decision-Making Capacity
Robin Elliott, M.A., Executive Director, Parkinson's Disease Foundation; Representative Ann de la Blanchetai Donahue, J. D., Vermont House of Representatives; Sharon M. Grandinette, M.S., President, California Association of Physical and Health Impairments

Remarks by Robin Elliott: Cognitive Impairment and Participation in Parkinson's Clinical Trials

Mr. Elliott introduced himself as a generalist who has prepared for this presentation by conversations with colleagues in medicine, clinical research, and some of the social work disciplines. He focused his remarks on issues related to research participation by persons with Parkinson's Disease who may have some degree of cognitive impairment.

Parkinson's disease (PD) is officially termed a "movement disorder," but increasingly it is being recognized, by doctors as well as patients, as a "full-body" disorder whose effects extend beyond the movement system. Symptoms can include fatigue, gastro-intestinal problems, depression, psychosis, cognitive decline, and dementia. The disease affects one to two percent of people over the age of 60 (500,000 to one million in the U.S. alone).

Cognitive impairment is a common dimension of PD. More than 80 percent of people with PD will experience some level of cognitive impairment within 15 years of diagnosis. Compare with age-matched controls, the incidence of cognitive impairment has been found to be 8 or 9 times higher among persons with CD. Commonly, loss of executive function and visual-spatial competence is more significant than loss of memory.

Referring to the key ethical principle of "justice," highlighted in the Belmont Report, Mr. Elliott stressed the need to ensure that people have the opportunity to participate in research opportunities; he saw this is as important as ensuring appropriate protection from adverse results of participation. He said that mild to moderate cognitive impairment may not interfere with participation in Parkinson's clinical trials. However, more serious impairment may require safeguards (for example, a legally designated representative or prior signed document indicating willingness to participate in trials). The caregiver, typically the spouse, is often able to help think through issues related to participation. At least one lawyer Mr. Elliott has talked to did not feel a prior signed document was an especially good idea and questioned to what extent it would be upheld in court.

People with dementia all commonly excluded from clinical trials. In fact, of the 47 clinical trials on the Web site managed by the Parkinson's Disease Foundation, www.PDtrials.org, every single intervention excludes people with a diagnosis of dementia. Given the need for potential treatments that could retard the process of increasing dementia, Mr. Elliott questioned the appropriateness of such blanket exclusions. Given the appropriate constraints and safeguards, participation should at least be considered.

The type of trial and the subject of the trial should also be taken into consideration in decisions about participation. It must also be clearly understood that, in PD, cognitive impairment is a "moving target" that will change over time. Consequently, there may be a need to reconsent the subject at appropriate times. Mr. Elliott added that participation in a clinical trial can have therapeutic value for many people with PD, and many of them have told him that their lives were enriched by participation. Many subjects appreciate the opportunity to contribute to science.

Mr. Elliott pointed to specific research needs pertinent to the understanding of cognitive impairment and PD. He highlighted the need to:

- Define and measure the nature and characterization of the many forms of cognitive impairment;

- Improve the use of existing long-term databases containing information on dementia among the PD population; and

- Increase public and private sector commitment to developing treatments for cognitive impairment in Parkinson's and other disease conditions.

Currently, the speaker said, there is no specific treatment for cognitive impairment in PD, although Exelon, a drug that is commonly prescribed to patients with Alzheimer's Disease, has proven moderately or mildly effective for some people for some of the time.

There are also policy issues that relate to cognitive impairment and PD. In this area, Mr. Elliott pointed to the need to:

- Better define the terms in which a cognitively impaired person with Parkinson's can participate in a clinical trial (based on research and analysis defining cognitive impairment among people with Parkinson's);

- Develop models to manage participation by a cognitively impaired person with PD; and

- Develop polices and programs that engage the wider Parkinson's community, including potential clinical trial participants, family members and caregivers, physicians, and other allied health professionals.

Mr. Elliott closed by stressing the importance of providing opportunities for people to be agents in their own health care and to contribute to their communities.

Remarks by Ann B. Donahue: The Perspective of a Legislator, Journalist, Consumer, and Advocate

Ms. Donahue prefaced her remarks by explaining that she brought with her four distinct perspectives. First, as a consumer, she has personal experience of the effect of mental illness on the ability to make informed choices. Currently, her illness is in remission and she is able to reflect on her experience from the perspective of being "well." Secondly, she has been involved in the consumer community as an advocate. She stressed that all ethical dilemmas are shaped by the individual experience of humans; among consumers, for example, one of the most contentious topics is forced treatment of persons deemed "not competent." Ms. Donahue herself received electroshock treatment without giving adequately informed consent, an event that has had devastating consequences in her life. She is also a legislator who has helped the state of Vermont address issues of capacity and informed consent, including rewriting the state law on advanced directives for health care. Finally, she is the editor of *Counterpoint,* Vermont's quarterly newspaper for mental health consumers.

As a consumer, Ms. Donahue has experienced cycles of responding to treatment, relapsing, and then beginning to respond again. In some periods, she felt, she was not herself, and the person she was at those times had no right to speak for her true self. Sometimes she would be considered legally

competent, and other times she would not. Her experience represented not merely a spectrum of decision making capacity, but a spectrum in motion.

The speaker stressed the importance of appreciating the psychiatric consumer movement and the political and social context in which it exists. The movement began as a civil rights movement that argued for the rights of individuals to make their own choices, and the right to refuse treatment is particularly controversial within the movement. Resistance emerges wherever it is perceived, rightly or wrongly, that civil rights protections may be reduced.

Inconsistencies in the legal process for involuntary treatment or medication add to the complexity of the issue. In Vermont, there was no statutory guidance related to court orders or guardian decisions related to medical interventions for a person found unable to protect his or her own health due to mental illness. The law provided that an advanced directive can be revoked at any time, including by a person who lacks capacity; such a person could not make an informed decision in advance that authorizes a guardian or relative to make a choice on his or her behalf (a provision known as the "Ulysses Clause," after the Greek hero who asked the crew to tie him to the mast and ignore his orders as the ship passed the sirens who might lead the ship to the shoals). To remedy this situation, Vermont created a unique hybrid statute that allowed the use of a Ulysses Clause in an advanced directive. Thus, it raised the threshold of protections for the decision to surrender one's right to revoke an advanced directive when incompetent. A consideration of what is in the patient's "best interest" is permitted only if a fact finding agent has exhausted all available means of trying to interpret what the person would have wanted under the circumstances.

Ms. Donahue shared her experience of electroconvulsive therapy, following which she suffered a devastating loss of years of memory. She had been told that allegations of the risk of memory loss were nonsense. She noted that a journalist has raised the question of whether consent to such a radical therapy can ever be truly informed if a person is sick enough to need it. If the intense desire for relief constitutes an unacceptable influence or impairment of capacity, however, research for many conditions would be put in question – not just those related to mental health.

Another difficult legal issue is the standard for replacing an individual's judgment with that of another person. For example, in Vermont, in the case of court-ordered psychotropic medications, the preferences expressed by an individual when competent are followed initially; however, if evidence demonstrates that following the patient's preferences has not resulted in significant clinical improvement in the past, a decision can be made in the patient's best interest.

Despite these difficult issues, Ms. Donahue did not want to rob herself or future generations of better opportunities for survival, recovery, and quality of life. One of the recommendations of the Report of the President's New Freedom Commission on Mental Health (2003) is to "accelerate research to promote recovery and resilience, and ultimately to cure and prevent mental illness." Ms. Donahue stressed the need to transform the ways we think about the effects of mental illness on decisional capacity so that creative ways to overcome barriers to human subject research can be found.

Remarks by Sharon M. Grandinette: Understanding Acquired Brain Injury & How It Affects Decision Making Skills

M. Grandinette focused her remarks on how acquired brain injury affects decision making skills. As background, she explained that brain injury is the leading cause of death and disability worldwide. Acquired brain injury is a very broad category that includes mild, moderate, and severe levels of severity. Even those who have mild injuries, however, may have impaired decision making ability.

Deficits in decision making vary by type and cause. Acquired brain injury may result from traumatic events or nontraumatic events. *Traumatic* brain injury (TBI) is not of a degenerative or congenital nature; instead, it is caused by an external physical force that disrupts the normal function of the brain. One type of TBI is an open brain injury in which the skull is broken and penetrated, resulting in bleeding and bruising inside the brain. Such injuries tend to be concentrated in a specific area of the brain. A second type of TBI encompasses closed brain injuries that result from the brain moving inside the skull; these are more diffuse and global in nature. Examples of the many *nontraumatic* causes of brain injury include strokes, exposure to toxic substances, epilepsy, brain tumors, and infections of the brain, such as encephalitis and meningitis. Populations with such injuries now survive in greater numbers because of medical advances.

It is important to realize that cognitive impairments resulting from brain injuries are often hidden, though they can affect decision making. Attention and concentration may be affected, as well as short or long-term memory (or both categories of memory). They may confabulate (essentially, make things up) to conceal their memory loss. They may remember something on Monday that they cannot access on Wednesday. Many have only limited recognition of their deficits.

Individuals may experience varying degrees of confusion and disorientation as to time and place. Executive functioning skills may be affected, causing difficulty in formulating goals, planning for the future, and problem solving. Some individuals may function well one day, but not the next. Often, there are deficits that affect communication; for example, the person may understand what is said, but lack the expressive ability to communicate this understanding. Some individuals have impaired reading comprehension, difficulty with abstract concepts, or difficulty understanding other people's intentions.

Social and behavioral aspects of acquired brain injury should also be taken into account. Individuals may not accept their deficits; depression and withdrawal are common. They may be impulsive and make decisions quickly, or they may show poor judgment (for example, misperceiving social situations). They may have difficulty in adapting to new situations or meeting behavioral expectations. Often, there is a mismatch between what they think they can do and what they actually can do; it is common for them to believe themselves capable of tasks they can no longer perform.

Many individuals still test with a normal IQ following acquired brain injury. In most cases, their capacities are not static, and many of them continue to make progress over time if support is available.

The consent process requires capacity for gathering information, establishing trust, identifying risks, advocating for oneself, making choices, and then sticking to a choice. Ms. Grandinette explained that she modifies educational strategies for these individuals, and accommodations are likely to be needed in the consent process. Special educators have expertise that can be useful to investigators. For many of them, the cover sheet Dr. Strauss described earlier would be helpful.

Asking the right questions during the consent process is critical. Among them are the following:

- Does the individual have a memory problem?
- Does the individual have the ability to solve problems?
- Can the individual understand the purpose of the research and procedures to be followed?
- Can the individual repeat them back to the person who is consenting them?

- Does the individual have a desire to participate, or is he or she being pushed by a parent or guardian desperate for a cure? Does the individual see the risks and benefits the same way the parent or guardian does?

- What safeguards can be put in place to ensure the ABI survivor is involved in the decision even if they have a surrogate?

- Can the individual schedule and keep appointments?

- Does a surrogate exist? Should one be assigned?

- What is the motivation for participation? Are individuals participating in the hope of alleviating suffering, because they have no insurance and need services, to receive attention, to have some control over their lives, or because they want to contribute to something?

DISCUSSION

SACHRP members asked panelists follow-up questions.

Does a problem exist? What are your feelings about the need for additional populations for this population?

- Ms. Donahue sees a significant problem because of the history of abuses in research involving persons with impaired decision making. She sees a need for guidance but doubts that such complex issues can be codified in specific regulations.

- Mr. Elliot was unsure of the best regulatory approach; he emphasized the need to send a strong signal to the research community, IRBs, and decision makers that people with cognitive impairments should not be excluded from research by virtue of that condition alone. He feels that the pendulum has swung too far toward a cautionary approach that denies these individuals the opportunity to participate in research.

- Ms. Grandinette suggested categorizing studies according to level of risk and preparing a matrix that captured both these levels and the level of impairment.

- Ms. Donahue added, in reference to stigma, that she longs for the day when no one will speak of her courage in discussing her mental illness, but it will be perceived in the same way as if she had been describing an experience with bone cancer.

How do we translate these concerns into frontline practice? Who are the gatekeepers to be considered? What can we reasonably accomplish and expect? What role should advocates play in this process?

- Ms. Donahue stressed that mental health care is moving in the direction of a strong focus on recovery, consumer-directed care, and consumer involvement. It is critical to ensure consumer involvement. This is complex, however, in that consumer advocacy groups have a range of strongly held views on the subject of consumer participation in research.

- Ms. Grandinette observed that many of the different conditions associated with impaired decision making have their own associations; however, they all have different agendas that should be taken into account, including a strong interest in Federal funding.

- Mr. Elliott noted that many foundations do not consider themselves to be patient advocacy groups; rather, they see themselves as representing the science relating to the condition or disease, often to the government; they hope, however, that their factual presentations are in the patients' best interest.

Should a person with impaired decision making be allowed to participate in a Phase 1 trial with no direct benefit to the individual?

- Ms. Donahue said individuals should be allowed to participate, but suitable assistance in the decision making process may be needed. The degree of incapacity and the changing nature of that capacity must be taken into account, including memory loss. Severely impaired populations should be used only when their participation is the only way to get needed information. She added that when an agent makes a decision for another person solely on the basis of the best interest of the potential subject, they are likely to say no; if, however, the person making the decision on the individual's behalf knows the person, his or her values, and his or her wishes and is making a decision using substituted judgement, the outcome may well be positive.

- Ms. Grandinette noted that many people go through extensive neuropsychological evaluations following an injury; results change when the same tests are given after five months. It is important to look at what assessments are being used, and a short mental exam will not be sufficient.

- Mr. Elliott added that many trials will not benefit the patient if their interest is narrowly conceived. Trials are designed to advance science, not serve the interest of individual patients in the narrow sense. People still do things for altruistic motives, whether or not they are impaired.

Are there empiric data on the decision making processes IRBs are using?

- Dr. Strauss said there have been surveys of institutions within New York State on how decisions are made, and Mr. Chadwick is participating in a national project on the topic.

- Mr. Nelson called attention to a paper by Laura Roberts included in meeting notebooks, which also addresses the topic.

- Dr. Jones stressed the importance of the subcommittee contextualizing issues they bring forward so the decisions can be better understood. She also asked Dr. Strauss to pay close attention to the practical aspects of inclusivity, including costs.

- Mr. Elliott urged the subcommittee to test their recommendations with reference to "hard cases."

- Dr. Lux said there is a need not only for empiric data on research ethics, but also on the assessment of the capacity to consent.

Before making determinations about what regulations should look like, shouldn't there be an RFA from the National Institute of Mental Health or a similar agency that calls for research related to long-term solutions, including a consideration of ethical issues?

- Dr. Strauss said there is a growing field of empirical research ethics, and they hope to involve some of the leaders in the field in the subcommittee.

- NIH has a relevant program announcement on research ethics.

PUBLIC COMMENT

Sarah Putney is an IRB member and is involved in IRB Administration at the School of Public Health at Harvard. Noting that the Commonwealth of Massachusetts is one of many states that has no helpful law defining who can be considered a legally authorized representative for a proxy consent for cognitively impaired adults, she is looking forward to guidance from OHRP that can be shared with state legislators. She observed that some IRBs are happy to exploit the silence of state law.

In reference to research involving prisoners, she stressed the importance of gangs in prison and wondered if they might contribute to issues of coercion issues and undue influence regarding research involving prisoners.

Dr. Prentice responded that the IOM Committee that produced recommendations on the protection of prisoners as subjects included individuals who are experts on all aspects of the penal system, including ex-prisoners. He thought it likely that the committee had given due consideration to the current gang climate prevalent in prisons.

Wrap-Up and Adjourn

The Chair thanked panelists and SACHRP members for the excellent discussion.

Dr. Prentice said that the opportunity to serve as Chair had been a fascinating experience and a privilege. He thanked the OHRP Director and OHRP staff members for their support, which is essential to SACHRP success. Dr. Schwetz then thanked the Chair and other departing SACHRP members for their work and hoped they would stay in touch.

The Chair noted that SACHRP faces many future challenges. Upcoming meetings in 2007 will be March 29-30, July 30-31, and October 29-30.

Secretary's Advisory Committee on Human Research Protections
November 2-3, 2006
Arlington, VA

Certification of the Summary of Minutes

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

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