Secretary's Advisory Committee on Human Research Protections
July 30 and 31, 2007 – Arlington, Virginia

Minutes

MONDAY, JULY 30

Welcome and Opening Remarks
Sam Tilden (M.D., J.D., LLM)

Dr. Tilden, SACHRP Chair, reviewed the role of SACHRP as described in its charter:

> *SACHRP will advise the Secretary on matters concerning the protection of human subjects with particular emphasis on special populations such as neonates, children, prisoners, the decisionally impaired; pregnant women, embryos, and fetuses; international studies; identifiable samples; investigator COI; and OHRP activities.*

He also reviewed a list of members and *ex-officio* members of SACHRP. The Chair then provided an overview of the agenda for the day.

Minutes for the previous meeting (March 29 and 30, 2007) were approved unanimously.

Report from the Director
Bernard Schwetz, D.V.M., Ph.D., Director, Office for Human Resource Protections (OHRP)

Dr. Schwetz summarized the status of recommendations submitted by SACHRP:

- The last SACHRP recommendations on Subpart D (Research involving Children) and Subpart A were approved by the Secretary of Health and Human Services (HHS). OHRP is following up on these and other approved recommendations.
- Recommendations regarding training of individuals involved in the review, oversight, and conduct of research have been submitted to the Secretary.
- OHRP has been gathering information from other agencies under the Common Rule on Subpart C. It is considering this input, SACHRP recommendations, and the report of the Institute of Medicine (IOM) as it decides on next steps.
- Regarding the recommendation to harmonize the requirements of the Common Rule with those of the Health Insurance Portability and Accountability Act (HIPAA), some unresolved issues between offices and agencies are still being addressed.

Other OHRP progress and actions of interest to SACHRP include the following:

- OHRP has posted a new set of Frequently Asked Questions (FAQs) on informed consent on its Web site.

- OHRP continues to engage in conferences with special populations. The next one is a conference it is co-sponsoring in Denver on August 22nd and 23rd. Its focus will be on American Indian and Alaskan native issues related to human subject protection.

- OHRP is continuing to hold workshops on Quality Assurance for institutions holding Federal-Wide Assurances (FWAs). Two of these have been held at institutions that do not have internal IRBs; this experience has highlighted issues related to local training needs.

Personnel changes were also highlighted:

- Dr. Ivor Prichard has been on detail from the Department of Education until last week, when he officially became an employee of OHRP. He will be working in the office of the Director.

- Dr. Schwetz will be retiring on September 30th.

The Director expressed gratitude to all SACHRP members and subcommittee members for maintaining a high level of productivity, commitment, and independence. He especially acknowledged the contributions of the former SACHRP Chair, Dr. Prentice. Finally, he thanked his colleagues at OHRP and *ex officio* members of SACHRP who have helped make SACHRP and its subcommittees more effective through their input.

Dr. Tilden, SACHRP Chair, presented a plaque to Dr. Schwetz in appreciation for "exceptional vision, leadership, and service." He credited the Director with contributing to SACHRP's success.

Report of Subcommittee on Issues Impacting Those with Impaired Decisionmaking Capacity (SIIIDR)
David Strauss, M.D., and Laurie Flynn, Co-Chairs

Ms. Flynn explained that Co-Chairs will present an initial report on the subcommittee's progress so far and its plans for moving forward, in hope of receiving feedback from the main committee.

SIIIDR met for the first time on May 8 and 9, 2007; a teleconference occurred June 7, and a second meeting was held July 9 and 10. It has reviewed reports representing the conclusions of prior efforts to develop regulations to address issues related to "decisional impairment" and is trying to understand why prior efforts have not succeeded. Members have benefited from expert presentations on adults with mental retardation, Alzheimer's disease, traumatic brain injury, and psychiatric illness. It also reviewed the newly developed FAQs on informed consent, received a presentation from Ann Donahue on the status of "applicable" state and local laws regarding legally authorized

Framework for SIIIDR Activities: Key Questions to Explore

- How do we identify those who have limited ability to consent and those who are unable to make consent decisions for themselves?
- How do we decide who may provide consent for those who are unable to consent for themselves? What kind of decisions can these surrogate decisionmakers make?
- How do we define a reasonable risk/benefit balance when the ability to consent is limited or absent?

representatives (LARs), and received a presentation from David Forster on institutional policies with regard to those unable to consent. Based on these presentations and initial discussions, the subcommittee has reached the following preliminary consensus points:

- Regulations require that information provided to subjects to obtain their consent be "understandable to the subject." Subcommittee members have debated the meaning of this requirement and how it is possible to ensure it is met. Members agree that some assessment of "understanding" is required in all cases of consent.

- While "additional safeguards" are required for vulnerable subjects, it is not clear that these core protections are well understood and consistently applied.

- A national approach to the definition of Legally Authorized Representative (LAR) and related protections for individuals who are unable to consent to research is needed.

The subcommittee has identified three key questions that form a triangular framework for its deliberations (see text box above). The group recognizes a need to engage all the necessary stakeholder groups as these questions are explored. To this end, it intends to engage and seek comment from academic and professional organizations, IRB professionals who struggle with these issues regularly, and patient advocacy groups. SIIIDR also recognizes that these concerns are related to issues being addressed by the Subpart A subcommittee, especially informed consent, and will bear this interrelationship in mind as it proceeds with its work.

In regard to its charge to determine "whether guidance and/or additional regulations are required for individuals with impaired decision-making capacity," the subcommittee is clear that there is such a need. Existing federal regulations and regulatory guidance relevant to individuals with "impaired decision-making" do not adequately address key ethical concerns regarding the rights and welfare of this most vulnerable category of research participants. In addition, for those prospective subjects who are "unable to consent" for themselves, the absence of adequate, consistent, or in many cases, *any* state law creates significant problems for research protections. As recommendations are developed to address this need, however, it is essential to find solutions that both protect subjects and help advance the science needed to support recovery.

Dr. Strauss continued the presentation by introducing subcommittee members, who represent a variety of viewpoints and expertise. All are leaders in their field. He stressed the need for the subcommittee to envision a pragmatic regulatory and oversight structure that is able to support the translation of principles into meaningful practice. Members will seek models related to informed consent, the assessment of capacity to consent, and identification of subjects at risk for decisional impairment that can be used by investigators, IRB members, and institutions.

Returning to the three questions that form the framework for SIIIDR activities (see textbox above), Dr. Strauss pointed out that they are interrelated; no one question can stand alone. He then elaborated on each point, beginning with preconditions for informed consent. He said the ability to consent requires:

1. Effective disclosure of required information;

2. A capacity to understand, appreciate, and reason about the relevant facts and consequences related to participations; and

3. A context which promotes voluntary choice, free of undue influence.

These three preconditions are essential for formed consent. Of these, the subcommittee is focusing on the second and third requirements, which relate more closely to the characteristics of research subjects rather than what the investigator is required to do.

The Co-Chair then explained the importance of conceiving of the ability to consent along a continuum rather than as a black-and-white determination. The continuum shades from persons who are unconscious or delirious through a grey area toward those who are clearly able to consent. He pointed out that:

- Some individuals will be assessed as being able to make a consent decision *despite* some impairment or limitation in ability.

- Others will have limitations to a degree that they will be assessed as unable to consent.

- The ability to consent can be enhanced in some circumstances by improving contextual factors, enabling some individuals to give their consent.

- The ability required to make a decision about participation in a specific research study is "task specific": it depends on the complexity, novelty, level of risk, and level of benefit of the proposed research. Consequently, an individual may be assessed as being able to make a consent decision to participate in one research study, and unable to consent to others.

- An individual unable to consent for himself or herself may nevertheless be able to appoint a proxy decision-maker.

Dr. Strauss stressed the importance of casting a "wide net" capable of capturing the variety of circumstances that might limit or impair the ability to make a decision. Impairment in ability to consent occurs in a range of populations and in many circumstances. Previous efforts to address this have failed in part because they neglected to address the full range of populations that may have impaired decisionmaking capability (besides those with mental impairments), such as persons in the intensive care unit. Consequently, Ms. Flynn continued, SIIIDR plans to address the range of "populations and circumstances" in which there is "impairment or limitation in ability to consent." Based on this analysis, members have concluded that some real assessment of the subject's ability to consent should occur in *all* studies. In some circumstances, this assessment may be simple and intuitive. In others, ascertaining the ability to consent may require a more elaborate or formal mechanism or instrument. She assured SACHRP that there is clear empirical support for a variety of specific methods that can be used either to assess or to enhance subject's capacity.

In addressing the second key question in the SIIIDR framework, which relates to identifying surrogate decision-makers and defining their authority, Ms. Flynn noted that the Federal regulations require the subject's "legally effective informed consent" and also allow consent by a "legally authorized representative (LAR)" to the "procedures used in the research." However, the definition of a LAR is left to applicable State or local laws. Unfortunately, with rare exceptions, States have not developed definitions of LAR designed to apply in a research (as opposed to end of life) context. Neither State laws nor institutional rules consistently address the scope of covered research activities, the definition and identification of populations who are unable to consent, and identification of those

who may provide consent for those who are unable to consent themselves. Many do not address these issues at all. Further, there is almost no mention of what level of risk may be appropriately addressed by a proxy decision-maker on another person's behalf. This inconsistency creates a unique set of problems for multi-State studies. In fact, Dr. Strauss pointed out, even in California – which *does* have applicable legislation – there is wide variability among institutions in how these issues are addressed. Consequently, SIIIDR members reached consensus on the following:

- *A comprehensive and consistent national approach to the definition and use of "legally authorized representative" is necessary to provide protections and promote research for those who are unable to consent.*

SIIIDR plans to give further consideration to the merits and practicalities of Federal regulation defining the LAR and to the possibility of developing model State legislation for this area.

Dr. Strauss continued to explore the third and final element of the SIIIDR framework: *How do we define risk of harm?* He noted that current regulations and guidance give rise to inconsistencies in the estimation of risk, which occurs along a continuum. In considering the possible impact of rules on practice, the subcommittee is well aware that defining an upper limit of risk may discourage researchers from pursuing critical scientific endeavors and could also encourage IRB to "game the system." Similarly, the real world of "benefits" to counterpoise against the risk of harm is "far more complex" than the black-and-white distinction between "prospect of direct benefit" and "no prospect of direct benefit." For example, some studies may confer only a temporary benefit. Others may address fundamental questions that are essential to lay the foundation for studies that would potentially confer benefit. As the subcommittee continues to develop recommendations, it will carefully consider the relative merits of categorical as opposed to other approaches to risk/benefit analysis.

In the near term, the subcommittee plans to seek additional data on current practices, the needs of the field, and whether subject health and safety or scientific progress appear to be hampered by the current situation. The subcommittee expects to hear from stakeholders on these issues. Dr. Strauss said the subcommittee has been given the opportunity to conduct a "town hall" on this topic at the upcoming meeting of Public Responsibility in Medicine and Research (PRIMR). John Luce has also prepared a questionnaire on surrogate consent that will be distributed to a range of professional organizations and advocacy groups. The subcommittee hopes to bring forward specific proposals at the next meeting. Co-Chairs welcomed feedback from SACHRP members on their work thus far and proposed approach.

DISCUSSION

Various members congratulated Co-Chairs on the progress made to date and the proposed framework. Key points arising from discussion included the following.

Short-term guidance. Dr. Chesley of the Agency for Healthcare Research and Quality (AHRQ) encouraged the subcommittee to pursue the development of guidance to address the short-term need for clarity, even if a regulatory change is ultimately sought as well.

Role of industry. Dr. Powell asked how the subcommittee plans to get the perspective of people who are developing products to treat people who are decisionally impaired. Dr. Strauss agreed that the subcommittee needs to reach out to industry, which is a key stakeholder, in a systematic way. Dr.

Tilden suggested that PRIMR provides one avenue for outreach. Ms. Flynn welcomed specific input from industry and would be interested to hear about research impeded by difficulties in testing potentially beneficial products with the target population.

Assessment of capacity. Noting that the type of informal assessments in common practice at present might fail to identify some decisionally impaired individuals, Dr. Powe asked whether tools for quick informal assessments are available. Dr. Strauss said that to date, the subcommittee has emphasized the need to create an expectation that the investigator will make such a determination through some interaction with the subject, through which the need for further assessment may become apparent. A "one size fits all" approach would not work well; rather, methods would need to be specific both to the proposed research and to the intended population.

Dr. Strauss added that a related issue is who among the members of the research team would have the appropriate credentials and experience to make the determination that a prospective subject lacks the capacity to consent. This is potentially as important as the tool selected for this purpose.

Dr. Shore, an *ex officio* representative for the National Institutes of Health (NIH), noted that many approaches have been used to assessing capacity within the last decade; these include having the investigator sign a statement that the person has the capacity to consent, asking the potential participant to summarize the study and its risks and benefits in an unstructured way, and specifically testing the understanding of the purpose of the study, the risks, and the anticipated benefits. Dr. Strauss said the subcommittee has considered a range of possibilities but has not developed specific recommendations. The minimum requirement should be an attestation by the investigator that the subject understood the risks and benefits of the study, as well as the alternatives to study participation. In cases in which people may have limitations, a more formal assessment of capacity would be called for. The McArthur Competency Assessment would be one possible tool. Mr. Nelson observed that in some cases, the subject's inability to consent would be clear and no such tool would be needed. Dr. Strauss agreed.

Dr. Botkin reinforced the concern that the requirement for assessment not be stated in such a way that it becomes complicated and burdensome. He added that the investigator has a responsibility to present material in a way that is understandable, and further definition of what this means will require further work on the part of SIIIDR and the Subpart A subcommittee. Dr. Strauss noted that poor literacy, and poor healthcare literacy in particular, are important limitations that affect the ability to consent; however, he felt that they were outside SIIIDR's charge.

Dr. Botkin questioned whether the assessment of ability to consent should be linked to an assessment of whether or not participation is voluntary. Ms. Flynn said this issue has not yet been explored by the subcommittee, but it is a critical component that has proved a contentious issue with some populations in the past. Dr. Strauss agreed that an assurance that participation is voluntary is part of any meaningful assessment of the ability to consent. Responsibility in this area is shared by the investigator and the IRB. A representative of the Department of Defense (DOD) said that DOD requires the use of an ombudsman when the research is greater than minimal risk and voluntariness is in question (for example, when participants are being recruited in the context of their chain of command).

Dr. Botkin highlighted the issue of assent, which may need to be "translated" from its application in pediatrics to this domain. Dr. Strauss saw this as a "level two" issue to be addressed.

Dr. Chesley of AHRQ said that many investigators lack sufficient knowledge of information technology that could help them include more populations in their research.

Risks and benefits. Dr. Genel commented that his colleagues in pediatric research find that the categorical approach to risk analysis and the variability in IRB interpretations do impede some necessary research. He hears that IRBs consider often emphasize discomfort as opposed to actual risk. Dr. Strauss observed that Subpart A allows a more holistic approach, as compared to Subpart D.

Identification of populations. Noting that under testamentary law one would generally presume someone to be competent unless there was an indication to the contrary, Dr. Tilden suggested that SIIIDR consider identifying populations in which incapacity or capacity are likely to be involved. He also suggested that NIH incorporate a requirement that requires grant applicants to explain how they would address the need for a LAR when they are working with populations in which decisionmaking could be impaired. He felt the threat to funding would result in a rapid change in State laws to address the situation. Ms. Flynn was concerned, however, that this approach would unfairly stigmatize groups – especially persons with psychiatric illness – and would prove controversial. She reminded SACHRP that, as previous panels on the subject have demonstrated, rigid categories will not be seen as helpful, given the broad range of impairments and the fluctuating nature of many impairments.

Dr. Tilden rejoined that some studies – for example, a study of cognitive function in individuals with head injuries from combat – would immediately flag the question of how informed consent should be addressed. In other studies, people who are impaired would be the exception, and would probably be dropped from the study. He was concerned that the expectation of assessment in all cases would be a burden. Dr. Strauss stressed the importance of the investigator being mindful of circumstances in which there is a greater or less likelihood of impairment. For example, he hoped that an IRB charged with reviewing a study of people over 55, as well as the investigator doing such a study, would realize that some people over 55 will be old enough to raise the question of whether they might have some form of cognitive impairment.

LAR. Dr. Tilden observed that overlapping jurisdictions and rights involving States and the Federal government complicate the issue of LAR. Dr. Genel said that a national commission for drafting model state legislation exists and suggested that it might be helpful.

Mr. Nelson emphasized that the increase in multi-State studies in today's research environment elevate the importance of addressing the LAR issue. However, while a national approach is a worthy goal and worth discussing, he felt it would be tough to accomplish.

Dr. Botkin added that in instances in which the impairment in decision-making is irrelevant to the research, it will generally not be appropriate to include those with such impairments in the research. A complex process to facilitate enrollment would not be warranted.

Coordination with Subpart A Subcommittee (SAS). Mr. Nelson assured the Co-Chairs that SAS envisions cooperation and collaboration in addressing issues of concern to both subcommittees.

ACTION

To facilitate the work of the subcommittee in addressing issues surrounding the role of the LAR, SACHRP passed the motion below, which was revised on the second day of the meeting for technical reasons.

SIIIDR, Summary of Legal Options

(As revised 7/31/07): SACHRP requests OHRP to provide the SIIIDR subcommittee with a summary of legal options to address a "roadblock" to inclusion of persons with decisional impairments in research: unresolved issues related to the use of Legally Authorized Representatives (LARs). The summary will identify and discuss such actions as national legislation or regulation initiated by HHS, development of model State legislation, and development of legislation on a State-by-State basis. Legal counsel is asked to provide a range of options, discuss the limitations of each, and indicate which are preferred.

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

Mr. Nelson reviewed the Subcommittee's charge and membership. He explained that at its most recent meeting, on June 1, SAS reassessed its progress, taking into account the feedback it has received from SACHRP. He noted that recommendations contained in the subcommittee's first letter to the Secretary have been accepted at that level and returned to OHRP for implementation. The second letter is now under consideration.

Examples of Minimal Risk

The subcommittee responded to SACHRP's request for examples illustrating the subcommittee's recommended approach to interpreting the concept of "minimal risk," which was accepted at the last SACHRP meeting. SAS mailed several examples to SACHRP members prior to the meeting for review. Mr. Nelson explained that the subcommittee does not assume OHRP will use any of these examples directly, but it believes the examples illustrate the approved approach and will be useful.

Discussion. SACHRP members raised a few issues related to the examples as follows.

Dr. Genel questioned whether, in Case. No. 3, the higher risk of the three bone marrow biopsies is related to the risk of harm or discomfort. Dr. Strauss said the notion of harm is included. Mr. Nelson reminded SACHRP that regulatory language requires the consideration of the magnitude of harm or discomfort. However, he noted that an IRB might overweight relatively minor discomforts or inconvenience.

Dr. Botkin thought the illustrations were helpful, but questioned the meaning of the error bars. Mr. Nelson explained they represent the "fuzzy line" indicating the spread of reactions throughout a population. Dr. Strauss added that the bars are a reminder that the notion of minimal risk is not quantitative. Dr. Botkin noted that there should not be a bottom boundary to minimal risk; it goes all the way down. Mr. Nelson agreed. Dr. Tilden suggested that the minimal risk threshold be shown as a solid box drawn from the horizontal access up to the top of the "fuzzy" bar.

Dr. Powell wondered whether, in Case No. 2, a healthy subject would face the same concerns regarding a breach of confidentiality as the cocaine-dependent subject. Mr. Nelson said there would clearly be less risk for the person without the substance abuse problem, but the confidentiality measures would apply to all subjects. Dr. Strauss clarified that the study is classified as minimal risk because of the special risk regarding the breach of confidentiality for the cocaine users included as participants. The risk level of the study as a whole, he reminded SACHRP, is only as low as the highest risk for any particular population.

SACHRP accepted the examples with minor changes.

ACTION

Minimal Risk Examples. *Examples were approved unanimously with the following changes:*

- *Error bars in figures will be removed; the threshold for minimal risk will be designated by a solid box to the bottom of the graph, rather than a single horizontal line.*
- *Item 3, p. 3, should read NOT relevant.*

- *The second line of the description of Figure 12 will be corrected to remove the second instance of "this."*

Waiver of Informed Consent

Co-Chairs made a number of proposals related to the waiver of informed consent, which the subcommittee believes is often used inappropriately by IRBs. Obtaining the informed consent of research subjects prior to their participation is traditionally regarded as a cornerstone for the ethical conduct of research and a fundamental protection for participants' rights. However, some valuable research would be difficult, or impossible, to conduct if consent were required, even though subjects can still be adequately protected without the normal consent process. Accordingly, the regulations also allow for waiver or alteration of some or all of the required elements of informed consent, as noted in 45 CFR 46.116(d). The regulations state:

> *An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:*
>
> *(1) The research involves no more than minimal risk to the subjects;*
> *(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;*
> *(3) The research could not practicably be carried out without the waiver or alteration; and*
> *(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.*

The waiver allows the interests of subjects to be balanced with societal interests in research, both of which will be "well served" if this regulatory provision is understood and applied appropriately. In practice, however, IRBs sometimes underuse this important provision or use it inappropriately. Stumbling blocks include uncertainty about how to correctly apply the criteria and inconsistencies in the use of the waiver across IRBs and institutions (a variability that is especially evident when the waiver provisions are applied in research conducted at multiple sites). To date, little guidance has been issued by OHRP to address this problem.

Dr. Strauss wondered if anyone had more information about the intent of the framers in regard to the waiver, especially the stipulation regarding "rights and welfare" of subjects. Dr. Chadwick, a member of the subcommittee, said he understood the intent was to assure that people who participated in research would not later feel they were tricked into participation or that their rights had been violated. Ms. Porter added that the stipulation reflected a particular concern for research that involves deception.

Recommendation 1. Development of Guidance. Mr. Nelson reviewed the subcommittee's first recommendation, which called for the development of guidance on this topic.

> **Recommendation 1.** *OHRP should develop guidance on the implementation of the provisions under HHS regulations at 45 CFR 46.116(d) for IRB approval of a waiver or alteration of informed consent requirements. The guidance should emphasize the following general points:*

- *This part of the regulations is intended to allow IRBs to waive informed consent in its entirety or any of the required elements of informed consent. IRBs should use this provision for considering a waiver of any or all of the elements of informed consent under HHS regulations at 45 CFR 46.116(a).*
- *It is important to remember that IRBs must document that a waiver is being applied and how the criteria for a waiver are being met.*
- *FDA does not have the same criteria for waiver of informed consent that correspond to subpart A. Therefore, if research is subject to FDA jurisdiction, these provisions do not apply.*
- *The OHRP guidance should also incorporate recommendations 2-6 below.*

DISCUSSION

Dr. Tilden asked how the waiver might apply to an initial phase of research in which information about prospective participants is accessed from a data base, after which their consent to participate in research would be sought. Mr. Nelson did not think the use of the waiver in this situation would be universal among IRBs. In this context, Dr. Strauss questioned whether waivers might be used to access information that the subject thought was private, or for which there was a "reasonable expectation" of privacy. Dr. Carome explained that OHRP did issue guidance to the effect that IRBs would ordinarily grant a waiver for activities preparatory to research if certain requirements are met. Clearly, it is not practical to get consent if you have not yet identified the potential subject.

Dr. Strauss suggested that it would be useful to include examples of this type of application in the guidance.

ACTION

Recommendation 1 was approved unanimously without revisions.

Recommendation 2. Interpretation of Minimal Risk. Mr. Nelson explained that the intent of this recommendation is simply to cross-reference the analytic framework previously approved by SACHRP regarding minimal risk (March 29 and 30, 2007).

> **Recommendation 2.** *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(1) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should interpret minimal risk in accordance with SACHRP's recommendations regarding the definition of minimal risk, as approved March 29, 2007.*

ACTION

Recommendation 2 was approved with one abstention without revisions or discussion. .

Recommendation 3. Rights and Welfare of Subjects. Mr. Nelson presented the following recommendation.

> **Recommendation 3.** *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(2) for IRB approval of a waiver or alteration of informed consent requirements, in order to determine whether a waiver of informed consent would adversely affect the rights and welfare of subjects, IRBs should consider the following points:*

- *Whether there are other federal, state, or local laws that provide rights to potential subjects to require informed consent. IRBs should seek advice from their legal counsel when appropriate to help the IRB with these determinations. This would be especially important for state-specific regulations.*
- *Whether the subject population, in general, would consider that their rights were violated if they knew of the waiver, or that the waiver has the potential to cause adverse consequences for their welfare or general well being.*

The Co-Chair explained that the first bullet was intended to address the fact that there could be other statutes pertinent to the waiver of informed consent, and those should not be ignored. This is an area of confusion for many IRBs. The second bullet might be called the "reasonable person" standard; the question is how such a person might respond to learning of the waiver after the fact. For example, if research has been approved in which specimens or data for individuals are used without their consent, would they believe their rights were violated?

Mr. Nelson then presented two scenarios in which a waiver of consent *would* adversely affect the rights of subjects. In the first scenario, this is so because subjects' rights under a Federal law would be violated. The second scenario is one in which the community affected might consider its rights violated.

- The Family Educational Rights and Privacy Act (FERPA; 20 U.S.C. § 1232g; 34 CFR Part 99) is a federal law that protects the privacy of personally identifiable information contained within a student's educational record. FERPA applies to all educational agencies or institutions (K-12 and postsecondary) that receive funds under various programs from the U.S. Department of Education. Except under stated conditions, educational agencies and institutions must have written permission from the student (or parent if the student is a minor) in order to release any personally identifiable information from a student's education record. If an investigator from a local university's college of education requests a waiver of consent to review the educational records of students at the university for the past 20 years and maintain identifiers for a research project, and none of the specified conditions under FERPA apply, the rights granted to students under the federal legislation of FERPA would be violated.

- In some cultures, the placenta has special meaning and significance, so that waiving consent to use placental samples for research might be interpreted by that community as adversely affecting their rights and welfare.

DISCUSSION

Waiver for unconscious subjects. Dr. Strauss presented a case example for discussion:

> A subject is homeless and has no next of kin. He or she lives in a state where there is no such thing as an LAR and is in an intensive care unit. The research, which is minimal risk, involves a blood test and could not practicably carried out in this population with informed consent. Fifty percent of the subjects are also homeless and without available next of kin. Does doing a blood test on an unconscious or comatose patient in an intensive care unit constitute a violation of the subject's rights?

Dr. Strauss suggested that most IRBs would not consider a sample drawn only for research purposes under such circumstances would merit a waiver of consent. However, he could see others coming to a different conclusion. Dr. Shore called attention to the "distributive justice" issue: Why would you select people who are unconscious if you could do the test on a less impaired population? Mr. Nelson hoped that the IRB facing such a decision would look at all four criteria in the aggregate.

Rights and welfare. Regarding the example involving the use of placenta samples in a community that regards them as significant, Dr. Botkin suggested that research that clearly violates community norms should be considered above minimal risk. He found the language regarding "rights" potentially confusing. Mr. Nelson agreed that it is difficult to define rights; as a society, we trust IRBs to be able to ensure that *perceived* rights – as opposed to rights that are legally defined – are not violated. He distinguished rights from welfare by interpreting welfare as associated with physical wellbeing, though he was not sure to what extent this concept was shared in the IRB community. Dr. Botkin then asked how protecting a subject's welfare would differ from protecting the subject from being exposed to more than a minimal risk of harm. He suggested recasting the "rights" issue using language such as, "strongly held community values." Dr. Tilden supported this suggestion. Mr. Nelson countered, however, that the word "rights" is embedded in the regulatory language. Dr. Strauss added that one does not usually think of violating someone's values.

Dr. Tilden observed with approval that the language of the recommendation was consonant with previously approved recommendations relating to Subpart D. He suggested that OHRP consider this recommendation along with those for parents and guardians. He also found it confusing that different terms were used within the same recommendation to describe what might be adversely affected by the waiver (rights, welfare, or general wellbeing).

Dr. Strauss commented that the language and concepts for risk and rights are different. In general, he said, the regulations prefer to talk about potential harm rather than the violation of rights. He noted that invasion of the right to privacy was referenced in the OHRP guidebook, adding that people do care about this right. The reasonable person would probably not only consider whether his or her rights were violated, but also whether they were violated for a good purpose.

Mr. Rodamar commented that an amendment to FERPA, the Protection of People's Rights Amendment (PPRA), allows for "passive consent" in studies dealing with sensitive subjects. He also stressed the importance of making a good faith effort to let the study population know about the effort.

Dr. Shore emphasized the role of the IRB in speaking for potential participants, adding that it should have representatives of the type of population effected by the study. He felt that the concern that someone might one day be upset should not be considered suitable grounds for withholding a waiver. Mr. Nelson agreed that the IRB must be able to speak on behalf of the intended subjects.

ACTION

Recommendation 3 was approved unanimously with underlined revisions as follows.

> **Recommendation 3.** *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(2) for IRB approval of a waiver or alteration of informed consent requirements, in order to determine whether a waiver of informed consent would adversely affect the rights and welfare of subjects, IRBs should consider the following points:*

- *Whether there are other federal, state, or local laws that provide rights to potential subjects to require informed consent. IRBs should seek advice from their legal counsel when appropriate to help the IRB with these determinations. This would be especially important for state-specific regulations.*

- *Whether the subject population, in general, would object if they knew of the waiver and its intent.*

- *Whether the subject population, in general, would consider that the waiver has the potential to cause adverse consequences for their welfare or general well being.*

Recommendation 4. Points to Consider in Determining Practicability. Mr. Nelson noted that the subject is one that has caused a good deal of confusion, so the recommendation is longer than others to ensure the sources of confusion have been adequately addressed. In particular, IRBs struggle to determine when "the research could not practicably be carried out without the waiver or alteration" and in what situations it would apply. Often, IRBs misread this, thinking it applies to situations in which it is not "practicable" to obtain *consent,* as opposed to impracticable to *do the research.*

The Co-Chair observed that some criteria are drawn from "Best Practices for Protecting Privacy in Health Research," published in September, 2005 by the Canadian Institutes of Health Research, which the subcommittee found helpful and relevant. This document may be reviewed or downloaded on the Web at the following location: http://ehip.blogs.com/ehip/files/CIHR_Privacy.pdf. The criteria were subsequently included in a national white paper on tissue banking issues prepared by PRIMR.

Recommendation 4. *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(3) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should consider the following points when determining whether research could not practicably be carried out without the waiver or alteration:*

- *The commonly accepted definitions of the term "practicable" are (a) feasible; (b) capable of being effected, done or put into practice; and (c) that may be practiced or performed; capable of being done or accomplished with available means or resources.*

- *It should be noted that this criterion states that the research could not practicably be carried out without the waiver or alteration. Put another way, it would not be practicable to perform the research (as it has been defined in the protocol by its specific aims and objectives) if consent was required. The emphasis being that it is impracticable to perform the research, and not just impracticable to obtain consent. The following concepts may help an IRB determine whether the research could not be practicably carried out without the waiver of consent.*

(a) Scientific validity would be compromised if consent was required. Examples of this might include the following:

- *The sample size required is so large (e.g., population-based studies, epidemiology trials) that including only those samples/records/data for which consent can be obtained would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.*

- *The subjects for whom records would be reviewed are no longer followed and may be lost to follow-up. For example the proportion of individuals likely to have relocated or died may be a significant percentage of the subject population and the research results may not be meaningful and lose statistical power.*

- *The disclosure of the study purpose as part of the consent process would bias the research subjects so that the results will not be meaningful.*

(b) Ethical concerns would be raised if consent were required. For example:

- *There is a risk of creating additional threats to privacy by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek consent.*

- *There is a risk of inflicting psychological, social or other harm by contacting individuals or families.*

(c) There is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained.

(d) Informed consent should never be waived for convenience, nor waived solely for reasons of cost or speed if doing so dilutes the protection of subjects' rights and welfare.

DISCUSSION

Criterion (d). Dr. Tilden suggested that the concept of practicability includes a cost-benefit ratio; while research would never be waived solely because of concerns related to cost or speed, they would be weighed in the equation. The decision should always be more complex than, "let's save money and not do it that way." Mr. Nelson agreed that cost and speed might be among the factors considered but should not be the only reasons the research is considered impracticable.

Dr. Botkin suggested that this criterion should emphasize cost and convenience, since rights and welfare are addressed elsewhere. He felt it should be tied more closely to the issue of practicability. He proposed a revised version of this criterion that was ultimately approved (see Action, below).

Deception. Dr. Strauss observed that some type of deception occurs in many different types of research (for example, in double-blind studies). He wondered if such cases would be considered waiving consent or an element of the consent process. Mr. Nelson suggested that the degree of deception might be envisioned as a continuum. In double-blind research, the investigator is not withholding any information the investigator has from the subject. The subject understands the concept of the study as part of the consent process.

ACTION:

Recommendation 4 was approved as amended. The original was:

(d) Informed consent should never be waived for convenience, nor waived solely for reasons of cost or speed if doing so dilutes the protection of subjects' rights and welfare.

It was REVISED to read:

(d) Practicability should not be determined solely by considerations of convenience, cost, or speed.

Recommendation 5. Providing Additional Information after Participation. Mr. Nelson continued with the subcommittee's fifth recommendation, which incorporated two common scenarios in which the fourth criterion in the regulations might be applied. He emphasized that the qualifier "when appropriate," used in the first bullet, is intended to convey the fact that not every protocol will require a debriefing.

Recommendation 5. *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(4) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should consider the following points when determining when it would be appropriate for investigators to provide subjects with additional pertinent information after participation when the requirements for informed consent have been waived:*

- *It is important to note that the phrase "when appropriate" in this criterion means that, while the IRB must consider if this applies each time a waiver is reviewed, not all protocols that include an informed consent waiver are required to incorporate a debriefing process.*

- *This criterion is intended to refer to the need to consider debriefing after research is conducted. In these situations it may be ethically required or determined to be respectful to provide the subject with pertinent information after the research is complete. IRBs may want to consider this requirement if:*

  - *a subject is included in research that exposes them to situations or conditions to provoke a response for research purposes, and the situation would not have ordinarily occurred at that point in time (e.g., a debriefing after so-called "deception research" in which some aspects of the study are not fully disclosed upfront); or*

  - *information is obtained during the course of the research that directly impacts on the safety or welfare of the subject (e.g., a retrospective review of medical charts that revealed something of relevance to ongoing care of patients whose records were included).*

Mr. Nelson commented that while the first scenario speaks to human behavior studies, which frequently use deception and which were apparently the primary reason that regulations highlighted the potential need for a debriefing in some circumstances, the second scenario shows a possible application in a clinical care context.

DISCUSSION

Removing data at subject's request. Dr. Powell asked whether patients who have never given informed consent to allow their data to be used in a study can require it to be withdrawn if they later learn of the study and disapprove. Mr. Nelson responded that this would be a rare circumstance. If this issue arose and a patient that his or her personal data to be removed from a completed study, legal counsel might be involved. He noted that communication with the patient in the type of situation described (a finding relevant to their medical care) would be relayed through the patient's caregiver.

Dr. Strauss gave the example of a family genetic study in which a secondary subject, a family member unaware of the study, learns about it because the investigator finds it is important to interview him. The subject then angrily insists on withdrawing all data related to him. Mr. Nelson felt that most Principal Investigators (PIs) would probably comply with such a request.

Ms. Porter observed, however, that under the Health Insurance Portability and Accountability Act (HIPAA), investigators are not required to reanalyze data that has already been published.

Need to consider debriefing. Dr. Strauss focused on the use of the term debriefing, which is generally used in deception research, in the second bullet. He called for a clearer distinction between a face-to-face meeting with the subject that addresses a substantive issue and a simple provision of information, perhaps by mail. He probed the extent to which the criterion is intended to be specific to deception research or open to a variety of situations. He also questioned the wisdom of beginning on a "slippery slope" that raises a variety of questions about researchers' responsibilities to convey incidental findings. He suggested an example in which conveying some aspect of findings was clearly essential to patient health and welfare.

Mr. Nelson suggested replacing "….incorporate a briefing process" with "provide information to subjects after their participation." However, he said the subcommittee did not see debriefing as limited to one communication mode; rather, it was intended to encompass any situation in which information is being provided that was known to the researcher but withheld from the subject up front for the sake of conducting the research. Dr. Straus suggested that all cases in which additional information should be supplied after participation should be enumerated, since there is a lack of understanding about this in the field.

Communicating findings to individuals vs. all participants. Dr. Strauss asked whether debriefings could occur with the group of subjects as a whole. Mr. Nelson saw this process as incidental and patient-specific; however, Dr. Tilden disagreed, giving the example of a retrospective chart review that finds one type of hip replacement is better tolerated and safer than another. All study participants should be informed of the findings. Mr. Nelson, however, still wanted to restrict the guidance to instances in which an incidental finding was of relevance to a single individual.

Dr. Genel pointed to the "wiggle room" offered by the qualifier "when appropriate." He saw the larger issue of when information should be communicated back to subjects as one that SACHRP might want to explore in more depth. Dr. Botkin agreed that the issue is much broader than the subject of waivers. However, he could not think of a good example relevant to biomedical research. Another member questioned whether something seemed to be required when a waiver is used that is not explicitly required under other circumstances.

ACTION

Recommendation 5 was approved unanimously with revisions incorporated and underlined below.

> **Recommendation 5.** *Regarding the criterion under HHS regulations at 45 CFR 46.116(d)(4) for IRB approval of a waiver or alteration of informed consent requirements, IRBs should consider the following points in determining when it would be appropriate for investigators to provide subjects with additional pertinent information after participation in research for which the requirement for informed consent has been waived:*

- *It is important to note that the phrase "whenever appropriate" in this criterion means that, while the IRB must consider if this applies each time a waiver is reviewed, not all protocols which include an informed consent waiver are required to provide additional information to subjects after their participation.*

- *This criterion is intended to refer to the need to consider debriefing after research is conducted. In these situations it may be ethically required or determined to be respectful to provide the subject with pertinent information after the research is complete. IRBs may want to consider this mechanism when subjects are included in so-called "deception research," in which some aspects of the study are not fully disclosed upfront so that subject responses are not biased.*

- *Under most circumstances, this criterion does not apply to retrospective studies conducted under a waiver (e.g., review of existing medical records).*

Recommendation 6. Developing a Flowchart. Mr. Nelson showed SACHRP members an existing decision chart developed by OHRP that many IRBs find helpful in addressing the criteria for a wavier. This recommendation simply asks that OHRP update this useful resource as needed as a result of approved recommendations. However, no revisions may be needed.

> **Recommendation 6.** *IRBs may find it helpful to use a flowchart that summarizes the criteria under HHS regulations at 45 CFR 46.116(d)(4) for IRB approval of a waiver or alteration of informed consent requirements when considering requests for such waivers. OHRP should revise its decision charts to reflect recommendations in this area, as needed.*

ACTION

Recommendation 6 was approved unanimously as presented without further discussion.

Topics for Future Consideration by Subpart A

Mr. Nelson reported that the subcommittee formed working groups in three areas: informed consent, exemptions, and institutional responsibilities. Each working group is addressing a number of key issues.

Informed consent. Among the many areas to be addressed are waivers of documentation, delinking §46.116 and §46.117, use of the short form, use of addenda, readability, overly-complex or long consent documents, liability and consent issues, testing for comprehension, the concerns of subjects, and consent in international settings.

Exemptions. A variety of questions have been identified, including the following.

- The Common Rule preamble suggests that the exemptions apply to research with "little or no" risk. Does this mean less than minimum risk research?

- If confidentiality risks are the most important risk for a given study, how do we assess whether those risks are less than minimum risk?

- Since exempt research is not covered by the regulations, do IRBs still have a responsibility to assure the exempt studies meet basic ethical standards? If so, how should these ethical standards be met, especially regarding informed consent and protection of confidentiality?

- Does designation of exempt status amount to a *carte blanche* approval? Does the IRB have any ethical or administrative responsibilities to make sure the research is carried out properly? What about continuing review? For purposes of IRB recordkeeping, when does the IRB's designation of exempt status lapse?

- Should we encourage the use of exemptions in order to reduce administrative burden? Are IRBs that review exempt research during a convened meeting engaging in regulatory overkill?

- Should each exemption category be viewed and understood on its own merits or interpreted in light of the provisions of other exempt categories?

- Is randomization an allowable procedure under any of the exemptions?

Mr. Nelson observed that differences in interpretation among agencies are a confounding factor and noted that the subcommittee has reached out to Common Rule agencies to get their feedback on these issues.

Institutional responsibilities. The subcommittee includes a variety of topics in this broad umbrella, including assurances, the meaning of engagement in research (a subject OHRP is addressing internally), the responsibilities of institutional officials (a key audience Dr. Schwetz has reached out to), and multi-site studies, including the allocation of responsibilities and why institutions are increasingly "unchecking the box" to exclude themselves from voluntary compliance with the subparts and with the Common Rule except where required by funding. Is this trend good for the research enterprise?

Mr. Nelson told SACHRP the subcommittee expected to return in October with further recommendations on these areas.

DISCUSSION

Dr. Botkin found the proposed agenda interesting but ambitious. He wondered whether the subcommittee had developed a list of priorities it would want to address if SACHRP's charter is not renewed in a year and a half. Mr. Nelson responded that the subcommittee has distilled these priorities from a much longer list and is addressing "low-hanging fruit" wherever possible. He believed the three topic areas outlined can reasonably be addressed using the work group approach in the available time frame. Dr. Gyi added that the subcommittee welcomes SACHRP's guidance on priorities and direction.

PUBLIC COMMENT

Ms. Pollack, the Director of Public Relations for the Association of Psychological Science, highlighted issues faced by anthropologists related to oral vs. written consent. She said that tribal chiefs often lose trust when they are asked to provide written consent. She urged the subcommittee to address oral vs. written consent processes.

Dr. Chadwick objected to references to "consenting someone" in reference to this process. He stressed that individuals give consent. He emphasized that from both ethical and moral perspectives, consent is an individual issue.

Wrap-Up Discussion
Sam Tilden, M.D., J.D., L.L.M.

The Chair thanked subcommittees and SACHRP members for good presentations and discussions. He asked SACHRP members to respond to OHRP regarding the possible meeting dates identified for next year.

TUESDAY, JULY 31

Opening Remarks
Sam Tilden (M.D., J.D., LLM)

Dr. Tilden requested approval for a technical change to the recommendation regarding a summary of legal options to facilitate the work of SIIIDR. The motion to make such an amendment was made and approved unanimously. The final recommendation (p. 7) reflects this change in wording.

Briefing on Final Report of National Conference on IRBs
Bernard Schwetz, D.V.M., Ph.D., Director, Office for Human Resource Protections (OHRP)

Dr. Schwetz reviewed the various ways that OHRP has responded to SACHRP's concern about the need to promote efficient approaches to human subject protection in multi-site trials. This concern was reflected in a minute (October 4-5, 2004) recommending a workshop to gather information on the use of central review mechanisms. With collaborating agencies, OHRP convened such a workshop in 2005, which established the framework for a more recent public conference in the fall of 2006. The final report for the conference, *National Conference on Alternative Models: Optimizing Human Subject Protection*, was distributed to SACHRP members in advance of the meeting (www.aamc.org/research/irbreview/start.htm). Since the conference, NIH has also developed a draft document based on key information related to conference issues called "Points to Consider." The agency plans to place this summary on the Web as well.

Sponsors represented on the planning committee, in addition to OHRP, included the American Association of Medical Colleges (AAMC), the National Institutes of Health (NIH), the American Society of Clinical Oncology (ASCO), and the Department of Veterans Affairs (DVA). The planning committee also consulted with the American Association of Universities (AAU), the Council on Governmental Relations (COGR), the Consortium of Social Science Associations (COSSA), the Department of Defense (DOD), the National Association of Colleges and University Attorneys (NACUA), and Public Responsibility in Medicine and Research (PRIM&R). The latter organizations are considered cosponsors.

Since the conference, the planning committee has continued its efforts to address participants' recommendations and the issues they raised. First, members have considered how to respond for conference participants' request for further guidance from OHRP, the Food and Drug Administration (FDA), and NIH to clarify the responsibilities of the local IRB when an alternative IRB is used. This includes how to structure appropriate agreements. To help avoid each institution having to "reinvent

the wheel," the committee has been actively exploring the idea of developing a toolkit for institutions, IRBs, investigators, and sponsors that would include model agreements, Standard Operating Procedures (SOPs), and best practices. These resources would be available at a Web site anyone could access as needed.

Committee members also considered how to structure future discussions, concluding that a more targeted approach focused on high-priority research areas would be most appropriate. Members are in the process of identifying appropriate target areas and participants.

Another follow-up issue is the need to communicate effectively with sponsors and advocacy groups. Regional meetings sponsored by NIH's Office of Extramural Research have given Dr. Schwetz an opportunity to address many Institutional Officials (IOs), who as a group are interested in IRB models. Planners also want to identify organizations and advocacy groups that represent specific patient populations who might be enrolled in multi-site studies. Dr. Schwetz suggested that a panel of individuals who represent these groups might be planned to inform SACHRP on the models these subjects feel would be appropriate.

Conference attendees expressed interest in empirical research on the various approaches to human subject protection in multi-site studies and recommended that OHRP be given the authority to issue grants to sponsor such research. However, Dr. Schwetz said it is not feasible to add enough staff members to OHRP to make this possible. Instead, the approach will be to encourage and publicize research sponsored by other Federal entities with this authority. For example, more investigators should know about the Clinical and Translational Science Awards (CTSA) offered by NIH.

DISCUSSION

Dr. Tilden endorsed the need for a clear articulation of roles and responsibilities when all or part of a program involving human subject protection is "outsourced." He added that the model agreements currently available do not really address the issues, including problem resolution. He said the regulatory risks of such arrangements are not clear.

Mr. Nelson expressed appreciation for the leadership of Dr. Schwetz and others in addressing these issues. He said he was "disheartened" after the November 2006 conference, however, to see how many perceived barriers to the use of alternative models are rooted not in evidence, but in human inertia or misperception. While the practical steps outlined to address common barriers are useful, he noted that the real barriers are "more in the heart than in the head." Dr. Schwetz agreed; he explained that this is one reason the planning group is stressing the importance of carefully targeted follow-up events with key audiences to encourage movement.

Dr. Botkin sought clarification on the problem that alternative models are designed to solve. Reading the report, he inferred they were primarily designed to address quality management and administrative issues rather than those related to human subject protection. He wondered whether key benchmarks have been identified that would evaluate the success of such initiatives. Dr. Tilden agreed that such benchmarks would be helpful, pointing to the recommendation for research on such issues that emerged from the November conference. Dr. Schwetz said he hoped the CTSA mechanism might be a way of exploring how models are functioning. Dr. Genel added that he recently received a notice of a CTSA Web workshop that will address the feasibility of a Central IRB model to support collaboration among CTSAs.

Dr. Strauss suggested that some basic collaboration and communication among IRBs working on the same protocol might help prepare the ground for more formal agreements. Specifically, he asked:

- What do we know about the extent to which IRBs actually communicate with one another when they're involved jointly in the review of the same research?
- How can communication actually facilitate or speed review, or resolve differences?
- Is this a mechanism to move things in the direction of contractual arrangements, when appropriate?

He also wondered whether OHRP and SACHRP could find ways to foster this type of communication.

Dr. Tilden asked Dr. Schwetz whether OHRP has the capacity to follow up on questions such as those Dr. Strauss posed. Dr. Schwetz said Federal entities could not conduct surveys with more than nine subjects without approval from the Office of Management and Budget (OMB). Mr. Nelson noted that other entities could probe these questions, and in fact a survey being carried out in connection with the National Cancer Institute (NCI) Central IRB project probes similar concerns.

Dr. Tilden suggested that the Subpart A subcommittee review the report on the November conference carefully to see whether it would be appropriate for SACHRP to endorse some or all of the recommended activities. In addition, he looked to the subcommittee to follow up on concerns and suggestions emerging in this discussion. SACHRP members agreed and passed the following motion unanimously.

ACTION

SACHRP requests members of the Subpart A Subcommittee to carefully review the November 2006 report on alternative IRB models, as well as points made about the use of alternative models at this meeting, with a view to developing recommendations for SACHRP review.

Remarks
John Agwunobi, M.D., Assistant Secretary for Health (ASH)

Dr. Agwunobi expressed deep gratitude for Dr. Schwetz's "long and illustrious" career in Federal government and led extended applause. He called on all those present to make sure HHS finds a replacement for him who will carry Dr. Schwetz's standard forward. He stressed the importance of this role, which includes education, communication, vision-setting, collaboration with the research community, and regulatory oversight and guidance to ensure adherence to standards. He explained that the human resource replacement process is slower in the Federal setting than in many others, but that the search will be transparent and open. In the meantime, an Acting Director will be appointed.

He also told SACHRP that Dr. Dorothy Height, who was scheduled to speak at this meeting, has been hospitalized but is now doing well. He praised her insight and experience in minority health issues and urged SACHRP to invite her back at another time.

The ASH reiterated his strong interest in SACHRP's work and urged members to be patient as their recommendations are processed. He explained that his role was to facilitate a dialogue between SACHRP and the Secretary as these recommendations are considered.

DISCUSSION

Dr. Genel asked how SACHRP could be of assistance in the process of selecting an acting and a permanent Director for OHRP. Dr. Agwunobi was uncertain of the rules regarding hires, but he said a panel would be formed to review candidates for the permanent position and it might be possible to identify an expert outside the Department. Through the Chair, he promised to communicate back to SACHRP about how it could appropriately assist in the selection of a qualified replacement for the OHRP Director.

Dr. Genel also inquired about the timing of the official announcement inviting applications for the position of the Director. Dr. Agwunobi said the job description is being redrafted and should be released soon. He suggested that it might be possible for a SACHRP member to review the proposed wording.

In closing, Dr. Agwunobi highlighted issues related to human subject protection when rapid enrollment is needed in emergency situations (such as a hurricane or a terrorist attack) and encouraged SACHRP to address them. He said he and the SACHRP Chair had been discussing the possibility of preparing for such events by providing training or template protocols to IRBs. The chief scientists at NIH and the CDC will be contacting the Chair to discuss ways the time required to initiate research in such circumstances could be shortened, while ensuring protection for the human subjects involved.

Panel on Informed Consent Issues
Howard Dickler, M.D., American Association of Medical Colleges; Gigi McMillan, Executive Director, WeCan Pediatric Brain Tumor Network; Jonathan Moreno, Ph.D., University of Pennsylvania; Alan R. Fleischman, M.D., Ethics Advisor, The National Children's Study, National Institute of Child Health and Human Development (NICHD)

The Chair explained that the purpose of this panel is to educate SACHRP members about some of the more problematic issues regarding the informed consent document and process.

Remarks by Howard Dickler: Creating Informed Consent Documents that are Approachable, Readable, and Brief

Dr. Dickler identifying the following issues related to informed consent documents:

1. *Many informed consent documents fail to include all the elements required by regulation*. One study found less than 10 percent of the sample of IRB consent documents reviewed addressed all regulatory requirements.

2. *Their reading level is generally too high.* Literacy studies show that approximately half the U.S. population cannot read at the eighth grade level, and a study of content forms posted on Medical School Web sites finds their average score reading level is above the tenth grade level.

3. *They are too long.* The longer the documents become – and they have been expanding over time – the less likely they are to be read. Experiments have demonstrated that comprehension is actually inversely related to the length of the form. Further, it creates distrust, since participants wonder why the form must be so much longer than the oral briefing.

Fortunately, work on simplifying informed consent documents is underway. A May 30 meeting sponsored by the AAMC invited presentations by three groups working to improve content forms. Dr. Dickler briefly reviewed highlights of these presentations.

- The Children's Oncology Group has created templates for informed consent documents that use simplified language and focus the consent form on the research question, placing related material in the appendix. The experiment demonstrated that it is preferably to develop forms using a group of experienced consent writers.

- The Agency for Healthcare Research and Quality (AHRQ) has developed an Informed Consent and Authorization Toolkit that makes effective use of formatting and highlighting. The toolkit also includes a "teach-back" component that trains the person doing the Informed Consent process to elicit questions from the prospective subject. It also includes a form that helps the investigator remember to cover all required aspects of the process.

- A commercial IRB has created a one-page consent form covering simple procedures research. The wording is concise and grouped under cohesive headings.

Although such efforts illustrate what can be done, there are a number of obstacles to reform, including the dearth of communication among institutions and IRBs, the lack of positive guidance and templates, inertia, lack of funding, the difficulty of writing more understandable forms, and the lack of incentive for change.

The panel assembled by the AAMC agreed that it would be helpful to treat informed consent as a process (not a document) consisting of three parts:

- ***Part A: Informed Consent.*** This is the informed consent document itself. It is limited to the research question and the essential elements of the consent process. Part A is presented in concise, easy language and format.

- ***Part B: Supplemental Information***. This section contains supplemental information – everything else the participant might want or need.

- ***Part C: Verification/Certification***. This could include "teach back" or testing, as well as certification that the entire process was carried out.

The AAMC has formed a working group to develop model templates for research of differing levels of complexity and risk. OHRP has agreed to review these templates to ensure consistency with the regulations and to endorse them if they are found to be consistent. A Web site is envisioned that will help IRBs access tools and information to help them improve informed consent documents.

The speaker encouraged SACHRP to engage in the change process by doing the following:

- Support positive, proactive action by OHRP, FDA, and NIH in the form of guidance and approved templates, best practices, and toolkits.
- Support funding to establish and maintain a Web site to distribute the above materials.
- Support funding for a pilot project to implement the change at two to four pioneer institutions.

Remarks by Jonathan Moreno: Theoretical Issues and Concerns in the Informed Consent Process and Form

Dr. Moreno highlighted areas of historical controversy related to informed consent. For example, some feel that doctors engaged in investigations will "do the right thing" without laws governing their behavior (and that those that *won't* act ethically are not likely to be bound by the law). Doctors themselves have been less than enthusiastic about informed consent procedures, in part because of the difficulty in many cases of distinguishing between standard practice and what may be considered innovative or experimental. Dr. Moreno also pointed out that the Hippocratic Oath emphasizes the obligation of the doctor to promote the patient's best interest, not necessarily to communicate all the details of the physician's proposed approach.

Persistent attempts to limit the discretion of physicians in studies have been made only within the past century (though even in medieval Europe, some doctors were taken to court for doing experiments without the consent of –at least – the medical faculty). Secret plutonium injections occurred in many U.S. hospitals as part of the Manhattan Project, an experiment that reflected scientists' concern about their graduate students' exposure to plutonium. After the war, the Atomic Energy Commission (AEC) required their physician investigators to follow new rules. These rules contain the first known use of the term "informed consent." Infamous experiments by Nazis also highlighted the issue of the subject's right to consent, and the word "experiment" itself fell into disrepute as a result ("trial" is now preferred). The Nuremberg Code stated, "The voluntary consent of the human subject is absolutely essential" (1947).

For a variety of reasons, including greater societal investment in research, issues such as informed consent are now more widely scrutinized and discussed. Continuing concerns include:

- What counts as adequate consent?
- What are indicators of capacity or lack of capacity to consent?
- How much can/should subjects comprehend?
- Is hope compatible with voluntary consent?
- When should the consent process be repeated?
- What risk-benefit ratios are unacceptable regardless of consent?
- Who do consent forms really serve?
- What is the desired level of literacy and numeracy?
- Who should control the content?

The speaker said he hears, with increasing frequency, the expressed concern that the "bioethics revolution" has overvalued informed consent *forms* and paid too little attention to the *process*, including the clear communication of risks and benefits.

Remarks by Gigi McMillan: The Perspective of Subjects and their Families

As Executive Director of the "We Can" Pediatric Brain Tumor Network, Ms. McMillan has heard the perspective of many families trying to decide whether or not to enroll their children in specific trials. She shared her observations of common issues for these families:

- Many hear about the trials when they are so overwhelmed and emotional they cannot absorb the information, although they want to understand and make the right decision. They feel at a great disadvantage.

- Most are medically uninformed and lack both the vocabulary and concepts they need to understand clinical trials. It is much like entering a foreign country, not knowing the map and unable to understand the road signs. They often lose confidence and feel demoralized in the face of "experts" who know more than they do.

- Many family members have read frightening stories about experiments, yet a trusted doctor may be recommending participation; they may be confused.

- While family members want to ask questions, they fear repeating themselves and looking stupid – and they don't know the right questions to ask. As a result, subjects rarely understand their basic rights, what kind of information should be available to them, or what kind of relationship with the study team they should have during the life of the study.

Ms. McMillan stressed that during the consent process and the life of the study, the family's "personal journey" is more important than the research. Their relationships with the research team are part of a network of relationships that may be increasingly stressed. As the trial continues, neighbors and relatives usually offer less support than they did in the initial crisis phase. These changes in the support available to families affect their study participation and their ability to keep commitments generally.

Families relate to the consent process and form in different ways. To some, the consent form is not very important; what matters is the oral discussion with the doctor. Others are just the opposite, going through the form line by line. Some put it in a drawer and never look at it again once it is signed, while others take it with them to every clinical visit. In almost all cases, however, families come to feel they failed to ask the right questions because they lacked the knowledge they needed to know what questions to ask.

Ms. McMillan made the following suggestions to improve the consent process:

- It would be helpful to have an "up front" description of the subject's role.
- The type of three-part format Dr. Dickler described would be well received by the families Ms. McMillan has worked with.
- A "checklist" that helps subjects focus on the right questions as they go through the consent process and test themselves afterward would be useful.
- Many subjects would like a chance to "reconsent" once they understand the study and are better able to process the issues involved.
- Peer mentors – people who have been through similar situations – would be very helpful to families as they educate themselves and learn to ask questions.

The speaker also stressed the importance of education for potential and current subjects:

- High school health classes should include the basic vocabulary and tenets of clinical research.
- Age-appropriate tools to help different family members understand the disease are very helpful.
- When tools are developed, it is important to realize that different levels of information are needed at different points in the learning process. Once the facts are understood and grasped at the simplest level, more complex information can be digested.

Finally, Ms. McMillan explained that subjects rarely receive the information they want when they *leave* the study. They would like exit interviews that explain any consequences of the study for long-term care and tell them how they can learn study results. In addition, any findings related to adverse consequences of the intervention should be relayed promptly.

Remarks by Alan R. Fleischman: The National Children's Study – A Bold Approach to Informed Consent

Dr. Fleischman presented the approach taken by the National Children's Study to the issue of informed consent. He noted that the study, which explores broadly-defined environmental factors that may affect health, is the "largest and most ambitious long-term study of child health and development ever to be conducted in the U.S." Rather than use a central IRB, the study has chosen to use an innovative "e-consent" process that involves showing a video, with research staff available to answer questions. All required elements of the consent process are included.

The process includes steps that confirm that essential elements have been understood. Planners believe that such an approach can improve understanding, inclusiveness, transparency, and standardization. *Understanding* should be enhanced by the use of illustrative visuals, easy- to-understand colloquial speech, and procedures to assess understanding of essential elements. Dr. Fleischman asserted that such a process would improve *inclusiveness* by picturing people from diverse ethnic groups, socio-economic classes, and regions of the country. It would improve *transparency* by making it clear exactly how the study was explained during the informed consent encounter. Finally, it would enhance the goal of *standardization* by ensuring that everyone has the same things explained to them and in the same manner.

Dr. Fleischman demonstrated the interactive video, which is designed to allow replays, adjustable volume for the hearing impaired, optional captions, and exit and re-entry as needed. An electronic signature is possible to indicate consent.

Researchers plan to compare the e-consent process to consent obtained through the type of written document that would have been done ordinarily for such a study. It is possible that continuity and retention will *increase* as a result of the e-consent process; however, some researchers are concerned that enrollment will actually *decrease* when people do really understand the consequences of participation. The study of the process will compare the two groups – those using the e-consent process with those using a process with a written informed consent document – and determine:

- Differential understanding and retention of information,
- Differential respondent rating of materials (e.g. engaging, appropriate, helpful, clear),
- Differential enrollment in the study, and
- Differential attrition rate.

DISCUSSION

SACHRP members were given an opportunity to ask questions of panel members. Key discussion points included the following.

Local site participation in NCS. Mr. Nelson asked Dr. Fleischman about plans to handle requests from local IRBs to modify the review process. Dr. Fleischman responded that pilot centers were involved in video development and a group of IRB liaisons has also worked on the process. In addition, IRBs can add information to the video using built-in "hooks" if they insist. The real difficulties will come if sites differ with core principles of the study.

Addressing legal concerns. Dr. Powell observed that pharmaceutical companies that want to shorten the consent form are often stymied by the concerns of the legal staff. Dr. Dickler readily agreed that industry consent forms would be the "toughest nut to crack." The game plan for change calls for starting with pilots at academic centers. However, he doubted that a longer form really accomplishes any purpose other than intimidation.

Participant advocates. Dr. Botkin asked for Ms. McMillan's comments on the role of participant advocates, who mediate between clinicians and potential participants. She said that well-trained advocates would be extremely helpful. Dr. Schwetz later suggested a distinction between the roles of research advocate and subject advocate, noting that research advocates typically advocate for the research, while a subject advocate focuses on helping the subject make a decision. He noted that the General Clinic Research Center (GCRC) requires the use of a research subject advocate, which is

intended to be a hybrid between the two. In practice, however, the Director understands that they interact very little with the subjects themselves, although they do other work intended to benefit subjects. He asked Ms. McMillan to clarify the nature of the need she was describing. Ms. McMillan explained that it is helpful to subjects to interact with someone who has been in the same place they are standing in; it relieves some of the sense of isolation. Such an individual can be a "lay mentor" and, as a "barometer" sensitive to the subjects' needs, ensure that family members find the right tools to help them make the difficult decisions they are facing.

Communication with subjects. Dr. Genel reflected that it is hard to convey the information subjects really need to make a decision in precise scientific terms. The final question he is asked is often, "Doctor, if this were your child…". Ms. McMillan agreed, adding that the consent document cannot solve this problem. It is best to be honest with the subject and admit that there are unknowns.

Dr. Genel also strongly endorsed the need for follow-up on the results of research studies. Unfortunately, though, there are no incentives that would encourage this step.

Dr. Strauss emphasized the need for more information about what kind of information is really wanted and used by subjects. He added that subjects differ in the level of information they want and their expectations of the research team. Many want help in making the choice. He wondered, "How do we best educate investigators and research staff as to how to go about discussing the choice to participate in a research study with research subjects?"

Dr. Moreno observed that many people learn to be clinical investigators from research nurses. It is important to make sure the skills needed to administer an effective informed consent process are part of the process of preparing researchers. Dr. Moreno suggested that certification of clinical investigators would help ensure they have needed skills. Dr. Dickler commented that AAMC has sponsored a task force on the subject of how clinical investigators should be trained.

Curriculum for high school students. Dr. Fleischman informed SACHRP that the Office of the Director of NIH, with the help of the Bioethics Division of the Clinical Center, is working on the development of a broad-based bioethics curriculum for high school students that will address issues related to research and the consent process.

Informed consent writing group. Dr. Dickler re-emphasized the utility of a writing group at each institution with the training needed to write consistent, readable informed consent documents. Dr. Strauss agreed and hoped someone would do a cost-benefit analysis showing that it would be cost effective for institutions to take this approach.

Cost and resources. Dr. Powe raised the question of essential resources to improve the informed consent process and their costs. He noted that a video such as the one prepared by the NCS would be prohibitively costly for most studies. Training, too, is expensive. He asked who should bear the cost of improvements. Ms. McMillan suggested that some bodies of information could be produced in advance and shared – for example, materials that explain clinical trials. Dr. Fleischman added that some videos can be generalized, while others are study-specific. The NIH program on Clinical Research Policy Analysis and Coordination is developing Web-based tools that include samples of informed consent documents; these are intended to become community resources. Dr. Dickler suggested, as a former Dean, that doing informed consent documents by committee would ultimately save hundreds of thousands of dollars annually.

Panel on Diversity in Clinical Trials
Giselle Corbie-Smith, M.D., Associate Professor of Social Medicine and Medicine, University of North Carolina/Chapel Hill (Moderator); Vivian W. Pinn, M.D., Director and Associate Director for Research on Women's Health, National Institutes of Health; Barbara Pence, MD., Texas Tech University, Health Science Center, and team Leader, EDICT Project; Leonard Sacks, M.D., Office of Critical Path Programs, Office of the Commissioner, Food and Drug Administration

This panel was invited to explore these questions:

- How well do clinical trials and other research studies involving human subjects represent the population whom the research is intended to serve?

- What can we learn from the experience of NIH, FDA, and others about the diversity of subjects in clinical trials?

- Are additional steps needed to further enhance the racial and ethnic diversity of subjects in human research? If so, what additional steps should be considered?

Remarks by Giselle Corbie-Smith: Diversity in Clinical Research – Ethical and Practical Considerations

Dr. Corbie-Smith noted that since the AIDS epidemic, in which AIDS victims campaigned to gain admission to clinical studies, the view of participation in clinical research has changed: rather than a risky burden, it is more commonly viewed as a prized benefit from which no one should excluded. Minority inclusion is an issue, she argued, because the participation of racial and ethnic minorities in clinical trials is critical to understand and eliminate racial and ethnic health disparities, to better understand disparities in health, and to ensure that research findings can be generalized. In 1993, the NIH Revitalization Act mandated the inclusion of minorities and women in clinical research. This mandate has highlighted numerous issues related to diversity, including how people engaged in research should be asked to identify themselves so they can be counted.

Key questions related to diversity in clinical research include the following:

- What is "race"?
  - Is it an appropriate variable?
  - Should we collect data on race? How should this be done?
  - What are the implications for understanding differences in health?
  - Should we continue to use racial classification to assess the role and consequences of "race"?
- What are the consequences of single race clinical trials?
- What is "appropriate representation" of racial/ethnic minorities and women?
- Do we need to re-examine the application of ethical principles in communities of color?
- What obligations do investigators have if they recruit underserved groups?

Issues related to diversity are complicated by the long-standing debate as to whether race is a biological or social construct. Some argue that overemphasis on race obscures other determinants of health that contribute to differentials; they also worry that it will reify race as a biological construct. In addition, it is difficult to be clear exactly what is being measured when data on race are collected. Advances in genetic research, which attribute some differences in health to genetic markers, add

complexity to the issue. The first race-specific drug has just been approved by the FDA; it may well be a forerunner for a variety of pharmacogenetics research to follow.

The speaker suggested three possible goals related to the inclusion of minorities in research:

- Goal 1: to test hypotheses about possible differences by race or ethnicity.
- Goal 2: to generate hypotheses about possible differences by race or ethnicity.
- Goal 3: to ensure just and equitable distribution of risks and benefits.

She suggested that investigators be explicit about which of these goals is pertinent to proposed research.

Finally, Dr. Corbie-Smith observed that when minorities from communities that lack economic and political power are included as subjects, the concept of "respect for persons" must be applied with particular care. It is especially important to consider all the ways in which subjects may be vulnerable as informed consent is operationalized. Often, she said, minority participants and their community representatives see the risks and benefits of research through a distinctive, culturally-influenced lens that should be taken into account. She cautioned that an overemphasis on genetics could divert attention from the social, economic, and political issues that lead to health disparities.

Remarks by Vivian W. Pinn: NIH Policy on the Recruitment and Retention of Women and Minorities as Subjects in Clinical Research

Dr. Pinn reviewed NIH's steps to ensure that women and minorities are included as research subjects. She explained that the attention to inclusion in clinical research at NIH was fostered by the women's movement and specifically encouraged by a Public Health Service Committee on Women's Health Issues established by the Assistant Secretary of Health in the mid-1980s. NIH's 1987 Guide to Grants and Contracts urged the inclusion of women as subjects in studies. Later in the same year, the policy was expanded to urge the inclusion of minorities as well. In June 1990, the Congressional Caucus on Women's Issues requested an audit by the General Accounting Office (GAO) to determine whether or not women were being included in studies. As a result of Congressional concerns, the agency established an office focused on women's health issues, which is intended to assure Congress and advocacy communities that women are included. (See http://orwh.od.nih.gov/inclusion.html.)

> It is the policy of NIH that women and members of minority groups … must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes…that inclusion is inappropriate with respect to the health of the subjects or the purposes of the research…
>
> *Federal Register* (March, 1994)

Since 1993, the NIH Revitalization Act has required women, minorities, and subpopulations to be included in studies in a way that facilitates a "valid analysis" of salient differences by gender and minority status. The intent is, in part, to ensure that the benefits of government-sponsored research are available to all members of the public. Specifically, the law requires NIH to:

- Ensure that women and members of minority groups and their subpopulations are included in all human subject research;

- For Phase III clinical trials, ensure that women and minorities and their subpopulations are included such that valid analysis of differences in intervention effect can be accomplished;

- Not allow cost as an acceptable reason for excluding these groups; and

- Initiate programs and support for outreach efforts to recruit these groups into clinical studies.

NIH instructions for developing the section of grant applications on the inclusion of women and minorities (PHS 398 and SF 424) require the applicant to state the following:

- Subject selection criteria and rationale,
- The rationale for any exclusions,
- The enrollment dates (start and end),
- Outreach plans for recruitment, and
- The proposed composition.

Applicants are required to meet these criteria in order to receive funding. To help applicants do so, NIH developed the Principal Investigators' *Outreach Notebook for the Inclusion, Recruitment, and Retention of Women and Minority Subjects in Clinical Research.* The notebook is available at the following address: http://orwh.od.nih.gov/inclusion/outreach.pdf. It includes a review of NIH's inclusion policy, guidance on outreach for women and minorities, human subject protections and inclusion issues, and frequently asked questions about the implementation of NIH's policy on inclusion.

The NIH Tracking and Inclusion Committee monitors adherence to the NIH policy on inclusion and issues periodic reports, the most recent of which tracks research as reported in Fiscal Years 2005 and 2006 (See http://orwh.od.nih.gov/inclusion/2007acr-5-2-07.pdf .) Dr. Penn cautioned that these reports rely on the individual's self-identification for race, ethnicity, and gender; analyses are also complicated by the 1997 changes in reporting requirements for OMB that affect data comparability across years.

Nevertheless, despite these limitations, some findings and trends are apparent. First, the involvement of women and minorities in NIH clinical trials has indeed been increasing over time. Overall, NIH now has more women than men engaged in NIH-sponsored studies (about 64 percent of subjects enrolled in aggregate extramural and intramural research are female). However, this includes many studies that focus specifically on women's health issues. Also, in the aggregate, about 43 percent of subjects are classified as U.S. minorities. The smallest and most poorly represented group includes Alaskan natives and Native Hawaiians.

A 2001 NIH Task Force sponsored by the NIH Office of Research on Women's Health issued a report highlighted by the speaker: *Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Clinical Role of Relevance*. A copy of this report, as well as additional relevant publications, may be requested from: http://137.187.172.239/request_pub3.asp

Finally, the speaker highlighted a self-paced, CME-eligible course on the science of sex and gender in human health – jointly developed by NIH and FDA – that is available at the following Web site: http://sexandgendercourse.od.nih.gov/index.aspx. The course seeks to convey a basic scientific

understanding of the major physiological sex differences; the influence of these differences on health; and the policy, research, and health care implications of these differences.

Remarks by Leonard Sacks: Racial and Ethnic Diversity in Clinical Trials (FDA)

Dr. Sacks focused his remarks on registrational trials for drug products at FDA, a small subset of the full spectrum of clinical trials. Ideally, he said, clinical trials would be very large and ensure that all subgroups are well represented, allowing the detection of rare adverse events (AEs) and enabling doses to be customized for each subgroup. In the "real world," however, participation is influenced by a variety of factors. For example, trials are performed in communities where the disease is easiest to study (examples include immunosuppressive drugs in transplant centers or anti-malarial drugs in Africa). Participation in clinical trials is a voluntary process, influenced by culture, education, convenience, personal beliefs and suspicions; it cannot be forced. As a result, it is seldom possible to include adequate numbers of all subgroups to achieve statistically significant results by every subgroup.

However, the speaker stressed the importance of recognizing the importance of ethnic and racial information when data are reported. FDA does assess the adequacy of information on race and ethnicity based on the specific application or drug. Factors to be considered in this assessment include the population who will use the drug, the likely differences in drug-metabolic pathways, and the likely differences in racial cofactors (for example, differences in nutrition or presence of other diseases). Upon review, if a racial concern is identified that has not been adequately addressed, the drug may not be approved. Of course, systematic exclusion of certain racial groups would undoubtedly raise concern and might also result in nonapproval.

The speaker stressed that genes that determine skin color and facial features are *not* those that determine different responses to drugs. In racial terms, he said, we are more similar than different. Further, definitions of racial differences are often social ones that are not meaningful from a medical standpoint. However, differences in breeding among groups result in certain genes occurring with different frequencies. These variations are not related to racial characteristics per se, but because they do exist, it makes sense to study drug response in whatever groups are most likely to be taking the drug, using scientific principles as the basis for selection.

The speaker argued that important racial differences should be considered on a case-by-case basis. First, the new drug should be characterized in the test tube and in animals to determine its receptors, targets, and mechanisms of action. Researchers must determine how it is metabolized, distributed, and excreted. These findings may point to race-specific concerns to be explored. For example, drugs metabolized by CYP 2D6, a gene known to be associated with different responses to drugs, would be of concern. Drugs likely to affect patients with abnormalities that are common in certain racial or ethnic groups may also raise race-specific concerns (for example, sickle cell anemia, G6PD deficiency, and porphyria). In exploring such differences, genomics offers a promising tool.

Other medically important subgroups of patients have a much more serious impact on drug responses. Especially important are gender-related considerations (hormones, pregnancy, types of diseases, body fat, the presence of menstruation) and those related to age (renal and hepatic maturity, immunological responses, and hematological responses). One cautionary example is thalidomide, which was perfectly safe for men but disastrous when prescribed for pregnant women. Another is aspirin, which is safe in adults but may cause Reye's syndrome in children.

Considerations in determining how many subjects are needed in specific subgroups are based on these differences. For example:

- Safety: If a gene of concern is present at a low frequency in one racial group and absent in another, it would be best to enroll most study participants from the racial group with the gene of concern.

- If a condition is more prevalent in one racial group, it makes sense to study the drug in that group.

- If a given disease manifests differently in different racial groups, the study of a drug for that disease should be powered to reflect efficacy in each racial group.

In conclusion, Dr. Sacks stressed the following points:

- The overarching societal goal is the availability of safe and effective medical products for all who need them.

- Race and ethnicity should be addressed in a practical way, employing emerging technology, that promotes efficient drug development and obtaining pertinent information about subgroups.

- Scientific principles should be used to optimize the study of racial/ethnic concerns in drug development.

- Modern tools (e.g. genomics) should be used to expedite study of drugs in different populations.

Remarks by Barbara Pence: EDICT – Eliminating Disparities in Clinical Trials

Dr. Pence summarized the EDICT project, a 4-year collaboration between the Baylor College of Medicine (BCM) and the Intercultural Cancer Council (http://www.bcm.edu/edict/home.html). The project is designed to improve the participation of minority and underserved populations (such as rural persons) in clinical trials.

The policy research arm of the study has been designed to increase knowledge of the processes involved in developing and implementing health policy that affect what the speaker called the cycle of "the Three R's**":** Recruitment (active recruitment and access), Retention (keeping participants satisfied and "on protocol,") and Return (giving back to participant populations by providing information on the safety and efficacy of drugs for their subgroup).

The EDICT program emphasizes the importance of policy development. Specific objectives of the policy research component include:

1. To assess policy issues related to underrepresented populations participation in clinical trials,
2. To organize and conduct a National Policy Development Summit Meeting, and
3. To conduct dissemination activities involving policy education and advocacy relating to minority or under-represented populations' participation in clinical trials.

Dr. Pence stressed that current literature shows a significant under-representation of minorities, elderly persons, and underserved participants in clinical research. She argued that minorities are willing participants but are approached less frequently than other groups.

The project includes the development of National Standards for Culturally and Linguistically Appropriate Services and Clinical Trials (CLAS-ACT). It also seeks to identify existing evidence-based and promising practices to help eliminate disparities in clinical trials. The speaker reported that a field demonstration is in progress to test the effect of various interventions on the accrual and retention rates for members of underrepresented populations in specific trials. Baylor College will be involved in testing ideas and best practices, as well as in developing appropriate tools to support differential recruitment.

Dr. Pence stressed the importance of a culture change that would lead to holding both investigators and sponsors responsible for equitable inclusion. Policies and regulations related to inclusion should be bolstered by oversight and enforcement. She said research design should not only actively address issues of literacy, language, and socioeconomic barriers to enrollment, but also formulate differential plans for retaining minority participants in clinical trials.

DISCUSSION

Members probed the rationale for involving subpopulations in studies. While Dr. Sacks noted that ethnic differences are seldom relevant in drug trials, Dr. Giselle and Dr. Corbie-Smith saw inclusion as an issue of distributive justice. For Dr. Pence, both medical and social justice issues could be viewed as drivers. A member observed that if diverse populations are not adequately studied, differences that do exist may not be recognized. Another noted that patients may well ask a doctor to "show me that this works on people like me."

Other concerns and issues raised by members included the following:

- As a matter of policy, does it make sense to promote diversity in all studies all the time?
- What is the implication of diversity requirements for recruitment costs?
- What can be learned from NIH data on minority enrollment – for example, differences between targeted and actual enrollment?
- What is the role of the IRB in ensuring that subpopulations are appropriately included in the studies they review?

PUBLIC COMMENT

Armand Whiteburg, Principal Investigator for EDICT, highlighted the need for more research to identify and explore differences among subjects. He also underlined the important role of the IRB in ensuring that research is explained in ways that are accessible and understandable to a variety of groups.

Dr. Michelle Rollins of the Office of Minority Health expressed the hope that offices throughout HHS would continue to explore issues related to diversity.

Wrap-Up
Sam Tilden, M.D., J.D., L.L.M.

Dr. Tilden highlighted the major issues of access and communication. He suggested that IRBs become aware of the prevalence of diseases in their community and the populations affected. As

study enrollment data become available, IRBs should be alert for access issues that might affect members of these populations.

Secretary's Advisory Committee on Human Research Protections
July 30 and 31, 2007
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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Sam Tilden, M.D., J.D., L.L.M., Chair **Date**