Secretary's Advisory Committee on Human Research Protections
March 29 and 30, 2007 – Arlington, Virginia

Minutes

THURSDAY, MARCH 29

Welcome and Opening Remarks
Sam Tilden, M.D., J.D., L.L.M.

Dr. Tilden informed the committee he will be acting as Chairman for the foreseeable future. He thanked the Office for Human Research Protections (OHRP) and the Department of Health and Human Services (HHS) for selecting him for this role. He introduced three new SACHRP members: Lisa I. Leiden, Ph.D., CIP; Patricia Marshall, Ph.D.; and Davis Strauss, M.D. The Chair then reviewed the agenda.

Minutes for the previous meeting (November 2 and 3, 2006) were approved unanimously.

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

The Director congratulated and thanked new SACHRP members. He also congratulated Dr. Powe, who has been honored as the 2007 distinguished educator by the National Association of Clinical Research Training. Dr. Schwetz then provided updates on activities of concern to SACHRP.

Dr. Schwetz reported on the progress of SACHRP recommendations through the HHS review process. He explained that Dr. Kevin Prohaska leads OHRP's response to recommendations related to Subpart D, and Julia Gorey is the lead for recommendations related to prisoners as research subjects, including those of the Institute of Medicine (IOM) as well as the recommendations of a previous SACHRP subcommittee.

- The Assistant Secretary for Health has been briefed on IOM's recommendations regarding prisoners, and OHRP has requested and received input on them from other Federal agencies and departments under the Common Rule.

- SACHRP's recommendations on the Health Insurance Portability and Accountability Act (HIPAA) have been forwarded to the Office of Civil Rights (OCR) for review and action.

- The first set of recommendations related to Subpart A has been forwarded to the Secretary, and OHRP is awaiting guidance from the Secretary's office on the desired response.

- SACHRP recommended that FDA and OHRP develop guidance on adverse event reporting. OHRP has now issued final guidance, which has been posted on its Web site. FDA is working on its guidance.

The Director also told SACHRP that draft Guidance on the Engagement of Institutions in Human Subject Research has been posted for public comment, and OHRP is in the process of reviewing comments received with a view to possible revisions.

OHRP has sponsored several recent educational initiatives and conferences:

- A regional training conference was held at Baylor University in Dallas, Texas last January, and a second is planned for June 22 in Pittsburgh, Pennsylvania.

- OHRP is working with HHS's Regional Office in Denver, Colorado, to develop a workshop on research issues related to Native Americans. It will be held August 22-23. A variety of stakeholders are expected to attend.

- Shirley Hicks, the Director of OHRP's Division of Education, has overseen four quality assurance workshops for less experienced members of the IRB community to familiarize them with the subtleties of regulations and help them write Standard Operating Procedures (SOPs).

- Ms. Hicks is also considering how to reach out to FWA-holding institutions that do not have an IRB.

- Efforts to reach out to Institutional Officials (IOs) continue to have momentum and are being well received.

Swearing in of New Members

The following new members were welcomed and sworn in by Ms. Deborah Wise of HHS: Lisa I. Leiden, Ph.D., CIP; Patricia Marshall, Ph.D.; and David Strauss, M.D.

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

Mr. Nelson reviewed the subcommittee's charge and briefly reviewed its accomplishments to date. The subcommittee has developed twenty recommendations on continuing and expedited review that have been approved by SACHRP and have been submitted to the Secretary. Mr. Nelson expressed concern that Institutional Review Boards (IRBs) spend too much of their time on processes that have little to do with actually protecting human subjects. The Co-Chair stressed the importance of striking a balance between regulations and guidance that leave too much to the imagination and those that are over restrictive.

Recent meetings of the subcommittee included a retreat in February to "think globally" and identify priorities, followed by a teleconference in March. Dr. Strauss, who will co-chair the new subcommittee on persons with decisional impairments and is now a SACHRP member, has resigned from this subcommittee. New members include Ricky Bluthenthal of the RAND Corporation and Ernest Prentice, formerly the SACHRP Chair.

Training and Education

Co-Chairs reviewed pertinent requirements and guidance related to education and training.

> *The IRB shall be sufficiently qualified through the experience and expertise of its members… to promote respect for its advice and counsel… In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice…"(45 CFR §46.107).*

Related citations include the following:

- Item 11 of the OHRP Terms of Assurance "strongly recommends" that the institutional signatory official (IO), the human protection administrator, and the IRB Chair complete relevant OHRP assurance training modules or comparable training before the Federal Wide Assurance (FWA) is submitted.

- Item 12 of the Terms of Assurance "strongly recommends" that the institution and designated IRBs establish "educational training and oversight mechanisms appropriate to the nature and volume of its research…". It also recommends that IRB members and staff complete relevant training before reviewing human subjects research and that investigators have training before conducting it.

- OHRP Frequently Asked Questions (FAQ) include a specific recommendation that investigators are knowledgeable about "relevant ethical principles, relevant federal regulations, written IRB procedures, OHRP Guidance, other applicable guidance, state and local laws, and institutional policies."

Mr. Nelson pointed out that OHRP has sometimes cited institutions for failure to provide adequate training, underlining its importance. Last December, OHRP published a Notice of Proposed Rulemaking in the *Federal Register* indicating its intention to develop a Subpart E to the Common Rule focused specifically on training and education.

The Co-Chair presented a series of recommendations regarding training and education. As originally presented, they were as follows:

Recommendation 1. *SACHRP strongly recommends that OHRP require that institutions provide initial and continuing training for IRB members. Such training should include relevant ethical principles, such as the Belmont Report, Nuremberg Code, Declaration of Helsinki, relevant federal regulations, written IRB procedures, OHRP Guidance, other applicable guidance, state and local laws, and institutional policies for the protection of human subjects. Training should be initiated before members review human subjects research and IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB members.*

Recommendation 2. *SACHRP strongly recommends that OHRP require that institutions provide initial and continuing training for IRB staff. Such training should include relevant ethical principles, relevant federal regulations, written IRB procedures, OHRP guidance, other applicable guidance, state and local laws, and institutional policies for the protection of human subjects. IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB staff.*

Recommendation 3. *SACHRP strongly recommends that OHRP require that institutions provide initial and continuing training for the institutional signatory official and the human protection administrator as identified in the FWA; for example, the human subjects administrator or the human subjects contact person. Such training should include relevant ethical principles, federal regulations, institutional policies for the protection of human subjects and the terms of the institutions' federal assurance. Ongoing training should occur in a manner appropriate to assure the continued competence of these institutional officials.*

Recommendation 4. *SACHRP strongly recommends that OHRP require that institutions provide initial and continuing training for investigators. Such training should include relevant ethical principles, relevant federal regulations, and institutional policies for the protection of human subjects. Initial training should be completed before investigators are allowed to conduct research that involves human subjects. Ongoing training should occur in a manner appropriate to assure the continued competence of investigators.*

DISCUSSION

SACHRP members raised the following questions and issues regarding the four recommendations.

Research Team Members in Need of Training. Dr. Botkin asked what members of the research team would be included as "investigators" (Recommendation 4). Mr. Nelson responded that the subcommittee grappled with this and decided not to be prescriptive. He observed that most institutions have extended their concept of key research personnel to include members of the team who play such roles as getting consent from subjects. Dr. Leiden said that faculty make this decision at her institution, so key personnel have been defined broadly. However, Dr. Marshall was concerned about letting investigators, faculty members, and institutions make the decision about "how far down to go." She stressed the importance of ensuring that research assistants who are actively involved in investigations also receive training. Dr. Flanzer agreed, noting that institutions tend to underestimate the need for training. With this in mind, Dr. Botkin suggested replacing the term "investigator" with more expansive language.

Retraining. Dr. Botkin wondered whether the recommendations should contain an explicit timeline for retraining. Mr. Nelson said the committee had decided to stop short of being too prescriptive, given the need to tailor training to specific types of research and other considerations. Dr. Strauss agreed, arguing that an overly prescriptive approach would add to regulatory burden. He suggested that in the absence of clear evidence related to best practices in this type of training, it would be best simply to send a message underlining how important it is to ensure appropriate training is provided. Dr. Powe agreed, noting that whatever period was identified would become the requirement. Dr. Tilden agreed; his institution offers annual training, but if a three-year retraining period were prescribed, that would be likely to become the period.

Dr. Flanzer suggested referencing the need to take turnover rates into account in selecting the interval for retraining. Dr. Botkin felt language should be added to note the need for training to keep IRB members abreast of changes in the regulations and relevant literature.

Ensuring Training is Provided. The word "ensure" was suggested, given that some institutions do not directly provide training themselves.

Use of Other IRBs. Dr. Botkin asked whether, in cases in which an external IRB is responsible for an institution's reviews, that IRB is also responsible for ensuring that the institution does adequate training. Dr. Gyi pointed out that OHRP's responsibility and jurisdiction is over the institution rather than individuals. External IRBs typically operate under the institution's "umbrella."

Endorsement. Dr. Botkin asked whether OHRP would be willing to endorse particular training programs that have the desired content. Dr. Schwetz did not feel this was appropriate, given that the guidance might outlast the program itself.

Accreditation. Dr. Schwetz suggested that SACHRP consider whether the accreditation process creates a "floor" for training expectations. Dr. Leiden observed that Association for the Accreditation

of Human Research Protection Programs (AAHRPP) allows institutions to make choices regarding training elements.

Relevant Ethical Principles. Dr. Marshall suggested adding to the list of relevant reading in Recommendation 1. However, Mr. Nelson conveyed the subcommittee's sense that the existing list might be overly lengthy and prescriptive. Dr. Genel argued against including a list that might actually limit instruction to its contents. Members agreed to characterize rather than list desired contents.

ACTIONS

The recommendations on training and education were revised and accepted unanimously by SACHRP as follows:

> **Recommendation 1.** *SACHRP strongly recommends that OHRP require that institutions ensure that initial and continuing training is provided for* ***IRB members.*** *Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, written IRB procedures, OHRP guidance, and institutional policies relevant to the protection of human subjects. Training should be initiated before members review human subjects research, and IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB members.*
>
> **Recommendation 2.** *SACHRP strongly recommends that OHRP require that institutions ensure that initial and continuing training is provided for* ***IRB staff****. Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, written IRB procedures, OHRP guidance, and institutional policies relevant to the protection of human subjects. IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB staff.*
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> **Recommendation 3.** *SACHRP strongly recommends that OHRP require that institutions ensure initial and continuing training for* ***the Institutional Signatory Official and the Human Protection Administrator*** *(e.g., Human Subjects Administrator or Human Subjects Contact Person). Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, and institutional policies relevant to the protection of human subjects, and the terms of the institution's federal assurance. Ongoing training should occur in a manner appropriate to assure the continued competence of these institutional officials.*
>
> **Recommendation 4.** *SACHRP strongly recommends that OHRP require that institutions ensure initial and continuing training for* ***investigators and other members of the research team with responsibility for conducting human subjects research****. Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, professional standards, and institutional policies relevant to the protection of human subjects. Initial training should be completed before investigators are allowed to conduct research that involves human subjects. Ongoing training should occur in a manner appropriate to assure the continued competence of investigators.*

Members were concerned that these recommendations be harmonized with the policies of the Food and Drug Administration (FDA). Mr. Nelson reminded members that SACHRP has passed a standing, overarching recommendation that all SACHRP recommendations are intended to be harmonized. Linda Tollefson of FDA said she felt the recommendations were consistent with existing FDA regulations and guidance. She also assured SACHRP that FDA and OHRP coordinate closely and comment on each other's regulations.

Dr. Tilden raised the question of whether there should be a recommendation from SACHRP regarding the role of OHRP in providing or supporting effective training and education. The Chair asked the subcommittee to consider this possibility.

Minimal Risk

Mr. Nelson reminded SACHRP members that the subject of how to interpret and apply the concept of minimal risk has been deliberated by the subcommittee for an unusually long time – nearly two years. The goal of the Subpart A Subcommittee (SAS) is to present an analytical framework for approaching this area, which has been variously interpreted by IRBs, resulting in confusion. At the November meeting of SACHRP, SAS presented extensive materials documenting its proposed approach.

Dr. Strauss stated that it is the consensus of SAS that a careful and consistent application of the term minimal risk is central to the human subjects protections provided under Subpart A. Minimal risk establishes a threshold beneath which the risks posed by the proposed research are sufficiently low to justify waiving certain standard or default requirements related to IRB review, including the requirement that it be reviewed and approved at a convened IRB meeting. Certain default requirements for full and informed consent may also be waived.

Dr. Strauss then presented the proposed analytical framework for understanding and applying minimal risk, which was documented in an accompanying one-page brief entitled, "SAS recommendations Toward an Analytical Framework for Understanding and Applying Minimal Risk" *(see Attachment A to these minutes)*. In the proposed approach, study risks are estimated relative to the resilience and vulnerability of the subjects and the nature of the proposed procedures, then compared to a fixed threshold—the risks ordinarily encountered in daily life. The framework treats risks as *varying* based on the circumstances of the population and the specific procedures to be used in the research; however, it treats the notion of "acceptably low" risk as a *fixed* threshold.

This approach illuminates the process IRBs should use and points to the type of factors that should be taken into consideration. For example, the risks attendant to a breach of confidentiality will vary greatly depending on the population and its location. For example, they may be greater for individuals who are HIV positive than many other subjects. The location may also affect the degree of risk. For example, in Pakistan, revealing that a woman has been the victim of a sexual crime may put her at risk of execution. Clearly, the risk of a breach of confidentiality would be far greater for a Pakistani woman than for victims in other locations that do not face such a risk.

Risks may vary according to the timing and nature of the procedures, as well as population characteristics. For example, Dr. Strauss compared the risks posed by the following:

- Participation in an interview on end of life decisionmaking by patients diagnosed on the day of the interview as having amyotrophic lateral sclerosis (ALS).
- Participation in the same interview by patients who have been participating in a support group for persons with ALS for several weeks or months.

Risks would be greater for those in the first group. Similarly, risks for this type of study could vary based on the experience and training of the interviewer.

Specific individuals and populations vary in terms of the risks they face on a daily basis, an ethically meaningful notion of harms and discomforts ordinarily encountered should reflect *background risks that are part of the routine experience of life for the average person in the general population.* This concept is not one that can be reduced to a mathematical calculus. However, the intent is that the risks

posed to the specific population are compared to those faced by an individual toward the middle of an imaginary graph in which those at one end lead highly risky lives (for example, frequent skydivers) and those at the opposite end whose careful lives expose them to few risks. The minimal risk threshold established by thinking of such an average person is a "fuzzy" line. When the harms and discomforts of the proposed research as they are anticipated to impact the study participants are judged to fall below this acceptably low risk threshold, the research is said to be "minimal risk."

DISCUSSION

SACHRP members raised the following questions and issues regarding the proposed treatment of minimal risk:

Consistency of approach. Dr. Botkin found the approach consistent with previous work on Subpart D. He stressed the importance of consistency across subcommittees. Dr. Strauss agreed. He added that the approach is not really different from OHRP's thinking on the subject.

Risk probability. Dr. Botkin sought to verify that the concept of varying probabilities of certain risks occurring were taken into the account in the approach. Dr. Strauss assured him that this was the intent.

Operationalizing the Approach. Members were concerned about how the approach could be conveyed to IRBs across the country so that it can be more universally understood and applied. Guidance is a first step. Mr. Nelson saw OHRP guidance on coded data (August, 2004) as a good model for the format needed. Dr. Powe added that "case law" will need to be established within individual IRBs.

Dr. Botkin stressed the importance of examples in clarifying the intended approach. Mr. Nelson said SAS has already developed a number of examples and presented several of them at the last SACHRP meeting (November, 2006). Dr. Schneider suggested that examples should emphasize such critical issues as the psychological distress that could result from a breach of confidence. Dr. Goldkind added that too many studies are currently identified as minimal risk – for example, some IRBs view bone marrow biopsy as a minimal risk procedure. Clear examples are extremely important to clarify how the concept should be applied.

Dr. Schwetz asked whether the approach described is intended to be universally applicable or whether a long list of exceptions might be generated. Dr. Strauss said he could think of no circumstances in which the approach could not apply. Dr. Gyi suggested that even if there were exceptions, the end result would be superior to the current state of affairs.

ACTIONS

SACHRP unanimously *approved* the one-page summary of the recommended position on minimal risk included in the references for the meeting.

SACHRP also unanimously *approved* a motion that illustrative examples be developed by the subcommittee and presented as an appendix.

SACHRP also *approved* a recommendation asking the Subpart A Subcommittee to provide examples to illustrate how the proposed concept of minimal risk will be implemented. Examples are to be forwarded to the Secretary with the approved summary.

In closing Mr. Nelson expressed the subcommittee's deep appreciation for Dr. Strauss's contributions.

Future Topics to be Considered by SAS

Mr. Nelson told SACHRP that the topics subcommittee intends to consider in the future include IRB membership, assurances, multi-site research, recordkeeping and reporting, investigator responsibilities, and informed consent (including alternatives to the 30-page consent forms common at present), and key definitions such as "human subjects" and "research." Issues related to vulnerable populations are not projected for short-term consideration, given the existence of the new subcommittee on issues impacting those with impaired decisionmaking. Issues related to adverse events have also been deferred, in this case because the Federal Adverse Task Force is currently working on this issue.

Report of Subcommittee on Issues Impacting Those with Impaired Decisionmaking Capacity
David Strauss, M.D., Co-Chair

Dr. Strauss explained that the new committee will be called the Subcommittee on Issues Impacting those with Impaired Decisionmaking in regard to Research (SIIDR). The Chair reviewed the charge of the new subcommittee that will be developing recommendations related to research involving individuals with impaired decision-making capacity. He noted the absence of specific guidance or interpretation of existing regulatory context to help IRBs review and approve such research. For example, it is not clear what "additional safeguards" are needed for this population or what it means to be "mentally disabled." He emphasized the need for protections that recognize the fact that impairment occurs along a spectrum. (See Dr. Strauss's previous presentation on the work of the new subcommittee in the minutes of November 2-3, 2006; see also minutes summarizing panel presentations on related topics held at that same meeting and at the previous one, July 31-August 1, 2006.)

The subcommittee will:

- Examine current problems related to the inclusion of individuals with decisional impairment in research;
- Review prior efforts to regulate the involvement of individuals with decisional impairment in research;
- Review relevant empirical work;
- Work to translate ideals into meaningful practice within the IRB structure; and
- Evaluate the risks and benefits of regulatory change or guidance.

Essential principles underlying the subcommittee's work include the following:

- Vulnerability related to decision-making impairment is not simply *present or absent*. It may exist only in some times or circumstances. Therefore, protections must be tailored to the nature and proportional to the extent of vulnerability and the magnitude of the experimental risk.
- Capacity is task specific—it is capacity *to do something*. An individual may have the capacity to consent to certain activities but not to others.
- Impaired decision-making is not limited to those with disorders of the central nervous system. Nor are all persons with mental illness mentally disabled.

Possible focus areas for consideration include the definition of populations and/or circumstances that require additional safeguards or other regulatory action or guidance. The subcommittee may also seek to define the meaning of "additional safeguards" within the Federal regulatory framework. Dr. Strauss pointed out that critical information on the progression of diseases such as Alzheimer's is lost if certain populations are excluded and surrogates (such as a spouse) are not allowed to give consent on their behalf. The subcommittee will need to consider circumstances under which surrogate consent is appropriate when research offers no prospect of direct benefit for the subject.

Dr. Strauss highlighted some of the challenges the subcommittee will face as it pursues its work:

- Research risk, vulnerability and decisional-impairment occur along a spectrum. Can a simple categorical approach to protection (as in Subpart D) work? If not, what are the alternatives?
- Protections must not "protect" those who do not require protection; this would further stigmatization.
- We are currently confronted by genuine gaps in regulatory coverage where pressing research questions for the most vulnerable subjects are at issue.
- We must find the proper balance between the protection of individual subjects and the interests of science.

Dr. Strauss reported that about half of the members have been selected. An introductory teleconference was held on March 2, 2007, and the first face-to-face meeting of the subcommittee will occur on May 8 and 9, 2007.

DISCUSSION

Dr. Botkin asked whether the new subcommittee plans to address issues in which potential subjects are under purely situational impairment as a result of emotional stress, perhaps because of a circumstance related to health. Dr. Strauss noted that the subcommittee will take direction from SACHRP on what it should consider. He was not certain whether the subcommittee would consider this a focus, though consideration of such circumstances might benefit from its review of issues associated with decisional impairment.

Panel on Issues Impacting Those with Impaired Decisionmaking Capacity
David Rothman, Ph.D., Professor of Social Medicine, Columbia College of Physicians and Surgeons; Scott Kim, M.D., Ph.D., Bioethics Program, University of Michigan;, John M. Luce, M.D., Professor of Medicine, University of California at San Francisco; Laura Odwazny, Senior Attorney, Office of General Counsel, HHS

A panel moderated by Dr. Strauss presented pertinent background related to some of the issues the subcommittee will take into consideration. Speakers and selected key points were as follows.

Remarks by David Rothman, Ph.D.: Informed Consent and the Cautionary Legacy of Willowbrook

Dr. Rothman reminded SACHRP that investigators have long been drawn to institutionalized populations, largely because such "captive" populations are seldom lost to follow-up. For example, Lutein was tested on orphans in the early 1900s, and Goldberger tested pellagra in southern prison farms. In World War I and World War II, the national emergency was seen as justifying research on such populations: malaria, gonorrhea, flu, and dysentery were researched in institutions for the mentally retarded, prisons, or asylums. The wartime mindset was readily able to rationalize such important work, which had clear benefits for soldiers. As the Cold War continued, the mindset often did as well.

Willowbrook was, according to Dr. Rothman, the Tuskegee of the world of the decisionally impaired. Institutionalized retarded infants were deliberately infected with hepatitis, with the rationale that they would contract it anyway. The consent form used by Saul Krugman, the investigator, suggested that the intervention was therapeutic.

In the middle 1980s, with the advent of the HIV AIDS epidemic and the drive for a cure, subjects began to view participation in research as a "front line chance at life." Research was confounded with treatment. Today, as new treatments emerge that are of vital interest to persons with decisional impairments, the subcommittee will necessarily be performing an "exquisite balancing act" in "very slippery territory."

Remarks by Scott Kim, M.D., Ph.D.: Ethics and Policymaking for Surrogate-Based Research

Scott Kim, M.D., Ph.D., presented data that could inform policies on surrogate-based research (SBR) and the implementation of these policies. Her remarks focused on the current state of SBR policy and practice at both State and IRB levels.

Dr. Kim sought to review the status of State statutes in regard to the subject, but found many of them were unclear. Only two States, California and Virginia, have relatively modern laws on SBR that specifically address research; the rest have a variety of restrictions and conditions that date back in time. Eleven State laws mention the possibility of family members as surrogates for research consent, but the applicability varies, making it impossible to generalize. For example, State laws may apply only to people with mental illness, those with mental retardation and developmental disabilities, or people with terminal illness. A State law may specifically *exclude* those with mental illness.

As of July 2004, according to the American Bar Association (ABA) Web site, 39 States allowed some form of surrogate consent when no one has been specifically appointed in advance. However, it is not clear how many of these laws apply in the research context. New York, for example, specifically allows surrogate consent only in regard to "do not resuscitate" (DNR) directions. In short, the speaker characterized State laws as "mixed, unclear, and confusing."

A survey of IRB Chairs suggests that many IRBs are unaware of their state laws or confused by them. Over half of the respondents said they did not understand the legal situation, while another 14 percent thought there were no applicable laws or regulations. Several institutions, including the University of California/Los Angeles and Vanderbilt, have temporarily suspended SBR due to a lack of clarity on what is permissible. Even in the State of California, which did have a modern applicable law, only one-third of respondents in that State were aware of the law as a basis for the IRB's policies and practices. Instead, IRBs seem to look to the Federal government for guidance.

Dr. Kim commented on the ethics of pursuing research with people identified as unable to give informed consent. The argument for such research, she suggested, must be based on a "social contract" rather than one that is purely utilitarian. Policies based on this approach should give a "voice at the table" to those most affected by them, including lay stakeholders, future patients, care givers, and older members of the general public. Given the complexity of the research at issue, they should be educated and given an opportunity to "digest" information on their choices. She shared research on older persons at risk for Alzheimer's Disease who responded positively to a variety of possible research scenarios in which they or others might participate.

Dr. Kim noted that people with advanced Alzheimer's Disease tend to respond to hypothetical studies in ways very similar to those without such progressed impairment, suggesting that they may have an appropriate role in decisionmaking even when surrogates are also used.

Remarks by John M. Luce, M.D.: Clinical Research with Persons who are Critically Ill

Dr. Luce highlighted ethical issues involving clinical research with persons who are critically ill. This is a highly vulnerable population that contains a number of patients with limited decisionmaking capacity resulting either from their disorders or from the interventions they receive. This group has been relatively neglected in discussions of decisional impairment and research, but it is highly relevant.

Critical care medicine encompasses the management of patients in critical care units or intensive care units (ICUs). Most patients in ICUs have either a dysfunction or failure of at least one organ system. While most patients leave post-anesthesia care units (PACUs) alive, this is not true of "regular" ICUs. Most patients are intubated and mechanically ventilated; consequently, many are physically unable to engage in dialogue with someone seeking consent to participation in research. Most are extremely vulnerable. Most of them also lack decisional capacity, as a result of the underlying disorder or of the treatment they receive, or often, both. Dr. Luce pointed out that as the population ages, more of us are likely to end up in an ICU, so research on how to improve treatment of these patients is increasingly relevant.

Often, such critical illness occurs unexpectedly and evolves rapidly, with little opportunity to obtain informed consent. Many lack surrogates entirely. Even for those who have surrogates, the surrogates themselves may be overwhelmed by the ICU and so desperate to help their loved ones that they are likely to confuse research with treatment. Very few State laws define the role of surrogates in such situations.

Emergency research consent waivers, which have been available since 1996, have been helpful to critical care investigators; however, they are primarily applicable to patients in the emergency department rather than those in ICUs. They may be granted only when the patient is in a life-threatening situation, when obtaining consent from the patient is not feasible, when the research holds the prospect of direct benefit, and when the research cannot be conducted without the waiver. There is a defined "therapeutic window" (too short to make most ICU patients eligible) and the investigator is required to attempt to contact a legally authorized representative (LAR).

In a 2004 article (Luce, Silverman, and Schwartz) cowritten with other members of the Acute Respiratory Distress Syndrome network, Dr. Luce proposed that protections for decisionally impaired adults also include protections for patients who are critically ill. Authors suggested that these protections might be modeled after those currently used for pediatric patients.

The speaker referenced a 2002 California law that lists a hierarchy of those who might serve as surrogates for patients in ICUs in descending order. If surrogates disagree, consent is not considered valid. When such research is done, Dr. Luce suggested that clinicians should not enroll their own patients. He also emphasized that IRBs should include critical care physicians when research on ICU patients is considered.

Remarks by Laura Odwazny, Senior Attorney: Legally Authorized Representatives

Laura Odwazny, Senior Attorney, discussed issues related to the "legally authorized representative" (LAR). The Common Rule provides for "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (45 CFR §46.102). There is no national standard for who may serve as an LAR; State and local law determine this (e.g., State statutes, regulations, case laws, a

formal opinion of the State Attorney General, or a combination of these). Applicable laws include those that specifically address surrogate consent to participation in research (of which there are few) and those that address consent to medical procedures or treatment. The latter could be construed as applicable to research involving similar procedures or treatment, but this can involve a complicated legal analysis. Ms. Odwazny recommended that IRBs consult with institutional counsel to identify applicable laws when research requiring the consent of a LAR is being considered.

In the absence of applicable laws, the LAR can consent to participation for a person who is decisionally incapacitated only if the individual is either appointed as guardian by a court or authorized to make such a decision by an advance directive executed in accordance with State law.

Ms. Odwazny reviewed a case that demonstrates the challenge of conducting research involving a decisionally incapacitated population. Unconscious subjects were enrolled in a study related to tidal volume positive pressure ventilation for treatment of acute lung injury and acute respiratory distress syndrome based on consent from family members, in some cases as distant as cousins and uncles. No State laws were found to be applicable, and none of the family members were either official guardians or appointed to act on behalf of the subject through a durable power of attorney. OHRP found that the institution had failed to obtain legally effective informed consent. The institution then suspended research on the population until a State regulatory agency created applicable regulations.

In response to a request from Dr. Strauss, the speaker provided an overview of the process by which a change in Federal regulations in this area might occur. This includes the following:

- The program drafts the new text of the regulation;
- The program seeks appropriate Departmental clearance;
- The proposed regulation is published, and public response is sought;
- The Office of Management and Budget reviews the regulation;
- The program proposes a final rule.

Ms. Odwazy noted that this process usually takes one Federal agency a minimum of 3 years. For new regulations to have federal-wide impact, each of the individual departments and agencies that fund and conduct human subjects research would either have to publish identical regulations or join under a common regulation (which is how the Common Rule was promulgated).

DISCUSSION

Members were given an opportunity to pose questions to speakers.

Would a Federal law defining LAR for all States be possible? Ms. Odwazny responded that this would be possible. However, it would involve some complicated legal analysis since the Federal government does not preempt an area normally addressed by State law without a compelling reason. She clarified that where Federal protections do exist, they preempt State laws that offer less protections, providing a floor rather than a ceiling.

Dr. Luce added that in regard to critical care research, he saw this as “a State issue that ought to be addressed by States.” However, SACHRP members observed that as research is increasingly conducted across state borders, reliance on the “patchwork quilt” of State laws in this area is problematic.

A SACHRP member asked whether Ms. Odwazny would view Subpart D as a precedent for preemption of a similar kind. However, the speaker observed that Subpart D defers to State law on the key issues of who is a child and who can be a guardian.

Is it possible to make substantive changes in interpretation without a change in the regulation? Ms. Odwazny responded that changes in interpretation were certainly possible but would have to be seen as growing from the exact wording of the regulation as currently stated.

Could findings from Dr. Kim's survey of older adults at risk for Alzheimer's Disease be extrapolated to the general public? Dr. Kim suggested that people involved in research are likely to be more pro-research than the general population. He added that people are generally more protective when they are acting as surrogate decisionmakers than they would be in regard to their own participation.

How important are clinical trials to providing good treatment in clinical care settings? Dr. Luce responded by citing a study that shows a survival benefit that occurred as a result of manipulating care in the intensive care unit; he believes many other studies offer similar potential breakthroughs and beneficial findings. Currently, he observed, it is often possible to turn off a patient's mechanical ventilator without a surrogate, but not to enroll the same patient in a study.

Has there been much work on cognitive assessments that could determine when a patient can give meaningful assent to participation in research? Dr. Kim responded that even patients with moderate Alzheimers tend to respond in the same way consistently to the same proposed research scenarios.

When you seek consent from surrogates, is this based on the "substituted judgment" standard (what the potential subject would choose) or a "best interest" standard? Judgments are likely to be closer to the "best interest" standard, Dr. Luce said, since most patients have never faced this kind of prospect before. Dr. Kim commented that a relevant question in this regard is how much leeway a person might want to delegate to a future surrogate; he noted that current research suggests that the majority of people are willing to give a future surrogate at least some leeway.

Since decisional impairment occurs along a spectrum, what type of framework would be appropriate? Is it possible to construct categories that would work for these populations? Dr. Kim noted that of the two modern State laws, Virginia's follows the Subpart D model, but the California law is striking in the absence of any directives regarding risk/benefit categories. He said he believed any categorical model would be problematic, and it would not be possible to predict what might happen "on the ground" if new ones were introduced. Instead, he suggested a focus on acquiring legal clarity on the LAR issue. Dr. Strauss was also wary of applying the Subpart D structure to decisional impairments, but he did feel some gradation in risk/benefit considerations would be appropriate.

PUBLIC COMMENT

The Chairman invited public comment. Alan Trachtenberg of the Indian Health Service (IHS) asked whether relevant tribal laws would apply in lieu of State laws and how tribal and State laws would interact where both exist. Ms. Odwazny said she was insufficiently informed on the issue to answer with confidence at present but would follow up with IHS counsel to provide an answer.

FRIDAY, MARCH 30

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

Dr. Agwunobi stressed the importance of SACHRP's work, underlining his desire to assist the group and ensure its voice is heard by the Secretary. He specifically applauded the committee's productivity and expressed his appreciation for the committee's decision to take on the nuanced and "critical" issue of protections for persons with impaired decisionmaking capacity. He also noted that SACHRP's consideration of conflict of interest and its impact on the human subject was timely and essential, since the subject is being discussed among many agencies and within academic settings. He also welcomed the consideration of how investigators should be trained. Too often, he said, we look at the aftermath of events. It is important to gain a better understanding of how government can be involved in prevention. Everyone involved in human subject protection needs training and education on how to fulfill their role.

The Assistant Secretary for Health (ASH) called SACHRP "one of most productive advisory committees in the entire system." He noted, however, that some of its recommendations are now 2 years old, and the committee has received no feedback regarding the response of the Secretary. He committed to work with Dr. Schwetz to determine the status of these recommendations and relay feedback. He will also do this for new recommendations on an ongoing basis.

The ASH encouraged members to convey issues requiring his personal attention to the SACHRP Chair.

DISCUSSION

Dr. Genel pointed out that SACHRP recommended nearly three years ago that the Health Insurance Portability and Accountability Act (HIPAA) be harmonized with the Common Rule. The lack of harmonization has complicated research, including IRB and oversight. Dr. Genel stressed the critical importance of this harmonization. The ASH responded that one of the critical issues the Secretary plans to address between now and the end of his term is the need for personalized health care. This is the notion that we may be able to diagnose an illness or the propensity to develop a particular illness based on unique genome profiles or similar personal data, responding with customized medical treatment. One barrier to accomplishing this is the need to address issues related to privacy. As a result, HIPAA-related issues are relevant to this high priority. Dr. Genel confirmed this, noting that researchers he has spoken with say that privacy rules limit their ability to make such new discoveries useful in a personalized way. Dr. Agwunobi promised to check the status of this SACHRP recommendation.

Referencing research involving prisoners and the need for a better system to track health issues as they transition to the community, Dr. Powell asked if HHS considered this a priority. Dr. Agwunobi confirmed that one of the Secretary's priorities is furthering the vision of ubiquitous use of interoperable health information technology using common standards. Last year, a major step was taken when an Executive Order from the President directed several Federal agencies and programs to commit to moving toward a common set of standards that would permit the transfer of electronic health records among their systems. The Secretary has been traveling the country to promote this concept and is getting support from managed care, physicians, hospitals, industry, employers, and others, including the American Medical Association (AMA). A new commission called the American Health Information Community (AHIC), another initiative of the Secretary, has developed a

Certifying Commission for Health IT that is reviewing health information systems and certifying that it believes will facilitate movement toward a common standard.

Dr. Powe asked for an update on Department activities aimed at reducing health care disparities among minorities. The ASH noted that every HHS agency has an Office of Minority Health. He believes that the Department's efforts to end disparities have contributed to an elimination of disparities among racial groups in terms of infant immunization for the three main antigens. However, there are worsening disparities in some areas, especially between Latino American men and the rest of our communities. Dr. Agwunobi pointed to the importance of the Committee's discussions about how to enroll more minorities in research protocols safely so that we can learn from these studies.

Dr. Gyi, a former SACHRP member, observed that accreditation is a voluntary program that has not yet received the full force of endorsement. He suggested it would be helpful to have a recognition of its value. He also called the ASH's attention to the challenge of harmonization among agencies. The ASH told SACHRP that Dr. Schwetz is currently engaged in facilitating discussions of regulatory interpretations among agencies. He did not comment on the accreditation issue.

In response to a request from Dr. Botkin, the ASH promised to send a list of the Secretary's ten priorities to the SACHRP Chair. However, he stressed the committee's ability to set its own priorities independently. The Chairman thanked Dr. Agwunobi for his interest and support.

Discussion on Conflict of Interest Among IRB Members

Members heard and discussed remarks on conflict of interest (COI) from several speakers.

Remarks by Leslie Wolf, J.D., M.P.H.: How IRBs Address Their Own Conflicts of Interest

Ms. Wolf reminded SACHRP that regulations require IRBs to address conflicts of interest. She noted that many IRB members are also researchers who might be tempted to review colleagues' work less critically than might be warranted in hope of reciprocal kindness. They may have relationships that interfere with their independence, or institutional interests might compromise the independence of the IRB.

She then reported on a recent survey by the Program in Medical Ethics at the University of California at San Francisco sponsored by a grant from the Greenwall Foundation. The study analyzed policies of IRBs at 121 medical schools that receive NIH funding regarding their policies on conflict of interest. She reported that 74 percent of IRBs have written policies regarding IRB conflicts of interest (which vary substantially) and the rest rely solely on the regulations. Of those with written policies, the majority have definitions based on project involvement (78 percent), financial interests (72 percent), or personal and professional relationships (52 percent). A few have policies that include personal beliefs (6 percent); these come into play in situations in which something the investigator proposes to do is otherwise permissible, but the member would not approve it no matter what the investigator did to address concerns because of personal beliefs.

She explained that IRBs define financial conflicts of interests differently. The greatest number of them requires a "significant financial interest" to define a problem, which 43 percent define as more than $10,000 in payments or equity. Twenty-seven percent give no definition, and 20 percent refer to *any* financial interests as constituting a conflict. One IRB required disclosure of "personal relationships" that might affect the review.

These policies apply to IRB chairs and members, and sometimes to IRB staff (15 percent), ad hoc reviewers or consultants (20 percent), and guests (4 percent). Only 20 percent of IRBs collect information about conflicts of interest systematically. If a conflict does develop, policies differ widely in terms of what the conflicted member is obligated to do. Only about one-fourth of IRBs had policies that included explicit statements on this. Of these, three permitted the member to serve as a reviewer as long as the conflict is disclosed and a few allowed the member to stay in the room while deliberations are occurring. Some allow the conflicted member to vote, and others have limited exceptions to required recusal based on the type of conflict.

In conclusion, the speaker observed that there are clearly some significant gaps and variations in IRB policies on conflict of interest. About one-quarter, disturbingly, have no written policies on the subject at all. Many other policies do not clearly state what a member with a conflict must do or do not apply to all those involved in review (e.g., staff). As a result, application is likely to be inconsistent. A primary concern is the fact that some policies actually conflict with regulatory requirements or OHRP guidance, such as those that allow conflicted members to remain in the room during deliberations or even vote on protocols. Clearly, such policies allow those with conflicts of interest to influence the outcome of the IRB's decision.

Remarks by Marjorie Speers, Ph.D.: Perspective from AAHRPP

Dr. Speers, who is the Executive Director of the Association for Accreditation and Human Research Protection Programs (AAHRPP), explored the topic from the perspective of the accreditation process. She felt that this process can help narrow inconsistency across IRBs and institutions and provide assurance that IRBs are doing a better job of identifying and managing COI. The applicable AAHRPP standard is as follows:

- *The IRB has and follows written policies and procedures so that IRB members and consultants do not participate in the review of protocols in which they have a conflict of interest, except to provide information requested by the IRB.*

This standard, which is based on the regulations and OHRP guidance, extends to any review by IRB members and encompasses both consultants and IRB members. Both financial and nonfinancial interests must be addressed in COI policies, and the definition of what constitutes a financial interest must be at least as strict as the policy for investigators. Procedures must describe how the IRB intends to identify the interests of IRB members. Procedures must also specifically assure that conflicted members are excluded from discussion – meaning absent from the meeting room – and are not allowed to vote or count towards quorum. Records must document that the conflicted member was in fact absent from the room.

At the time of their application for accreditation, only 10 percent of academic institutions had policies, procedures, and practices that met this standard. However, all of those who applied for accreditation did have policies and procedures, and site visits generally confirm that IRB practices are consistent with them. The most common deficiency was a lack of specified procedures to identify conflicts of interest among consultants (80 percent of applicants). Other common concerns are inconsistencies among multiple policies and procedures related to COI (40 percent) or failure to require a conflicted member to leave the room (30 percent). Some applicants did not document the reason for the absence in the minutes), while others failed to include family members in their policies (10 percent) or did not have procedures specifically for expedited reviews (10 percent). Additionally, institutions tended to focus either on financial or on nonfinancial interests; those that addressed both were rare.

The Director noted that AAHRPP finds fewer deficiencies in regard to COI now than 5 years ago; IRBs appear to be increasingly sensitive to the need to identify and manage conflict of interest by recusal. While it is true that COIs involving IRBs are not as carefully managed as those involving investigators, greater awareness of the topic does seem to be resulting in fewer problems over time.

Remarks by Ernest Prentice, Ph.D.: Management of COI at the University of Nebraska Medical Center (UNMC)

Dr. Prentice placed concerns regarding COI in context by reminding attendees of the role of COI in the tragic death of Jesse Gelsinger, a study participant who enrolled in a gene transfer experiment in 1999. The investigator and the institution sponsoring the study, the University of Pennsylvania, both had interests in the company involved; Jesse Gelsinger's father believed that if they had been disclosed, he might not have allowed his son to participate in the study. A cascade of articles on the subject followed, largely focusing on the potential for COI on the part of investigators. In part because of increasing awareness as a result of the accreditation process, however, more attention has been given to COI and IRB members. Several recent articles have focused on the topic (Campbell et al., 2006; Prentice et al., 2005; Wolfe & Zandecki, 2007).

HHS Regulations say very little about COI among IRB members. The only reference is as follows:

- *No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB [45 CFR §46.107(e)].*

"Initial and continuing review" may be expanded to include amendments, adverse events, and other actions taken in regard to protocols, but this is not explicit.

HHS guidance issued in 2004 identifies the following IRB responsibilities:

- *…establishing policies and procedures addressing IRB member potential and actual conflicts of interest as part of overall IRB policies and procedures would help ensure that financial interests do not compromise the rights and welfare of human research subjects.*
- *…reminding members of conflict of interest policies at each meeting and documenting any actions taken regarding IRB member conflicts of interest related to particular protocols.*

With the above in mind, the University of Nebraska Medical Center (UNMC) IRB uses the following definition of IRB member COI:

- *<u>Any</u> financial incentive, or other situation, which could cause an IRB Member to lose their objectivity (or create the appearance thereof) in the review of research, which in turn, may compromise the validity and integrity of IRB review and/or negatively impacts the public's trust in human subject protection.*

Dr. Prentice stressed that even the "appearance" of conflict of interest is important. Further, the fact that a COI exists does not necessarily mean that impaired judgment will inevitably result. It is important that neither investigators nor IRB members have the impression that their integrity is being questioned because a COI has been identified and must be addressed.

Persons covered by UNMC's policy include IRB members, IRB consultants, IRB staff, and the immediate family members of any of these (i.e., spouse, dependent child, sibling, or parent). A COI exists if any of the following are true in regard to these covered persons. He or she:

- Serves as an investigator or serves as a scientific/medical adviser to the Principal Investigator (PI).
- Serves as an adviser, or a direct supervisor, of a trainee's research.
- Receives any financial compensation to which the research under review is directly connected… over the past 12 months or during the course of the research.
- Owns any equity interest in the commercial company sponsoring the research excluding mutual funds.
- Holds a position as director, officer, partner, trustee, or any other significant position…, in the company sponsoring the research or has held such a position in the past 12 months.
- Holds patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving UNMC.
- Has a financial interest in a company that has a marketed product, or is in the process of developing a new product that is, or will be, in direct market competition with the product in the protocol under IRB review.
- Has a personal relationship, or a conflict, with any investigator(s) listed on the IRB application that potentially would cause the IRB member to be perceived as less than objective in his/her review.

Members are not considered to have a COI if their only involvement in the protocol is in the context of providing clinical care to subjects. They also do not have a COI if they are serving on an NIH study review or are consultants to FDA. It is less clear whether COIs may exist in cases in which IRB members serve as consultants to pharmaceutical companies whose protocols are under review but the individual has no involvement with the particular product being tested.

In regard to financial interests, UNMC's policies define *any* level of financial interest on the part of IRB members as a potential conflict of interest. For investigators, any interest that is $2,000 or above is considered "significant"; however, even financial thresholds below this must be declared and reviewed by a conflict of interest officer. A single dollar of investment would have to be disclosed in the consent document.

To remind IRB members to carefully consider whether or not they have COIs related to the protocols to be considered, each member receives an electronic copy of the COI policy prior to each convened meeting. UNMC plans to list each sponsor on the face sheet of the protocol as a further aid to reviewers. Members with COIs are asked to notify the IRB office (no explanation is required). Members are asked to reaffirm that they do not have undeclared COIs at the start of the meeting. Those who do are recused and must leave the room when the protocol at issue is discussed. They do not deliberate, vote, or count toward the quorum. The former SACHRP chair closed by emphasizing that the question must be not how to *minimize* COI but how to eliminate it.

DISCUSSION

Institutional Characteristics and COI. Dr. Powe wondered about the relationship between institutional characteristics and management of COI. For example, he suggested that a larger institution might have more alternatives in addressing COIs. Ms. Wolf responded that her study did look for such differences in the study sample. They found that larger institutions were more likely to define COIs and also more likely to allow the conflicted member to provide information to the IRB before leaving the room. No other differences were apparent.

COI and Institutional Relationships. Dr. Powe questioned whether people in the same organizational unit as those submitting the protocol should be considered to have a COI. Ms. Wolf noted that some IRBs did specify that being from the same organizational unit might be a conflict, but this was not common. She suggested that this was more likely to make a difference for smaller institutions where people work more closely with fewer people and may have closer relationships with them. Dr. Speers added that some larger institutions have multiple policies and procedures that actually make it harder for members to be clear and what is and is not a conflict. In her experience, obvious conflicts are handled well, for the most part; it is the less obvious ones where clear policies are needed and often to do not exist. She further noted that in many small institutions, it is sometimes challenging to avoid having people from the same unit submitting the protocol providing expert review. Dr. Leiden commented that an IRB Chairman from a prolific department may exercise a great deal of influence on IRB deliberations.

Dr. Speers observed that whether an institution is nonprofit or for profit, it still needs money; for either type, the issue of separation between the IRB function and the business function is germain to detecting potential COI.

Dr. Prentice noted that a reviewer could be a member of an NIH study section and be presented with the same protocol reviewed in the section as an IRB member. He said he did not consider this a conflict of interest in that the study section is reviewing multiple factors, not simply human research protection. However, if a member felt the discussion in which he or she participated would result in a conflict, the member should certainly opt for recusal. He added that sometimes members recuse themselves when they are not technically required to do so.

Experts are often engaged in intellectual conflict with each other, and Dr. Kirchner raise the question of when this may rise to the level of COI. Dr. Prentice noted that many forms of competition exist in institutions, and IRB members may be working on projects that are essentially in competition with those of colleagues.

Dr. Genel struggled with how best to define the degree of personal relationship that constitutes a COI. Even at a large institution, he observed, the community of researchers may be small, and people may have negative or positive feelings toward each other based on past experience. He wondered how best to define the point at which those feelings become a problem that should lead to recusal.

Mr. Nelson asked how people could be expected to verify that none of their close relatives had any financial interest in any of the sponsors for multiple protocols. Dr. Prentice responded that the Board of Regents policy at his medical center defines the family members to be considered, but he agreed that it was unlikely that every IRB member was calling every family member to research their stock holdings. Ms. Wolf added that the umbrella of COI is more commonly extended only to those with whom the individual shares household income.

Mid-Review Discovery of COI. Ms. Wolf said such discoveries could be problematic and might result in loss of quorum. For this reason, it is best to do whatever can be done to encourage members to carefully consider the potential for COI before protocol review begins.

COIs, Real and Irrelevant. Dr. Strauss stressed the fact that individual interests are generally diluted by group discussions and deliberations. He suggested that efforts to remove even the remote appearance of a conflict are often based on a purely speculative and doubtful series of events. For example, even if a member holds $10,000 in the stock of a certain pharmaceutical company, how would he or she expect to realize any gain on the basis of the member's review of a Phase 2 study? Dr. Prentice agreed to some extent, but felt that appearance was important. He also said that because

other reviewers often rely heavily on the opinion of primary and secondary reviewers, even seeming small conflicts on their part may be red flags. Ms. Wolf added that it is difficult to know how to convey small conflicts that might suggest one's opinion should be taken "with a grain of salt" to other reviewers.

Influence of COIs on Decisionmaking. Dr. Botkin asked if there was a clear evidence base related to the impact of COIs on decisions. Ms. Wolf was unaware of these data.

Next Steps. A SACHRP members asked speakers how the committee could help address this issue. Ms. Wolf pointed to a need for more specific policies and clearer guidance. Dr. Speers said it would be helpful to define what constitutes a conflict of interest, particularly in regard to nonfinancial interests.

Dr. Tilden asked Dr. Schwetz whether the issue surrounding what constitutes a COI has been brought to its attention in the past. Dr. Schwetz said OHRP has been looking at the issue and is aware of the increased attention it has received recently. OHRP would find a clear signal from SACHRP helpful before it begins to discuss specific guidance on COI issues. SACHRP did not specifically refer the issue to the Subpart A subcommittee, but members clearly felt related issues were important and deserved further consideration.

Panel on Investigator Responsibilities/Training and Certification
Ivor Pritchard, Ph.D., OHRP; Ron Keeney, M.D., Vice President, Pediatric Product Development, INC Research; Erich Lukas, Executive Director of the Society of Clinical Research Associates (SoCRA; Christine Pierre, R.N., President and CEO of RxTrials, Inc. and Chair, Association of Clinical Research Professionals (ACRP)

Remarks by Ivor Pritchard, Ph.D.

Ivor Pritchard, Ph.D., noted that the regulations are silent on the issue of education or training. OHRP has issued an Advanced Notice of Proposed Rulemaking (ANPRM) on the issue; it will take public comments into account as it decides what action, if any, is appropriate.

Remarks by Ron Keeney, M.D.

Ron Keeney, M.D., described a certification program administered by the Academy of Pharmaceutical Physicians and Investigators. The program has been encouraged by Pharma, which doesn't want to lose money supporting the work of investigators who don't know what they are doing. Certification categories include Certified Clinical Trial Investigator™ (former ACRP Exam, more than 260 certified), Certified Physician Investigator (former AAPP Exam, more than 52 certified), and Clinical Trial Investigator (Former DIA Exam, more than 106 certified). He noted that questions were based on a job analysis survey and exams are scored by an independent testing agency.

Remarks by Erich Lukas

Erich Lukas, Executive Director of the Society of Clinical Research Associates (SoCRA), explained that SoCRA is working to establish educational programming and provide continuing education for clinical research professionals, establish an internationally recognized certification program for

Clinical Research Professionals (CCRP), and foster the professional development and peer recognition of CCRPs.

Remarks by Christine Pierre, R.N.

Christine Pierre, R.N., expressed concern that many see the on-line exam supported by NIH not as the minimum requirement, but the full extent of what investigators need to know. She stressed the need for basic education *before* people become investigators. A major cause for concern is the loss of 63 percent of investigators each year, leaving less experienced investigators to conduct studies.

Respondents: Discussion Of Investigator Training and Certification

Linda Tollefson, D.V.M., M.P.H., noted that FDA's biological research monitoring program emphasizes the role of the clinical investigator. There has been an encouraging increase in recent years in the number of such inspections that find no problem. Common deficiencies, which have remained constant, include failure to follow the investigation plan, inaccurate records, failures of accountability, and inadequate subject protection, including informed consent.

Jean-Louis Saillot, M.D., expressed strong support for voluntary certification.

Chris Pascal, J.D., said that too much confidence is placed in mentoring; many institutions that say they rely on this process do not actually have functional mentoring programs available. Formal training requirements are a more reliable way of making sure basic requirements are meant.

DISCUSSION

Key points in the ensuring discussion included the need for affordable training and certification programs in low income settings; the diverse qualifications required to conduct various types of research (though a speaker stressed that a core set of requirements would be pertinent to all); the difficulty of ensuring physicians have adequate training and receive encouragement to conduct needed research; the importance of reliable outcome measures; the critical role of associations as sources of training for their members; the importance of the IO in creating a culture that supports skilled and informed investigators; and the need to avoid creating training requirements that are disincentives for investigators.

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ATTACHMENT

Subpart A Subcommittee (SAS) Recommendations Toward an Analytical Framework for Understanding and Applying Minimal Risk

- Under Subpart A, the definition of "minimal risk" distinguishes research that is eligible for review using expedited procedures from research that requires review by the convened IRB.

- "Minimal risk" also defines a threshold for other regulatory provisions, including waiver or alteration of the requirements for informed consent and its documentation.

- It is the consensus of the SAS that a careful and consistent application of the term "minimal risk" is central to the human subject protections provided under Subpart A.

- Inconsistency in the interpretation of minimal risk would weaken the protection afforded under subpart A, or would contribute unnecessary requirements that do not serve the interests of human subject protection.

SAS recommends the following interpretation of "minimal risk" and recommends that guidance be drafted in accordance with this interpretation:

- The regulatory intent of minimal risk is to define a threshold of anticipated harm or discomfort associated with the research that is "acceptably-low" or "low enough" to justify expedited review or waiver of consent.

- The IRB's evaluation of the harms and discomforts of the research should consider the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.

- In its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in the research including an evaluation of subject susceptibility, vulnerability, resilience and experience in relation to the anticipated harms and discomforts of research involvement.

- To satisfy the definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an estimate of "the harms and discomforts ordinarily encountered in daily life or during the performance of routine medical and psychological examinations or tests."

- While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of "harms and discomforts ordinarily encountered" should reflect "background risks" that are familiar and part of the routine experience of life for "the average person" in the "general population." It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population.

- In summary, minimal risk should be applied in manner that recognizes that risks are procedure-specific and population-dependent, but that the notion of "acceptably-low" risk is fixed. When the harms and discomforts of the proposed research as they are anticipated to impact the study participants are judged to fall below this acceptably-low risk threshold, the research is said to be "minimal risk."

Secretary's Advisory Committee on Human Research Protections
March 29 and 30, 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.

/original/ July 30, 2007

Sam Tilden, M.D., J.D., L.L.M., Chair **Date**