

Minutes
Secretary’s Advisory Committee on Human Research Protections
July 20-21, 2010 – Arlington, VA

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TUESDAY, JULY 20, 2010

Welcome: Opening Remarks

Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed everyone to the 23rd meeting of SACHRP. She welcomed Sarah Donohue as ex officio for the Department of Defense. She also noted that while this was officially the last meeting for SACHRP member Liz Bankert, she expected her to return for the October meeting because it was unlikely that a replacement would be approved by that time. Her many contributions will be acknowledged officially at that time.

The Chair also commented on the fact that three SACHRP members were unable to attend and all of those present were required to maintain a quorum. She then told SACHRP that a letter went to the HHS Secretary on March 24 conveying the committee's most recent recommendations, including the proposed charge for the subcommittee on harmonization.

Minutes. Minutes for the March 9-10 minutes of SACHRP were approved with the following revision, which will be placed in the discussion of SAS's Recommendation 10.1 (p. 11):

The intent of the recommendation was that the final IRB approval of a study – not the date of the preceding convened meeting – would start the continuing review “clock.” SAS envisioned that, as for expedited review, the dates of actual reapproval for studies approved by the convened committee would then determine the next reapproval date. OHRP's proposed approach follows SAS's original concept in the first year, but would revert to current practice (i.e., the date of the convened meeting sets the clock) for the second and all subsequent years.

Report of Issues/Remarks

Jerry Menikoff, M.D., J.D., Director, Office for Human Research Protections (OHRP)

Dr. Menikoff reported that since the last meeting, OHRP has posted two videos on line and on “You Tube” discussing issues related to user specimens, private information, and reporting unanticipated problems. For links to these and other videos, see the Web page of OHRP's Division of Education and Development: <http://www.hhs.gov/ohrp/education/>

The Director told SACHRP that OHRP is interested in becoming more engaged in the use of social media to reach large segments of the public.

OHRP has responded to a query on its position regarding central IRBs and made the response public. The letter clarifies that OHRP is in favor of moving toward the use of central IRBs when appropriate and considers having multiple IRBs review a single study to be less than an ideal arrangement. The Office welcomes opportunities to work with other agencies to address the issue. The letter may be found at:

<http://www.hhs.gov/ohrp/policy/r tqvqeqn'ekd20100430.html>

Later in the meeting, Christina Heide of HHS's Office for Civil Rights (OCR) will be discussing OCR's recent Notice of Proposed Rulemaking (NPRM) on the modifications to the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules as a result of the Health Information Technology for Economic and Clinical Health (HITECH) Act. The proposed new rules would allow a single HIPAA authorization that addresses the use of information with respect to a clinical trial and the storage of biospecimens. OHRP has been actively working with OCR on this and is engaged in improving the system to address administrative barriers and increase efficiency. The NPRM may be found at:

<http://www.gpo.gov/fdsys/pkg/FR-2010-07-14/html/2010-16718.htm>

Subpart A Subcommittee Report

Dan Nelson, M.S., CIP, Elizabeth A. Bankert, M.A., SAS Co-chairs

Subpart A Subcommittee (SAS) Co-Chairs presented revisions of recommendations on which SACHRP provided input at SACHRP's March meeting. These recommendations complete the set of recommendations and Frequently Asked Questions (FAQs) to be forwarded to the HHS Secretary on the controversial area of informed consent and the research use of biospecimens.

Questions Related to Informed Consent and the Research Use of Biospecimens

The meaning of "investigator." SAS offered a revised interpretation of the meaning of "investigator" in the context of research involving biospecimens. Current OHRP guidance defines the term as follows:

“...anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that **if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens**, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research.”

OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens, issued August 10, 2004; updated October 16, 2008
<http://www.hhs.gov/ohrp/policy/cdebiol.pdf>

SAS pointed to problems with this interpretation, arguing that there are many circumstances in which a secondary use of coded information or specimens would not constitute human subjects research, were it not for the peripheral involvement of the individual who gathered the original data or specimens. This involvement may be such that the secondary users, and sometimes even the original collector, are unable to ascertain the identity of subjects. Examples include:

- The original collector is involved as a coauthor on resulting manuscripts or listed on grants in recognition of his/her work in obtaining the data or specimens, but with an agreement that prevents release of the coding key to secondary users.
- The original collector joins with others to form a centralized repository, but has no continued personal access to identifiers.
- A professor provides a coded dataset for a graduate student to use in secondary analyses, but the professor has no intention or reason to share identifiers with the student.

Under these circumstances, current OHRP guidance defines the original collector as an “investigator” in the secondary use, even though their role may be limited to “solely providing” coded information or specimens. SAS felt that this interpretation is overly restrictive as well as poorly understood, and therefore variably applied by IRBs and investigators. Taking into consideration SACHRP’s suggestions on the previous draft of SAS’s recommendation on this subject, the subcommittee presented the following recommendation, which would be incorporated in the glossary that accompanies the series of FAQs on the subject:

Revised Recommendation on the Definition of “Investigator.” *OHRP should revise its interpretation of who is considered an “investigator” in secondary use of coded information or specimens. Original collectors who are providing such information or specimens without identifiers should not be considered to be “investigators” involved in human subjects research, even if they are involved in analysis of aggregate data or publication of results, provided the secondary users are unable to readily ascertain the identity of subjects. Under such circumstances, neither party shall decode or re-identify subjects.*

- *Mechanisms to support this interpretation could include (a) the presence of an agreement that prohibits release of the key from the original provider to secondary users; or (b) the existence of a repository or banking system that prohibits the secondary users from access to identifiers. These same interpretations and mechanisms should be applied whether the original provider and secondary user(s) are within the same institution or at different institutions.*
- *The intent is to support a conclusion that secondary uses under such circumstances do not constitute research involving human subjects (as defined under 45 CFR 46.102(f)) and therefore do not require IRB review and approval, in keeping with OHRP’s “Guidance on Research Involving Coded Private Information or Biological Specimens.”*
- *In circumstances where subjects need to be re-identified (e.g., recontact for research purposes, return of incidental findings), investigators should consult with the IRB and may be required to submit for review, if this activity now constitutes human subjects research.*

DISCUSSION

Discussion centered on the third bullet, which addresses the circumstance in which subjects need to be re-identified. Mr. Nelson observed that the scenario exists whether or not this recommendation is approved, so long as secondary use is not considered human subjects research. He held that most IRBs would handle the situation on a case-by-case basis unless incidental findings were anticipated, in which case the procedure should be built in proactively. He added that SAS would be comfortable striking the third bullet, which was added to address questions raised by SACHRP. Members agreed that the third bullet was unnecessary and should be struck.

Dr. Sodeke observed that scenarios such as those described will continue to face us as long as we fail to reconsider the critical starting point: the definition of human subjects research.

ACTION

SACHRP approved the recommendation as originally presented, with the exception that the following words were struck (the third bullet):

- ~~*In circumstances where subjects need to be re-identified (e.g., recontact for research purposes, return of incidental findings), investigators should consult with the IRB and may be required to submit for review, if this activity now constitutes human subjects research.*~~

All but one SACHRP member voted in favor of the recommendation. Dr. Sodeke said his dissent was based on the belief the redefinition would not solve the central problem, which is the question of what constitutes human subjects research.

Frequently Asked Questions and Responses

Co-Chairs reminded SACHRP of the definitions of “honest broker” and “limited data sets,” noting that OHRP does not consider a Limited Data Set (as defined under the HIPAA Privacy Rule) to constitute individually identifiable information under 45 CFR 46.102(f)(2). This interpretation was confirmed at the October 27, 2009 meeting of SACHRP. They also reminded members that the full set of FAQs (#1- 28) were previously presented and approved, modified, or deleted, with the exception of #11 and #15. These have been revised to address SACHRP concerns.

FAQ #11 (revised). SAS revised the response to this in order to make it very clear that the default is that the subject should be recontacted to give consent. The points to consider remain the same.

FAQ #11

An academic medical center has established a centralized tissue bank of specimens that it receives from a variety of sources. The bank was reviewed as human subjects research and has IRB-approved policies and procedures in place. These policies and procedures stipulate that the bank will release only coded specimens to researchers, without identifiers.

The institution now plans to begin moving excess clinical specimens to the bank in a prospective, ongoing manner, after their original purpose has been served. The specimens would be identifiable going into the bank, in order to facilitate linkage back to clinical data. Is this permissible if there was no research consent obtained from the patients?

Response. *Because the excess clinical specimens are identifiable, this is human subjects research and consent would be required. In **limited circumstances**, the IRB may determine that the conditions for a waiver of consent under 45 CFR 46.116(d) have been met.*

Points to consider include governance and oversight of the bank; protections in place to maintain privacy and confidentiality (e.g. coding, limited/controlled access, honest broker mechanisms, de-identification processes, limited data use agreements); policies regarding access to specimens; the nature of the research for which the specimens may be used; the ability to locate or contact subjects; risk of introducing bias into the collection; potential anxiety or confusion for subjects; the number of subjects; the length of time since specimens were first collected; and the likelihood that subjects would object to the research use of their specimens.

DISCUSSION

Dr. Menikoff said that he appreciated insertion of the term “limited circumstances,” but that OHRP still had concerns about the FAQ because the limited circumstances are not defined. He felt the fact patterns that would justify a waiver of consent should be defined and said he had not yet seen a fact pattern that SAS and OHRP agree would constitute an exception. An exception, he said, could “undermine the whole rule.” A uniform system that allows for consistent IRB decisions and reflects the Belmont principles is essential. He was concerned about the creation of repositories in which tissue was routinely deposited without donors ever being consulted and stressed the importance of getting appropriate consent in advance. Dr. Sodeke also felt that the FAQ as stated did not give IRBs sufficient guidance.

A SACHRP member said a waiver of consent might be justified in instances in which getting consent is clearly impracticable because it would skew the data badly. (This scenario was contained in a previously approved recommendation regarding criteria for waivers.) Another SACHRP member thought that handing over samples might become common, which was not the intent. Mr. Nelson observed that it is fairly routine for an investigator to go to the pathology department and ask for the last few samples of some collection for a single project. He felt that identifying specific FAQ patterns would be a “slippery slope,” but for the sake of argument, he would envision a case in which all of the identified points to consider listed in the scenario are addressed to the satisfaction of the IRB. Ms. Bledsoe added that patients may be stressed by

being approached with additional requests for consent. The Chair emphasized that the decision to waive consent is clearly stated to be subject to IRB review and approval. Members agreed to change the term “limited circumstances” to “rare circumstances” in order to underline the fact that cases like this in which consent may be waived are uncommon.

A SACHRP member wondered whether “rare” meant rare within an institution or rare nationally. Dr. Marshall felt the question went beyond the particular FAQ and observed that in the future, the understanding of what is included in “rare” cases will evolve as actual cases are experienced, especially in the area of genome science. She added that while SACHRP could spend days “deconstructing the meaning of rare,” it would not be a worthwhile exercise. She felt the use of the term “rare” closed the door more tightly on the potential for abuse.

ACTION

SACHRP approved FAQ #11 with a single change in language (the word “limited” was changed to “rare” in the response, as shown below). One member was opposed, and the others voted in favor.

FAQ #11

- **Response.** *Because the excess clinical specimens are identifiable, this is human subjects research and consent would be required. In rare circumstances, the IRB may determine that the conditions for a waiver of consent under 45 CFR 46.116(d) have been met....*

FAQ #15 (revised). Ms. Bankert noted that the FAQ was discussed at the March SACHRP meeting. In response to SACHRP’s input, there were no changes in the FAQ itself, but SAS sought to narrow the response to focus on the specific responsibilities of the institution and the IRB. It also added a new consideration of HIPAA issues.

FAQ #15

An investigator who collected and stored thousands of identifiable specimens from a number of studies accepts an offer at another institution, and plans to move the specimens to the new institution.

What are the issues that the IRB and/or institution should consider, when faced with this situation?

Response. *This is an institutional responsibility that may involve multiple components across the institution, including legal counsel, sponsored programs, and the IRB, as appropriate. The IRB’s role could include determination as to whether the transfer of specimens to the new institution is compatible with the consent under which the specimens were collected, or whether additional consent may be required.*

Beyond these IRB-related considerations, institutional policies regarding intellectual property will need to be considered. Formal agreements should be established that govern the transfer of specimens from the institution that provides the specimens to the investigator and/or receiving institution. These agreements should specify as appropriate the rights and obligations of both the provider and the recipient, including intellectual property terms and publication rights, as well as the rights of subjects (e.g., whether subjects would have the ability to withdraw specimens once they pass to the new institution).

HIPAA Issues. *If the institution is a HIPAA-covered entity, then the institution also needs to consider whether the transfer of information from it to another entity was encompassed in the original HIPAA authorization or waiver of authorization, or if another HIPAA permission applies.*

DISCUSSION

The Chair wondered if intellectual property should be mentioned twice; it seemed to give too much weight to this. Co-Chairs edited the FAQ to ensure it was mentioned only once. She also wondered whether it was critical that there were “thousands” of specimens; she felt the subjects’ rights would be the same regardless of the volume. Co-Chairs agreed.

A SACHRP noted that the scenario did not specifically make clear that the samples were being transferred with identifiers. The Co-Chair agreed that this was what was intended and added language to this effect.

A SACHRP member said the receiving institution would need a protocol and oversight to be in place before the transfer could take place. The Chair was not sure this was the case, but felt the institution would need to be clear that it would not proceed with research until a protocol was reviewed. Others agreed it would be wise to spell this out.

A SACHRP member observed that the scenario is really resolved at the institutional level. The Chair agreed that the issue must be addressed at this level before it comes to the IRB. Another member also said institutional policies would be a determining factor. Dr. Strauss added that the use must be compatible with the original consent.

A member suggested it would be a useful addition to add a FAQ in which the specimens are moved *without* identifiers.

ACTION

SACHRP approved the revised FAQ unanimously with the following changes:

FAQ # 15

An investigator who collected and stored **identifiable** specimens accepts an offer at another institution, and plans to move the specimens **with identifiers** to the new institution.

What are the issues that the IRB and/or institution should consider, when faced with this situation?

Response #15

- *This is an institutional responsibility that may involve multiple components across the institution, including legal counsel, sponsored programs, and the IRB, as appropriate. The IRB's role could include determination as to whether the transfer **and use of specimens** at the new institution is compatible with the consent under which the specimens were collected, **whether additional consent may be required, or whether there are concerns relating to the communities or populations represented by the specimens.***
- *Beyond these IRB-related considerations, other institutional policies will need to be considered. Formal agreements should be established that govern the transfer of specimens from the institution that provides the specimens to the investigator and/or receiving institution. These agreements should specify as appropriate the rights and obligations of both the provider and the recipient, including intellectual property terms and publication rights, as well as the rights of subjects (e.g., whether subjects would have the ability to withdraw specimens once they pass to the new institution).*
- *Similar considerations at the receiving institution would apply, including the need for IRB review of proposals for ongoing use of identifiable specimens.*

HIPAA Issues. *If the institution is a HIPAA-covered entity, then the institution also needs to consider whether the transfer of information from it to another entity was encompassed in the original HIPAA authorization or waiver of authorization, or if another HIPAA permission applies.*

FAQ #15b

FAQ 15b. Ms. Bankert explained that because SACHRP members commented that the scenario would be different if the specimens in 15b were *not* identified. FAQ 15b was developed to capture that scenario as well. Changes in bold were made to FAQ 15 to change the scenario.

FAQ #15b

*An investigator who collected and stored specimens accepts an offer at another institution, and plans to move the specimens **without identifiers** to the new institution.*

What are the issues that the IRB and/or institution should consider, when faced with this situation?

Response. *This is an institutional responsibility that may involve multiple components across the institution, including legal counsel, sponsored programs, and the IRB, as appropriate. The IRB's role could include determination as to whether the transfer of specimens at the new institution is compatible with the consent under which the specimens were collected or whether additional consent may be required **or whether there are concerns relating to the communities or populations represented by the specimens.***

Because specimens are being transferred without identifiers, subsequent uses would not be considered to be research involving human subjects under 45 CFR 46.

Beyond these IRB-related considerations, other institutional policies will need to be considered. Formal agreements should be established that govern the transfer of specimens from the institution that provides the specimens to the investigator and/or receiving institution. These agreements should specify as appropriate the rights and obligations of both the provider and the recipient, including intellectual property terms and publication rights, as well as the rights of subjects.

DISCUSSION

The Chair pointed out that issues in this case include the compatibility of the use of specimens. Language was added to reflect this.

Dr. Ross observed that the concerns of communities about the use of their samples might still apply, even if they were de-identified. Mr. Nelson pointed out that the concern crosses a number of scenarios. Dr. Ross felt it was a particularly strong consideration in this FAQ, which sets up a scenario similar to the Havasupai Case (to be discussed later in the agenda). Members agreed and added language to reflect this point as well.

Mr. Forster wondered if it was necessary to reiterate that de-identified samples do not constitute human subjects research. Mr. Nelson pointed out that this was clarified in previous scenarios. Mr. Forster suggested that FDA guidance should be referenced as well. The Chair reminded SACHRP, however, that FDA guidance was not addressed on any of the FAQs, with the understanding that the FAQs would be sent to the Subcommittee on Harmonization for consideration and annotation from this perspective. Mr. Forster agreed.

ACTION

SACHRP approved FAQ #15b unanimously with the following changes to the first paragraph of the response:

Response. *This is an institutional responsibility that may involve multiple components across the institution, including legal counsel, sponsored programs, and the IRB, as appropriate. The IRB's role could include determination as to whether the transfer **and use** of specimens at the new institution is compatible with the consent under which the*

specimens were collected or whether additional consent may be required, or whether there are concerns relating to the communities or populations represented by the specimens.

Future of SAS

Informed Consent. Co-Chairs reviewed SAS’s work in progress, which currently focuses on the major issue of improving the form and process of informed consent. Ms. Bankert observed that while the regulatory elements of consent have not changed, the level of detail provided in consent forms has steadily increased over recent years. This focus on “form over process” has shifted the emphasis from protection of subjects to protection of institutions, sponsors and investigators, and may work against truly informed consent.

A new work group within SAS plans to address the following specific topics:

- Regulatory issues, including:
 - Subpart A language on the elements and process of informed consent;
 - Reviewing comments in the *Federal Register* relevant to historical context and intent;
 - Holding interviews and discussions with people who were there as Subpart A was created.
- Issues related to the informed consent document, including:
 - Why forms have grown in length;
 - Study-specific content vs. institutional boilerplate language;
 - Possible development of sample language addressing some or all of required elements;
 - Repackaging of key vs. supplemental information; and
 - Coordination with other ongoing efforts to improve consent documents.
- Issues related to the informed consent process, including:
 - Identifying “best practices” for obtaining informed consent;
 - Identifying mechanisms for evaluating participant comprehension and understanding;
 - Creating a virtual repository/catalog of such practices.
- Other issues, such as:
 - The legal implications of moving some information from the consent form into supplemental materials;
 - Whether “repackaging” really is an improvement or just a rearrangement;
 - Whether the consent form is a contract; and
 - What it will take to change current practices.

DISCUSSION

Comments from SACHRP included:

- One SACHRP member was not interested in “why” forms have grown in length and was more interested in how to cut them back to size.
- Key issues in regard to consent forms include readability, emphasis, and the placement of information.
- “One size doesn’t fit all.” Prospective subjects differ in their information needs.
- It would be helpful if SAS identified alternative models for consent (both forms and process). Many IRBs misunderstand the requirements.
- What subjects want to know and what others think they want to know do not necessarily match.
- Often, the consent form addresses the regulatory criteria for informed consent in the order in which they appear in the regulations, with no understanding that this is neither helpful nor required.
- Some noted that the crux of informed consent lies not in the form but in the opportunity to discuss what is important with the subject. One remembered working with a population in which one out of twenty subjects were illiterate. However, the OHRP Director emphasized that a signed form is a relatively inexpensive way of verifying that key information is covered.
- It would be helpful for SAS to produce a document capturing questions IRB should ask themselves when they assess the consent form or process for securing consent.

Dr. Menikoff said OHRP was interested in exploring the proposition that consent forms can be prepared more efficiently. He wondered not only whether information could be better placed or condensed, but also whether information that is needed was commonly omitted.

Additional subjects to be addressed by SAS. Co-Chairs reviewed the lengthy list of SACHRP recommendations that have already been forwarded to the Secretary and invited comments from members on productive areas for future work.

DISCUSSION

SACHRP members suggested a number of subjects they felt would warrant SAS’s attention. These included issues unique to social science researchers, who are often “marginalized” by IRBs. Problems include IRBs acting as gatekeepers unnecessarily because, for example, they fail to understand unique issues in dealing with populations that do not relate well to documents and signatures. It would be helpful to include the perspective of social science researchers on issues related to identifiability, risk, and the return of research results.

Other issues highlighted by SACHRP members included:

- Community members as researchers.
- Community-engaged and community participatory research (e.g., in genomic research).

- The emerging field of human environmental research, including the effects of research on third parties or on the environment.
- Quality improvement as compared to research. (OHRP issued guidance in 2009 many find useful; it would be helpful to know if there is a continuing problem.)
- What constitutes human subjects research.
- Return of research results.
- What justifies additional protections for human subjects; this includes a systematic look at research results.
- Unique issues in reviewing international research.
- Research issues related to the use of the Internet (the subject of a later panel).

SACHRP members asked the OHRP Director to comment on the current status of OHRP guidance on what constitutes human subjects research, which SAS has postponed addressing. Dr. Menikoff said that OHRP continues to work on this area and is unsure how beneficial it would be for SAS to address it. He observed that one issue that quickly arises is why there should be a dividing line between research and nonresearch, given that significant harms can result from nonresearch activities.

Public Comment

Public comments were invited, but none were offered.

Panel: Ethics Consultations as Part of IRB Review

- *Norman Fost, M.D., M.P.H., Professor, Pediatrics and Medical History and Bioethics, and Director, Program in Bioethics, University of Wisconsin Hospital*
- *Benjamin S. Wilfond, M.D., Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Hospital, and Professor and Chief, Division of Bioethics, Department of Pediatrics, University of Washington School of Medicine*
- *Joachim F. Hallmeyer, M.D., Associate Professor, Psychiatry and Behavioral Sciences Stanford University School of Medicine*

The Chair explained that Susan Kornetsky, expected to be a panel member, was unable to attend. Dr. Fost will attempt to present her views as well as his own.

She observed that it is a longstanding expectation that IRBs are responsible for reviewing research from the standpoint of ethical concerns. Over the last few years, however, consultation services focusing on ethics have become a common part of deliberations. She asked:

- Is this separation of functions beneficial?
- How does ethics review relate to other IRB responsibilities and to the responsibilities of the investigator?
- Who, finally, has the responsibility and authority to identify ethical issues and ensure that they are addressed?

Note: PowerPoints for all presentations by speakers are posted on the OHRP Web site. Please see these resources for more detailed information.

Remarks by Norman Fost: Research Ethics Consultation: The Central Role of the IRB

Dr. Fost argued that bioethicists have a place in IRB review of research. He noted that research ethics is more complex and far-reaching than medical ethics; consequences of faulty ethical decisions have ripple effects that can affect untold numbers of people, blight the careers of investigators, and harm institutional reputations.

As a collection of diverse people, IRBs approach the ideal ethical observer – that is, someone who has a deep understanding of relevant knowledge, experience as a Principle Investigator (PI) and as a patient, is disinterested in the outcome, is dispassionate, and who is consistent in decisionmaking in similar situations. A qualified ethics consultant can play a role in educating and advising IRB members, as well as PIs. The ethicist should not be a “stranger at the bedside,” but rather be a fully integrated and contributing part of the treatment and research enterprise. The speaker believed, for example, that an ethicist who works at a medical center should attend teaching conferences and “hang out” in the clinical environment so that he or she recognizes the situations that arise and their context. Ideally, the ethicist should have experience as an IRB member. All protocols, he said, should have the benefit of input from ethicists.

Dr. Fost held that a workable model for IRB review is one in which the IRB uses qualified staff to verify regulatory compliance, with quality control from the IRB, while the IRB focuses on its original mission of ethical review. Alternatively, a subcommittee of IRB members could be responsible for the regulatory compliance review, freeing the full IRB to focus on complex issues.

Remarks by Benjamin S. Wilfond: Research Bioethics Consultation: More Potential than Sequencing Genomes

While agreeing that the IRB should be the focal point agreement for review of ethical considerations, Dr. Wilfond noted that qualified external consultants can often help IRBs think “outside the box.” He quoted the following definition of ethics consultation:

An advisory activity available throughout the lifecycle of a study. It involves interaction with the researcher or others stakeholders in the research enterprise and one or more individuals knowledgeable about the ethical considerations in research, regarding an ethical question related to any aspect of planning conducting, interpreting, or disseminating results of research related to human health and well being. The purpose of the interaction is to provide information; identify, analyze, and or deliberate about ethical issues; and recommend a course of action (Beskow et al., 2009).

Dr. Wilfond compared research ethics consultation to clinical consultation. Similarly, it is a mechanism for providing advice on ethical issues. He stressed that there are many points in the research review process at which ethical issues may be recognized and addressed, including before and after IRB review. For example, an NIH Institute Director asked for a consultation on the ethics of an approved study in which children were paid to serve as subjects. Bioethics consultants can speak to researchers as well as the IRB.

Ethics consultations have diverse clients. They provide in-depth discussion of “fine grained concerns” that are more detailed than those the IRB typically addresses, encompass broader issues, and may be helpful with unique or unresolved issues.

The consultant pointed out that of the 48 institutions participating in the Clinical and Translational Science Awards (CTAs) sponsored by NIH’s National Center for Research Resources, 36 use consultation services for bioethics (9 of which were in existence prior to receiving CTSA funding).

Remarks by Joachim F. Hallmeyer: Research Ethics Consultation

Dr. Hallmeyer pointed out that clinical ethics consultation has been used for over two decades to assist in research design (such as how to deal with incidental findings), help researchers respond to funding agency concerns, summarize relevant ethical literature on a topic, and assist with long-term examination of a difficult and controversial topic that requires extensive research. Ethicists can also offer advice on research issues that are not subject to IRB review, such as research that does not involve human subjects or large social questions. He commented that, from an ethical perspective, “some things need to be reviewed no matter what you call them.”

Examples of areas in which ethicists are frequently asked to consult include the following:

- Handling “incidental findings”;
- Returning research results;
- Tissue banking/DNA;
- Research in less developed nations;
- Methods of engaging communities in research;
- Stem cell clinical trials;
- Racial or ethnic groups; indigenous peoples; gender;
- Research with broad issues around social acceptability;
- Pediatric research (e.g., the meaning of “minimal risk” or “prospect of direct benefit,” or issues related to early phase “first in class” trials)

The speaker noted that in the current model for protocol oversight, the IRB assumes that investigators are staying up to date on relevant research ethics, while Principal Investigators (PIs) assume that IRB approval means that such issues are largely addressed; in reality, most scientists are not able to keep up with emerging ethical issues. Consultation in research ethics is able to address the gap.

DISCUSSION

Responsibility for ethics review. Referring back to an example given by Dr. Hallmeyer in which he sought ethical advice, Dr. Fost wondered what might have happened if he had not done so. Dr. Fost argued that IRBs might well not have picked up on the issue and the protocol might have been approved with limited attention to its implications. He felt that ethics consultation should happen routinely, not just in certain circumstances. Institutions that do not have access to ethicists should take advantage of regional resources to secure that perspective.

Dr. Strauss argued that rather than having to rely on secondary review by ethicists, this expertise should be included in the IRB. He suggested that IRBs may focus on regulatory compliance rather than ethical issues in part because such expertise is lacking on the board. An ex officio commented that some IRBs do not seem to understand that ethical considerations should be part of their job and was concerned that the availability of consulting ethicists would deepen this misunderstanding.

Dr. Wilfond agreed that ethics consultation should be elective rather than routine or required. However, he felt that ethical consultation does not in any way detract from the IRB's deliberations. He felt it was possible to be both an IRB member and an ethics consultant.

Observing that there has been a shift away from ethicists serving on the IRB to being accessed through consultation, Dr. Bierer expressed the view that ethical review is intrinsic to IRB review and approval. Another SACHRP member stated that "whatever the model for accessing expertise in ethics, it should be a function of the IRB."

Dr. Menikoff commented that as the ethics chair for a university, people routinely came to him to discuss ethical issues. He was concerned to find that when he was in charge of human research protection for NIH, his office had no representation on the ethics consulting service. He added that Dr. Wilfond's paper seems to belittle the capability of IRBs and imply that they should turn to consultants for complex analysis. He hoped that all IRBs viewed ethical analyses as part of their mission and said they should never be viewed as technocrats who only deal with the rules.

Dr. Wilfond said there were statements in his paper he no longer agreed with, and he conceded that the paper could appear inappropriately belittling of the IRB's role and capacity.

Dr. Ross asked how to ensure adequate time is spent on ethical aspects of protocol review, given that ethics consultation is a pro bono activity. Dr. Fost responded that being on the IRB should be part of the ethicists' obligations. He felt, however, that all IRB members should be paid. He added that people would be more willing to be on the IRB if it made better use of their time and suggested "offloading" routine compliance checks. He added that his IRB does its compliance review "offline." This, in turn, makes IRB service more enjoyable. Mr. Forster said he understood that Canadian law requires the presence of a health ethicist on the IRB.

Ethics consulting in practice. A SACHRP member wondered how it was possible to avoid ethical consultants being played against each other in search of the desired answer. Dr. Fost felt this was an argument for including an ethics consultant on the IRB.

A SACHRP member asked whether ethics consultants would recuse themselves from serving on an IRB if they have provided consulting services for the IRB. Dr. Wilfond said he would recuse himself in such a case.

A SACHRP member asked Dr. Hallmeyer why he sought ethics consultation in a case he described as part of his presentation. He explained that he could understand both arguments and wanted independent advice that he could take or leave.

A SACHRP member asked how an ethics consultant would respond to a call reporting a problem with the caveat, “don’t mention my name.” Dr. Fost said that the priority was to ensure that the right thing was done. If the caller must remain anonymous, it is usually still possible to find a way to make sure the allegation is investigated. He added that people often want to talk with him offline before a protocol is submitted, and he is always glad to do this as a colleague (not as the IRB Chair).

WEDNESDAY, JULY 21, 2010

Remarks

Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer reviewed the agenda for the day and introduced the panel on the Internet in human subjects research. She expressed the hope that SACHRP will be able to view the issues raised (e.g., when is the Internet “public space”?) in the context of the regulations. Issues of confidentiality, appropriate consent, subject privacy, identity of the subject (e.g., assuming an online identity such an avatar), and security are all active issues not explored or even considered when the regulations were written.

Panel: The Internet in Human Subjects Research

- *Elizabeth Buchanan, Ph.D., Director, Center for Information Policy Research, School of Information Studies, University of Wisconsin-Milwaukee*
- *Montana Miller, Ph.D., Assistant Professor, Department of Popular Culture Bowling Green State University*
- *Michael Zimmer, Ph.D., Assistant Professor, School of Information Studies, and Associate, Center for Information Policy Research, University of Wisconsin-Milwaukee*
- *John Palfrey, J.D., Vice Dean, Library and Information Services and Faculty Co-Director, Berkman Center for Internet and Society, Harvard Law School*

Remarks by Elizabeth Buchanan: Internet Research Ethics and IRBs

Dr. Buchanan pointed out that the Internet is both a tool for research (for example, a place where data is stored) and a medium or locale of research. Ethical issues are most likely to arise in the latter case. For example, a researcher was using the website “Gay Bombay” to survey the attitudes of gay Indian men at a time when homosexuality was illegal in India. The IRB was concerned about whether participation in the research might place subjects at risk. Other examples of questions that arise include:

- A student wishes to analyze blog postings as part of her Master’s thesis. Must she seek IRB review?
- A researcher wants to use a public list archive where membership is required. Must he gain consent? Or is this situation analogous to a “public park” in which consent is not required?
- Is aggregated Facebook data really anonymous?

Such questions require reinterpretation of the regulations and fresh consideration of ethical principles in a new context. Dr. Buchanan conducted an exploratory study to examine the state and perceptions of Internet research reviews in US-based IRBs. Fifty percent of the responding IRBs saw the area as an important one; those who did not generally said they had not received protocols for Internet-based research but were “bracing” for the experience. Most did not have any specialized guidelines for such research or a designated member of the IRB with expertise in the area; the vast majority did not have any specific training for members that addressed ethical issues for research using the Internet. Frequently, an ex officio person with technical background is brought in to assist the IRB with such protocols on a case-by-case basis.

Problematic areas for research involving the Internet include the following:

- *Anonymity/ Confidentiality.* Examples of issues include: Is there a truly secure online interaction? Is an “anonymous” survey possible? If e-betty is portrayed in research on an electronic support group for a medical condition, will she be identifiable? If so, at what risk?
- *Revealing Identities.* Examples of issues include: How should online participants be identified in research reports? By changing screen names, do you detract from the “reality” or “reputation” of the participant?
- *Public and Private Spaces.* Examples of issues include: Is a particular forum, listserv, chat room, or bulletin board considered *by its members* to be a public space or a private space? What expectations of privacy exist? What role does the researcher play in the space? Under what circumstances should researchers identify themselves?

- *Ownership/Stewardship of Data.* If we use outsourced “cloud” space, we may no longer be able to say with certainty that data will be destroyed at a certain time or retained for a specific period. Further, the security and privacy of the data are less well defined.
- *Respect for Persons/Autonomy.* How do researchers obtain informed consent?
- *Recruitment.* How does the researcher enter the research space to begin recruiting? What if some in an Internet community consent, but others do not?

A comprehensive collection of documents and scholarly articles on Internet research ethics may be found at: <http://internetresearchethics.org/>

Remarks by Montana Miller: Virtual Ethnographic Research: The Human Element in Fieldwork Online

Dr. Miller held that many IRBs are unfamiliar with the kinds of online places and communities where researchers are now carrying out qualitative research, and with the norms (including expectations for privacy) that apply in these spaces. The identities people assume in the hundreds of virtual worlds that now exist have widely varying relationships with their offline selves. For many reasons, it is not always clear when research on a site should be considered research involving human subjects and be subject to IRB review.

Examples of issues raised by the speaker included the following:

- When do you need to get consent when doing online research? Who do you get consent from, the avatar or the person behind it?
- If you are working in an Internet environment that is constantly changing, do you have to post consent continually?
- When is something “published work,” (text based), and when is it communication (person-based research)?
- Are you in a public venue or are you in a private venue? (Within a single site, there are varying ranges of what’s public and private. Familiarity with the specific context is critical, as well as appreciation for the sensitivity of the content that is discussed.)
- How and when should the researcher identify himself or herself as a researcher, as opposed to “lurking”? One ethnographer identifies herself by means of a “balloon” over her Second Life avatar, while others use consent cards answered in or outside the Second Life environment. Respondents are asked to respond as their avatars or in their offline identities.

As a teacher, Dr. Montana hears from students who have difficulty understanding why privacy concerns matter in an online environment. She finds that her students have difficulty distinguishing among journalism, memoirs, marketing research, and other ways of presenting

data. She observed that when we go through the IRB process we are acting as if we all live in a world in which people control information, which is often not the case on the Internet. Still, she said, we have to act “as if” this is the case in order to be true to our own professional ethics and values.

Remarks by Michael Zimmer: Research Ethics in the 2.0 Era: Conceptual Gaps for Ethicists, Researchers, IRBs

Dr. Zimmer held that 2.0 tools, environments, and experiences are creating new conceptual gaps in our understanding of privacy, anonymity vs. identifiability of subjects, consent, and harm.

Examples include:

1. Facebook data were sampled through the IRB-approved “Tastes, Ties, and Time” (T3) research project, which sought to understand the dynamics of the social network in large groups of students. Despite attempts to protect anonymity, the university was easily identified; the identity of individual subjects was also potentially discoverable based on information such as student majors retained in the data set.
2. Pete Warden, an independent researcher, harvested and proposed to release public Facebook profiles for 215 million users. He completed analyses at the aggregate level potentially of interest to the academic community. Under a threat of lawsuit from Facebook, however, he destroyed data that he had considered public.
3. Questions also arise in regard to consent for using “public” Twitter streams, which the Library of Congress plans to archive. The speaker posed a series of questions:
 - Is it ethical for researchers to follow and systematically capture public Twitter streams without first obtaining specific, informed consent by the subjects?
 - Are “tweets” publications or utterances? Are you reading a text or recording a discussion?
 - What are users’ expectations as to how their tweets are being used? Can users opt out from being in a permanent archive?
 - What about a public tweet that is retweeting a tweet intended as private?

The speaker held that the contextual nature of data sharing must be taken into account and stressed the ease with which datasets may be individually identifiable in the computer age. Researchers who operate on the assumption that the release of public data could not cause harm ignore the principles of dignity and autonomy; in addition, they may fail to consider unanticipated consequences of the use of these data. He said IRBs need specialized training as well as access to best practices and guidelines to address areas such as these.

Remarks by John Palfrey: Internet Research Ethics: Youth Media Usage Perspective

Mr. Palfrey concentrated his remarks on the implications of emerging technology for research involving youth. In particular, he highlighted the following trends:

- Youth do not distinguish between their online and offline lives. Increasingly, these environments converge; they do not think of themselves as having a “digital identity” distinct from the one they have in “real life.”
- The demand for interoperability means that information moves rapidly across different contexts. It is increasingly difficult to articulate principles to assist IRBs in reviewing that work across these various contexts over time; however, such a framework of stable principles is clearly needed.
- Although there is great concern about sexual predation, studies show that predation using the Internet is decreasing. The psychological harms done to young people using the Internet can be much more significant.
- It is a myth that young people do not care about privacy. They do. Often, they want to protect their privacy from adults and share information with a few close friends.
- We all have “digital dossiers,” but few of us are aware of the tracks we leave behind.

DISCUSSION

SACHRP members asked questions of panel members and explored topics raised in the presentation.

How can SACHRP help address issues regarding the Internet and research? Panel members suggested the following:

- Become educated on Internet-related issues and help to educate IRBs on the subject.
- Advise IRBs strongly to attend workshops and gain expertise on the subject.
- Articulate enduring and stable principles IRBs can use in decisionmaking, based on the rules we have already.
- Develop a FAQ on Internet research ethics that includes basic definitions and guidelines; link readers to <http://internetresearchethics.org/>
- Facilitate sharing of protocols across IRBs so we can “leverage what’s out there.”

Dr. Strauss commented that OHRP has difficulty mandating training, so guidance is the most practical thing SACHRP can offer. He asked for feedback on whether it would be possible to develop a useful FAQ that addressed issues such as whether avatars are subjects and the meaning of “publicly available” in an Internet setting. Dr. Miller said this would be a good start, but it would be important not to make guidance sound like “the answer.” Mr. Palfrey agreed, urging

that any guidance not conceal the fact that many of the issues discussed fall in a grey zone. He suggested trying to distill principles and cite some helpful cases, knowing that none of the cases will exemplify “bright line rules.”

Public and private spaces. Research exempt from IRB review includes “study of existing data if these are publicly available.” Panelists argued that even on the Internet, there may be an expectation of privacy for specific sites and activities (for example, a ListServe on which persons with a particular disease or condition become members and share their experiences). Ms. Bankert, however, was surprised that any Internet user would have an expectation of privacy and saw a need for increased public awareness around the ease with which their data can be accessed and used for research.

Dr. Miller observed that while some might assume it is up to users of Facebook to protect their own privacy by using the appropriate settings, there are frequent changes in the privacy rules, and people cannot be expected to know all their friends’ privacy settings and act accordingly. Information that was private can become public. Mr. Palfrey added that all sites have policies (which are typically unread by their users) that specify the site can change the rules.

Dr. Zimmer commented that one implication of technology is that ease of access to public information has increased dramatically. One can now find information online that once required a trip to the courthouse. While someone studying people’s behavior in a park would be restrained by their ability to take notes, the Internet makes data collection and analysis of aggregated data (including the potential to identify individuals) far easier.

Dr. Buchanan reported that a colleague does transaction log analyses based on IP addresses, which in the European Union are identifiable information. Zip codes in the United Kingdom are more unique. Ethics boards and researchers can find themselves debating the use of such common identifiers (for example, in the field of epidemiology).

Observation and intrusion. David Strauss commented that members of online communities may have expectations similar to those attending Alcoholics Anonymous meetings – that others who attend the meeting share a common purpose and agenda. Researchers observing chatrooms have met with a good deal of ire. He asked what investigators’ obligations are to research subjects when they are “lurking” to do research. Dr. Miller responded that there is an issue of whether it is even possible to reveal what you are doing to everyone. He suggested that IRBs ask, when reviewing research that might be considered an intrusion, whether there is another, more open way to get the same information. Such research should proceed only if it is the only way to do it and if it is really important.

Mr. Palfrey and Dr. Miller said that researchers sometimes need to distinguish between the norms of the community and their own professional norms, remaining accountable in the Internet environment.

Sharing and storing data. Storage of data in “clouds” calls for reconsideration about what researchers can tell subjects about what will happen to their data in the future. Researchers may want to select storage within the U.S. or negotiate to have certain conditions met by the service.

Dr. Buchanan suggested that psychological risks may accompany subsequent uses of data, and language should be included in consent forms that reflects these risks.

Responding to apparent emergencies. An ex officio SACHRP member asked panelists to comment on the researcher’s obligations when he or she “overhears” an Internet user who is threatening suicide or violent behavior. A SACHRP member noted that some people have mandatory obligations to report such behavior, even when they are not seeing the individual as a patient.

Dr. Miller responded that when people express themselves online, there is often an element of performance and dramatization that makes it impossible to take what is said at face value. Statements can easily be misinterpreted. “You don’t know what you’re observing,” she said; for example, an adult may be pretending to be a child, or vice versa. This is an instance in which the law “hasn’t caught up to the real world.”

Dr. Buchanan, however, reported the experience of a colleague studying a group of young girls who chose not to take action when one of the girls threatened suicide; the researcher later found she had indeed followed through on the threat. Mr. Palfrey said the observer’s good judgment would have to be the guide to what should be done – or even what *can* be done under the circumstances.

Veracity. An ex officio member noted an instance in which a teacher had a Facebook site manufactured for her by a student. A panelist responded that this is a problem, but such instances can be reported to Facebook and handled. Mr. Palfrey added that the veracity of information available online is a vector that researchers must take into account.

Implications from the Havasupai Case

- ***William L. Freeman, M.D., M.P.H., C.I.P., Program Director, Northwest Indian College Center for Health, and Human Protections Administrator, Northwest Indian College***
- ***Pearl O’Rourke, M.D., Director, Human Research Affairs, Partners HealthCare System, Boston, MA***
- ***Carletta Tilousi, Ph.D., Havasupai Tribal Council Member***

Remarks by William L. Freeman: Brief Chronology of the Havasupai Case and Settlement

Dr. Freeman presented a brief chronology of the Havasupai Case and settlement, in which a tribe that approached a researcher for help understanding its problem with diabetes learned that the blood samples they donated were being used for research the Tribe considered unauthorized and that it found offensive and hurtful. The tribe was ultimately settled its lawsuit and secured the return of the samples, along with a financial settlement and an apology. The speaker compared the priority placed by the tribe on the return of the specimens to veterans’ desire to ensure the return of remains of soldiers missing in action and give them respect and care. He noted that two other Canadian tribes had experiences similar to those of the Havasupai.

Considering the take-away lessons from the painful experience, the speaker noted that the impact of study participation for any participant depends in part on their values, which are held within a cultural context. To enable each individual to make an informed decision, the researcher must give information that is “understandable” (45 CFR § 46.116, General Requirements for Informed Consent) in terms of this context. He then posed the following question to SACHRP:

- Do participants have a continuing “privacy interest” in what research is done on their specimens?

An affirmative answer would run counter to the current policy of exempting research on anonymized specimens from IRB review on the grounds that such specimens do not constitute research involving human subjects. He noted that the decision of the Arizona Court of Appeals, which ultimately ruled in favor of the Havasupai, mentioned the plaintiffs’ “privacy interest” repeatedly and cited the following finding from two similar cases reviewed in the 9th Federal Circuit Court:

- “It goes without saying that the most basic violation possible involves the performance of unauthorized tests – that is, the non-consensual retrieval of previously unrevealed medical information that may be unknown even to plaintiffs.” See: <http://ftp.resource.org/courts.gov/c/F3/135/135.F3d.1260.96-16526.html>

If tribes can have “privacy interests” and suffer “dignitary harm,” the speaker cautioned, other communities may be entitled to similar consideration (for example, “disease communities”).

Remarks by Pearl O’Rourke: Implications for the Use of Tissue in Research

Dr. O’Rourke observed that tissue is and has always been an important resource for biomedical education and discovery. Recently, because of personalized medicine and genomic research, it has become even more important. While researchers ideally would like to have identifiable specimens, they often accept de-identified ones because of the cost and logistics involved in obtaining informed consent for identifiable specimens. Surrounding issues have increased in complexity, however, as subjects increasingly call for participatory research, recognition that they would like control over their specimens, and information about research findings. The Havasupai settlement raises profound questions related to:

- The adequacy of consent procedures;
- Control of specimens;
- Researchers’ responsibility to participants; and
- Community risk assessment.

Current regulations and related guidance hold that the concept of a “human subject” excludes de-identified tissue. The speaker stated, however, that in practice, “we spend way too much time trying to figure out identifiability” because of the regulations. She wondered, in fact, whether we are now at a point where “everything should be considered identifiable anyway.” She argued that

there were “specific disconnects” between the traditional view of tissue and the emerging public perspective. She pointed to three options for moving forward:

- Option 1: Maintain the status quo, but improve the consent process and educate clinicians, researchers, and the public.
- Option 2: Consider all tissue identifiable and maintain the regulatory status quo. This would result in a huge burden for IRBs, with little or no benefit.
- Option 3: Consider all tissue identifiable and re-evaluate and potentially modify the regulatory process to encompass new models of notification and/or consent.

The speaker held that Option 3 would be preferable. At the least, she argued, there should be broad-based discussion involving all interested parties with the goal of developing common practices for today and for the future.

Remarks by Carletta Tilousi: The Perspective of a Havasupai Tribal Member

Ms. Tilousi explained that the Havasupai Tribe includes 600 members, half of whom live in a village located at the base of the Grand Canyon. They believe that they have lived there since creation. The Tribe now sees itself as a victim of scientific research that used blood samples from 200 Tribal members – people who believed the samples would be used to help the Tribe address a problem with diabetes – to conduct research that runs counter to their cultural beliefs and values.

Because of their experience, they are now reluctant to participate in research. As they shared their experience with other tribes, many of them have become cautious as well. The Navajo Nation, for one, cancelled all research in progress in order to review related agreements more carefully.

The speaker stressed that economically or educationally disadvantaged groups require extra precautions when they are study subjects. Few of the Havasupai spoke English, for example, and the Havasupai language does not have a term for DNA. There are only three college graduates in the Tribe. The Tribe came together to fight for the return of their blood; Ms. Tilousi was surprised that the State of Arizona fought the Tribe with 3 million dollars in legal fees. The Havasupai were able to pursue their lawsuit with the help of other tribes and the National Congress of American Indians. She said the Havasupai appreciated the support they received in their long struggle, which the Tribe took on “for all indigenous people around the world.”

Ms. Tilousi showed the video “Blood Journey,” which was made by the *New York Times* about the Havasupai experience. It may be viewed at the following site:

<http://video.nytimes.com/video/2010/04/21/us/1247467672743/blood-journey.html>

DISCUSSION

Community benefits and harms. The Chair apologized to the Havasupai and expressed appreciation for Ms. Tilousi's willingness to share the Tribe's experience. She observed that many kinds of communities are affected by research and asked for comments on how community benefits or harms should be addressed in protocol reviews. Comments included:

- Dr. O'Rourke noted that many studies involve multiple communities, and community members may have differing perspectives.
- Ms. Tilousi said that while long-term harm was done to her community, one benefit was that it came together and was empowered.
- Dr. Freeman commented that the Indian Health Service (IHS) uses a system in which the tribe must review and approve research as well as the IHS's IRB. He also noted that communities have varying perspectives on the same issue. He said that IRBs themselves are not capable of community involvement; they can only act as a safety net, asking the researcher to work with the community, think through his or her responsibilities to the community, and show evidence of their input.
- Dr. Marshall observed that the notion of what constitutes "community" has not been addressed effectively historically, and the community's interest in research is often not recognized.

What went wrong. A SACHRP member asked why samples were not sent back as soon as Arizona State University (ASU), under whose auspices the study was done, understood there was a problem. Dr. Freeman said that while he could not speak for ASU, it was his belief that ASU did not mean to harm the tribe and did not understand that it had done so. Its view was that the requisite consent had been given. He added that the IHS's IRB did not approve the protocol, saying that it was "incomplete." OHRP commented that ASU had produced records of IRB meetings and signed consent forms.

Ms. Tilousi observed that the researchers seemed well respected, and the IRB must have been lax in its understanding and oversight of what was happening. Dr. O'Rourke said the culture of the whole research institution was part of the problem. A speaker observed that one lesson learned is that "there are some values that exceed the value of science" and that data represent living people.

Dr. Ross was concerned that there was apparently no agreement for creating a tissue bank as part of the study. She believed that the same scenario could reoccur, given that de-identified samples are not considered research involving human subjects.

Consent. Dr. Menikoff said that OHRP is currently struggling with the issue of whether it is a regulatory violation if someone uses de-identified tissue in a way the original donor could not have foreseen. He stressed that this issue is "very much on the table."

A SACHRP member commented that while IRBs are typically able to determine what secondary uses of data were approved by the subjects, it is difficult for IRBs to ask questions about potential benefits and risks from the perspective of the community.

Dr. O'Rourke stressed the importance of biobanks having procedures in place that address issues of consent.

Prevention. Ms. Tilousi said her Tribe was focused on prevention and did not want to see any others go through the pain they experienced. She said she believed that researchers should be more closely monitored and sanctioned when their actions are unethical. She said the tribe was concerned that researchers did not seem to be held accountable for their unethical actions.

Dr. Sodeke said the Havasupai's story resonated with him and could happen again, here or internationally. He said the Maori of New Zealand have struggled with similar issues. It is important to recognize the privileges and powers some people have over others, the diverse values people hold, and the different ways humans have of knowing, feeling, and being.

Dr. Strauss commented that storytelling is part of the tradition of research ethics; stories like the one we heard today are how we teach others. He felt this story was compelling and will be added to many other stories that local IRBs will hear as they try to address the needs of communities.

Office for Civil Rights Report on Notice of Proposed Rulemaking

Christina Heide, J.D., Senior Health Information Privacy Policy Specialist, OCR

On July 14, 2010, OCR published a Notice of Proposed Rulemaking (NPRM) to modify the HIPAA Rules in response to provisions enacted under the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009. Specifically, OCR proposes to revise the existing Standards for Privacy of Individually Identifiable Health Information (Privacy Rule); the Security Standards for the Protection of Electronic Protected Health Information (Security Rule); and the rules pertaining to Compliance and Investigations, Imposition of Civil Money Penalties, and Procedures for Hearings (Enforcement Rule) issued under HIPAA. The NPRM has a 60-day comment period. Compliance with the new rules will be required within 180 days after the effective date of the Final Rule.

Ms. Heide stressed that OCR has been working closely with OHRP to make progress on harmonization of the Common Rule and research provisions of the HIPAA Privacy Rule. In addition to the HITECH provisions, Ms. Heide noted specific proposed modifications of particular interest to the research community. The NPRM proposes to permit a single authorization to address the research use of information for a clinical trial as well as for the collection of biospecimens into a repository. The NPRM also requests comment on the specificity of authorizations for future research. Ms. Heide encouraged everyone to review the NPRM and submit any comments. The NPRM may be reviewed at this site:

Subcommittee on Harmonization Report

David Forster, J.D. and Mark Barnes, J.D., Co-Chairs

Co-Chairs reported that the Subcommittee on Harmonization (SOH) had its first in-person meeting April 15-16, 2010, and plans to hold monthly teleconferences. At the initial meeting the subcommittee identified “constellations” of issues where harmonization among the agencies could benefit the regulated community, then prioritized these “constellations,” proposing to address them sequentially. The process will be in each case to:

- Identify areas in which there is a lack of consistency;
- Develop proposals; and
- Bring the proposals to SACHRP for consideration.

“Constellations” identified by the subcommittee include the following:

- *FDA-related issues.* For example, the subcommittee would like a better understanding of how the IRB and investigator consider whether or not FDA regulations apply. Other topics include the comparative definitions of “clinical investigation” and “human subject” for FDA and OHRP, as well as specific issues related to registries and to risk evaluation and mitigation strategies.
- *Standard practice, innovative care, research, and clinical investigation.* The subcommittee is interested in how these terms are defined.
- *Definition of a non-scientist.* How do OHRP and FDA define a non-scientist? (The term appears on the IRB registration page.)
- *Tissue research.* The subcommittee sees a need for harmonization around a variety of issues related to tissue research, including the definition of what is “identifiable.” The greatest amount of potential overlap with the work of SAS is in this area.
- *Conflicts of interest.* The subcommittee is interest in standards for what constitutes a conflict of interest and how it should be managed across HHS entities.
- *HITECH.* Areas to examine include breach notification requirements as compared to the Common Rule and FDA reporting requirements, as well as breach notification issues related to limited data sets.
- *Recruitment of research subjects.* Harmonization issues include guidance on when research begins, paying subjects, and the use of social media to recruit subjects.

- *Engagement of community in research.* Examples of issues include guidance about how and when the community should be engaged in research and what constitutes community consultation in an emergency.
- *Consent Issues.* The subcommittee will consider guidance on the use of short forms for subjects who do not speak English, documentation of consent, and waivers of consent. This is another area that has “substantial overlap” with the work of SAS.
- *Application of Subparts B, C, D and additional subparts added by Common Rule signatories.* These vary greatly across agencies.
- *International research.* A wide variety of issues exist around regulations and standards related to international research, including those related to preemption.
- *Laws by States and non-HHS agencies.* This is the broadest issue and one of the most difficult for SOH to address productively.
- *Incapacitated adults.* SOH will consider whether a range of guidance from various entities can be harmonized.
- *Safety issues.* FDA, NIH, and OHRP have different guidance around unanticipated problems, assessment of safety by sponsors and others, and what issues are considered serious.
- *Local Attitudes.* Guidance from FDA and OHRP differs. The issue is timely given current emphasis on the use of central IRBs.
- *Exculpatory Language.* FDA and OHRP are both working on guidance in this area.
- *Procedural Issues.* The subcommittee would also like to explore broad procedural changes, including:
 - Creation of a single new agency to oversee all human subjects research in the US
 - Procedural changes in the way that the Common Rule agencies establish guidance in order to promote harmonized guidance, and
 - Procedural changes to require or promote joint regulations and/or guidance from OHRP and FDA and other HHS agencies.

The subcommittee is interested in hearing from the public about harmonization issues and the need to resolve them. The co-chairs have drafted a Request for Information that is being reviewed by HHS agencies.

Prioritized issues included:

- FDA-related issues,
- Conflicts of interest,

- “Unspecified future use” and secondary use,
- The implications of HITECH, and
- Issues related to international research.

Work groups have been established in each of these areas.

SACHRP Response to NPRM on Conflict of Interest

Mark Barnes, J.D.

On behalf of the Subcommittee on Harmonization, Mr. Barnes drafted a letter for SACHRP consideration in response to an HHS Notice of Proposed Rulemaking (NPRM) issued on May 21, 2010. The complex changes proposed, he said, would lower the financial threshold defining what constitutes a reportable conflict of interest for the Public Health Service, making the Federal requirements for reporting and managing such conflicts even less harmonious than they are at present. Specifically, he pointed to differences among the National Science Foundation, FDA, and the Public Health Service. He held that it was “inexplicable” that HHS articulated two such different standards governing conflict of interest and that it was inconsistent with the goal of harmonization.

The comment period had just been extended, making it possible for the committee to approve and provide input, albeit on short notice. The NPRM may be viewed at:

<http://www.federalregister.gov/articles/2010/05/21/2010-11885/responsibility-of-applicants-for-promoting-objectivity-in-research-for-which-public-health-service>

The draft letter as presented to SACHRP read as follows:

Re: Notice of Proposed Rule Making, Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought, 75 Fed. Reg. 28688 et seq. (May 21, 2010)

Ladies and Gentlemen:

The Secretary’s Advisory Committee on Human Research Protections (SACHRP) was chartered in 2003 to advise the Secretary of the United States Department of Health and Human Services (HHS) and its Office of Human Research Protections (OHRP) on policies and practices related to human subjects research, as they are used and applied by HHS and its constituent agencies and offices. SACHRP’s predecessor advisory committee, the National Human Research Protections Advisory Committee (NHRPAC), which also served in this advisory capacity to the Secretary, was disbanded in 2003, when SACHRP was chartered.

By this letter, SACHRP is pleased to submit its comments on the recent Notice of Proposed Rule Making relating to financial conflicts of interest in research funded by the Public Health Service (PHS). SACHRP’s submission of these comments is consistent with its previous involvement in these issues, and vindicates its responsibility to advise

the Secretary regarding changes in regulations that may affect the safety and welfare of human research subjects.

Over its history, SACHRP (and before it, NHRPAC) has initiated several working groups and subcommittees, each with a charge to analyze specific issues related to human subjects protections, with a view toward enhancing those protections and facilitating valuable scientific research. In 2001, for example, during the intense national conversation over the possible adverse effects on human subjects research of investigator financial conflicts of interest, NHRPAC provided to the Secretary a detailed working group report on these issues, with specific recommendations on how to strengthen oversight and management of financial conflicts of interest in research.

At that time, very specifically, NHRPAC was mindful of the need for the national research community to develop consistent standards for disclosure and management of financial conflicts of interest in human subjects research. Its report therefore endorsed the notion that institutions should consistently apply the PHS thresholds for financial disclosure (\$10,000, or 5 percent or greater equity interest in an entity, that might reasonably be thought to effect the research) to all human subjects research, regardless of source of funding, in order to provide the same standards for all researchers and the same level of protection to all research subjects. Similarly, at that time, NHRPAC noted the disparate standards for investigator financial disclosure under the regulations of PHS, the National Science Foundation (NSF), and the Food and Drug Administration (FDA), and suggested that these disparate standards be harmonized:

Ultimately, conflicts of interest financial thresholds and disclosure standards should be harmonized between the FDA, NIH and NSF. Strong consideration should be given to applying harmonized standards to all privately funded medical research, so that all research would be subject to the same standards of disclosure and analysis.

NHRPAC, Letter to Arthur J. Lawrence, Assistant Surgeon General, August 23, 2001, p. 2-3, available at: <http://www.hhs.gov/ohrp/archive/nhrpac/documents/aug01a.pdf>.

Most recently, in 2010, based on its awareness of increasing confusion in the research community caused by inconsistencies in human subjects research regulations among all the various parts of HHS, SACHRP initiated a new Subcommittee on Harmonization (SOH). The charge to SOH from SACHRP has been to:

[I]dentify and prioritize areas in which regulations and/or guidelines for human subjects research adopted by various agencies or offices within HHS would benefit from harmonization, consistency, clarity, simplification and/or coordination. The Subcommittee will then develop recommendations, for consideration and possible adoption by SACHRP, to harmonize and simplify these guidelines and regulations. The goal of this subcommittee effort is to reduce unnecessary burdens on research efforts, thus resulting in better allocation of research resources and promoting the safety and welfare of human subjects.

In this regard, SOH has reviewed the recent NPRM and its proposed changes to the structure and requirements for disclosure and management of financial conflicts of interest in human subjects research. Among the significant changes being proposed by PHS are: a reduction in the threshold amount for disclosure of “significant financial interest” from the existing \$10,000 threshold, to a threshold of \$5,000 over the previous 12 months, in a laudable attempt to increase transparency in this area; the inclusion of intellectual property rights of uncertain value as a “significant financial interest”; the adoption of a standard for disclosure as calibrated to an investigator’s “institutional responsibilities,” as opposed to his or her involvement in a specific PHS-funded study; and the requirement that institutions post on their public websites specific investigator financial conflicts of interest that have been deemed significant.

Consistent with its past and ongoing concerns with failure of the various parts of HHS to harmonize and make consistent their regulatory and policy approaches to human subjects research, SACHPR would express its concern that throughout the NPRM, there is little to no consideration expressed for the ways in which current and proposed PHS regulation and guidance in this area is fundamentally different from that of FDA, even though these disparate regulations often apply to the same researchers and the same studies, within the same institutions. As PHS is aware, FDA maintains its own financial interest disclosure processes and requirements, using specific FDA forms, and using financial interest standards that are set, in general, as \$25,000 in income from the sponsor of a study during the course of that study and for one year following the study’s completion, and \$50,000 in equity interest held by an investigator in a publicly-traded sponsor of his or her research. Further, the current and proposed PHS regulations focus on prospective management of financial conflicts of interest in order to reduce the possibility of adverse influence on research, while FDA regulatory structure focuses only on disclosure of conflicts to sponsors, and does not require management of conflicts by sponsors or institutions.

SACHRP notes and regrets that the proposed changes to the PHS regulations do not in any way move toward harmonization or reduction of inconsistency between these markedly different regulatory approaches to the common issue of investigator conflict of interest. Under the proposed revised regulatory structure, the standards for identification and disclosure of conflicts would continue to differ in vast and important ways, thus complicating compliance efforts by investigators, sponsors and institutions, and confusing research subjects who might seek to understand how and why financial conflicts of interest are handled in studies for which they have volunteered.

As one example, please note the NPRM’s proposed rule relating to instances in which a “PHS-funded project whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted or reported, by an investigator with a [financial conflict of interest] that was not managed or reported by the institution as required by the regulations.” 75 Fed. Reg. 28699. In such a case, according to the NPRM, the institution “must not only require the investigator involved to disclose the

[conflict] in each public presentation of the results of the research, but also to request an addendum to previously published presentations.” *Id.*

In this example, the discontinuities between the NPRM and FDA approaches become painfully clear: when a drug is tested with PHS funds but financial conflicts of interest of over \$5,000 received or held over the previous 12 months are undisclosed and unmanaged, HHS becomes so concerned about possible bias that it proposes to require disclosure by investigators themselves of their conflicts in any publications and presentations; yet in drug trials under the direct jurisdiction of FDA (for example, those conducted under an Investigational New Drug exemption), HHS requires no management of conflicts, and to the extent that conflicts must be disclosed to sponsors and FDA, assumes that financial interests of less than \$25,000 in income during the course of the study and for one year thereafter, and less than \$50,000 in equity investment, are insufficient to pose significant risk of research bias, or, presumably, risk of harm to research subjects.

SACHRP believes that the regulatory standards for identifying and managing financial conflicts of interest in human subjects research should be rigorous, in order both to protect human subjects from compromised study design or conduct, and to assure that risk of bias to results is minimized. Presumably, PHS and FDA share these concerns and these goals. It therefore strikes SACHRP as odd and unwise for these two constituent agencies within HHS to continue – and with the NPRM, even to broaden – their very significant differences in this area. Research subjects, researchers, and research institutions are, in SACHRP’s estimation, deserving of a greater consistency of regulatory approach to these critical issues. SACHRP therefore respectfully commends to the attention of PHS the failure of the new proposed standards to vindicate the important objective of regulatory consistency, and would recommend that PHS hold further consultations with FDA, as well as NSF, in order to address these long-held and pressing concerns of the national research community.

DISCUSSION

Key points in the discussion of the draft letter included the following:

- Some members felt the letter was too long.
- Members wanted to tone down language such as “odd and unwise” and maintain a more neutral voice.
- Some members wanted to make specific recommendations; however, given the time available, they determined to make any such recommendations in their institutional capacities rather than as SACHRP.
- The FDA representative stated that the letter was in error in stating that FDA regulations do not require that disclosures of conflict of interest be managed by the sponsor.
- SACHRP’s more recent work on the issue should be referenced.

ACTION

Expressing appreciation for Mr. Barnes's work crafting the draft letter, SACHRP unanimously approved the following revised letter:

Re: Notice of Proposed Rule Making, Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought, 75 Fed. Reg. 28688 et seq. (May 21, 2010)

Ladies and Gentlemen:

The Secretary's Advisory Committee on Human Research Protections (SACHRP) was chartered in 2003 to advise the Secretary of the United States Department of Health and Human Services (HHS) on policies and practices related to human subjects research, as they are used and applied by HHS and its constituent agencies and offices. SACHRP's predecessor advisory committee, the National Human Research Protections Advisory Committee (NHRPAC), which also served in this advisory capacity to the Secretary, was disbanded in 2003, when SACHRP was chartered.

By this letter, SACHRP is pleased to submit its comments on the recent Notice of Proposed Rule Making relating to financial conflicts of interest in research funded by the Public Health Service (PHS). SACHRP's submission of these comments is consistent with its previous involvement in these issues, and executes its responsibility to advise the Secretary regarding changes in regulations that may affect the safety and welfare of human research subjects. SACHRP's comments here are limited to the issue of the lack of consistency of conflict of interest regulations; our silence on other aspects of the NPRM should not be interpreted as support for or opposition to those aspects of the NPRM.

Over its history, SACHRP (and before it, NHRPAC) has initiated several working groups and subcommittees, each with a charge to analyze specific issues related to human subjects protections, with a view toward enhancing those protections and facilitating valuable scientific research. In 2001, for example, during the intense national conversation over the possible adverse effects on human subjects research of investigator financial conflicts of interest, NHRPAC provided to the Secretary a detailed working group report on these issues, with specific recommendations on how to strengthen oversight and management of financial conflicts of interest in research.

At that time, very specifically, NHRPAC was mindful of the need for the national research community to develop consistent standards for disclosure and management of financial conflicts of interest in human subjects research. Its report therefore endorsed the notion that institutions should consistently apply the PHS thresholds for financial disclosure to all human subjects research, regardless of source of funding, in order to provide the same standards for all researchers and the same level of protection to all research subjects. Similarly, at that time, NHRPAC noted the disparate standards for investigator financial disclosure under the regulations of PHS, the National Science

Foundation (NSF), and the Food and Drug Administration (FDA), and suggested that these disparate standards be harmonized:

Ultimately, conflicts of interest financial thresholds and disclosure standards should be harmonized between the FDA, NIH and NSF. Strong consideration should be given to applying harmonized standards to all privately funded medical research, so that all research would be subject to the same standards of disclosure and analysis.

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<http://www.hhs.gov/ohrp/archive/nhrpac/documents/aug01a.pdf> .

In October, 2009 SACHRP considered standards for the reporting, disclosure and review of financial conflicts of interest. By way of background, the SACHRP charter makes specific reference to investigator conflicts of interest, although 45 CFR Part 46 is essentially silent on this issue . A panel presentation included a summary of the of the April 2009 Institute of Medicine report on this issue (www.nap.edu/catalog.php?record_id=12598) as well as perspectives and commentary from leaders in academia and the pharmaceutical industry. SACHRP members were impressed with the fact that all speakers called for uniform guidelines or standards in conflict of interest disclosures, both in the interest of making multi-site reviews easier and in facilitating public disclosures. Indeed, it was noted that differences and discrepancies in reporting could lead to confusion and misunderstanding. SACHRP thought that uniformity in approach, for the entire research community, would decrease administrative burden and that all affected stakeholders (e.g investigators; academia; industry; human research participants; representatives of OHRP, FDA, VA, and other diverse government regulatory agencies) should participate in the development of appropriate regulations or guidance. SACHRP passed the following recommendation.

SACHRP recommends that the Secretary of HHS work with affected stakeholders to consider the need for regulations or guidance that define consistent standards for the reporting, disclosure, and review of financial conflicts of interest for those responsible for the design, conduct, or reporting of human subject research. These regulations or guidance should be uniform within the components of HHS (OHRP, NIH, FDA, etc.) and should include (1) uniform standards of reporting to any applicable entity, (2) uniform standards of public disclosure, (3) uniform expectations for appropriate information to permit human subject consent to be informed, (4) thresholds for evaluating and potentially limiting participation in human subject research based on financial COI s and (5) potential management approaches to limit undue influence and bias. Taken together, these approaches should promote industry-academic-public partnerships, allow transparency, ensure fair reporting, promote human subjects protections, and enhance public trust.

SACHRP Letter to The Honorable Kathleen Sebelius, Secretary of Health and Human Services, March 24, 2010, available at:
<http://www.hhs.gov/ohrp/sachrp/20100324lettertohhssecretary.html>

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interest. Under the proposed revised regulatory structure, the standards for identification and disclosure of conflicts would continue to differ in vast and important ways, thus complicating compliance efforts by investigators, sponsors and institutions, and confusing research subjects who might seek to understand how and why financial conflicts of interest are handled in studies for which they have volunteered.

As one example, please note the NPRM's proposed rule relating to instances in which a "PHS-funded project whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted or reported, by an investigator with a [financial conflict of interest] that was not managed or reported by the institution as required by the regulations." 75 Fed. Reg. 28699. In such a case, according to the NPRM, the institution "must not only require the investigator involved to disclose the [conflict] in each public presentation of the results of the research, but also to request an addendum to previously published presentations." *Id.* There is no such requirement in the FDA regulations.

The discontinuities between the NPRM and FDA approaches are clear: when a drug is tested with PHS funds, the NPRM proposes that financial conflicts of interest of over *\$5000 received or held over the previous 12 months* are disclosed, yet in drug trials under the direct jurisdiction of FDA (for example, those conducted under an IND exemption), HHS requires disclosure to sponsors and FDA of financial interests *greater than \$25,000 in income during the course of the study and for one year thereafter, and greater than \$50,000 in equity investment*. Both the amount (threshold) and the time period by which income and investment are measured differ.

SACHRP believes that the regulatory standards for identifying and managing financial conflicts of interest in human subjects research should be rigorous, in order both to protect human subjects from compromised study design or conduct, and to ensure that risk of bias to results is minimized. It therefore strikes SACHRP as an opportune moment for these two constituent agencies within HHS to harmonize their regulations. SACHRP therefore respectfully commends to the attention of PHS the important objective of regulatory consistency, and would recommend that PHS hold further consultations with FDA, as well as NSF, in order to address these long-held and pressing concerns of the national research community.

On behalf of SACHRP, I wish to thank you for your consideration of these comments.

Public Comment

Public comment was invited, but none was offered.

Wrap-up Discussion and Adjourn

The Chair said she planned to complete a Preface to the final FAQs prepared by SAS and approved by SACHRP, now being prepared for transmission to the Secretary of HHS, and finalize it with the assistance of SACHRP members. The meeting was adjourned by the Chair.

References

Beskow, L.M., Grady, C., Iltis, A.S., Sadler, J.Z., and Wilfond, B.S. (2009). Points to consider: The research ethics consultation service and the IRB, *IRB: Ethics and Human Research*, 30 (6), p. 3.