SACHRP Minutes, July 19-20, 2011

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Secretary's Advisory Committee on Human Research Protections (SACHRP)
Tuesday, July 19, 2011 – Wednesday, July 20, 2011
Minutes

Tuesday, July 19, 2011

Welcome: Opening Remarks
Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed attendees to the 26th meeting of SACHRP.

The minutes for March, 2011 were approved unanimously without changes.

She thanked Julia Gorey and Cecilia Chirinos, OHRP staff assigned to SACHRP, for their critical help in preparations for the meeting.

The Chair welcomed the Assistant Secretary of Health, Dr. Howard K. Koh.

Opening Remarks, Swearing in of New Members
Howard K. Koh, M.D., M.P.H., Assistant Secretary for Health (ASH)

Dr. Koh recognized the leadership of Dr. Menikoff and noted that working with Dr. Bierer, with whom he trained as a doctor, was a "special joy." He saw SACHRP as a "very important committee" and was "thrilled" to see the interdisciplinary of its members. Over the years, he said, SACHRP has focused its efforts on a portfolio of challenging topics. A large percentage of its recommendations have been accepted, and there is no question its work has made, and is making, a difference.

Dr. Koh then swore in the following four SACHRP members:

- Albert A.J. Allen, M.D., Ph.D.
- Gary Chadwick, Pharm.D,, M.P.H., CIP
- Susan Krivacic, M.P.A.
- Suzanne M. Rivera, Ph.D., M.S.W.

The Chair encouraged new members to be active in subcommittees, which make a crucial contribution to SACHRP's work.

A SACHRP member observed that a Notice of Proposed Rulemaking (NPRM) regarding Continuing Review is expected in the next couple weeks, with a due date for comments that will

precede SACHRP's next meeting. He asked whether comments from SACHRP would be considered after the announced closing date. The ASH responded that there will be "ample opportunity to comment." He added that ethical considerations and improvements in efficiency have both been considered in the proposed new rule.

Report of Issues

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

Dr. Menikoff reported that OHRP staff has been busy on a variety of fronts, including education and outreach initiatives such as a research forum for the research community held in Boston, Massachusetts. The Division of Compliance Oversight has been unusually busy. A new determination letter has been posted on the web site, and new procedures have been developed related to Federal-Wide Assurances (FWAs) to simplify administration burdens.

The Director emphasized that SACHRP has played a "huge" role in informing changes in OHRP guidance and proposed regulatory changes as well. He expressed his appreciation.

Briefing on the Presidential Commission for the Study of Bioethical Issues (PCSBI)

Valerie Bonham, J.D., Executive Director

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

Ms. Bonham briefed SACHRP on the activities of the PCSBI. She explained that the Commission was created in 2009 to fulfill specific charges given by the President of the United States. Its initial work focused on ethical ramifications of the synthetic creation of a self-replicating cell, including risks and benefits. It was asked to:

- Review the developing field of synthetic biology,
- Consider the potential medical, environmental, security, and other benefits as well as potential health, security, or other risks, and
- Identify appropriate ethical boundaries to maximize public benefits and minimize risks,

The Commission submitted its first report to President Obama on December 15, 2010. Entitled *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, the report is available online: http://bioethics.gov/cms/synthetic-biology-report

In October of 2010, President Obama called the President of Guatemala to apologize for U.S. - sponsored research in which Guatemalans were deliberately infected with Sexually Transmitted Diseases (STDs). He asked the commission to review contemporary standards for human subject protection in order to be assured that research participants, both domestically and internationally, are protected from harm.

In addition, an International Research Panel has been formed to determine the duties of the U.S. as a

funder of research that crosses international borders. The panel has been asked to determine:

- The dominant norms, and competing alternatives, driving the ethics of medical research in different global regions outside of the U.S.;
- The conflicts, if any, between U.S. norms and international standards;
- The challenges facing researchers conducting U.S.-funded research in global settings; and
- How best to address any major differences in regional norms for medical research.

To inform its work, the Presidential Commission for the Study of Bioethical Issues is requesting public comment on the Federal and international standards for protecting the health and well-being of participants in scientific studies supported by the Federal Government. Comments must be received by May 2, 2011. SACHRP's input will be welcomed.

Discussion

Ms. Bonham clarified that the Panel plans to issue a report, using public input received through its recent Request for Information (RFI) as one of many sources. The panel is trying not to duplicate work already done, while at the same time fully addressing the President's concern that regardless of where research is one, participants will be well protected. The speaker also clarified that while she coordinates with the ASH to receive input from HHS, the panel reports to the President directly.

Vulnerable populations. Dr. Allen noted that persons with mental illness were among those targeted in the research in Guatemala that came to light recently. He stressed the importance of being socially responsible as well as ethically responsible and emphasized that social justice concerns dictate special attention to vulnerable populations, which are generally less well understood.

Scope of charge. A panel member noted that work sponsored by private foundations requires special attention. Ms. Bonham said the panel has reached out to private foundations and hopes they will draw on the panel's work.

A SACHRP member asked why the effort to ensure ethical research internationally is limited to "U.S.-funded research in global settings." The speaker explained that the panel's charge was given by the President of the United States and was limited to research sponsored by U.S. entities. Dr. Bierer noted that in many ways human subject protections are tied to Federal funding, and protections for research not tied to government funding is limited. Ms. Bonham hoped that the principles articulated in the Panel's report would have a broader influence than on Federally sponsored research alone. A SACHRP member agreed this was possible, citing the widespread influence of the clear articulation of principles in the 1979 *Belmont Report.*

Working across countries and cultures. Dr. Allen suggested that the panel would find input from Japan from Japan especially helpful. Many pharmaceutical companies are involved there and recent disasters are likely to result in U.S.–sponsored research.

A SACHRP member observed that variations among countries in terms of human rights and political freedom pose challenges for research. In addition, a SACHRP member commented that the perspective of subjects is likely to differ from that of experts and should be solicited.

An ex officio representing the Indian Health Service asked how much attention is being given to biological samples and donors from members of indigenous communities. Ms. Bonham said the panel is exploring how people from different cultures view human subject protection and is emphasizing the need to engage and hear different perspectives. It is also aware of the importance of community engagement and the issues surrounding this.

Ms. Krivacic observed that the panel's charge does not appear to encompass the issue of outcomes as opposed to issues associated with regulations and standards. She said many IRBs follow the regulations, yet struggle with the justice and beneficence principle – especially when work is being conducted outside the U.S. The issue of "equivalent protections" is difficult to assess. Dr. Allen rejoined that nothing in the charge would prevent the panel from considering the issue of outcomes. Ms. Bonham added that it is looking at existing statutes with openness to the possible need for revision.

Harmonization. A SACHRP member asked how the panel is approaching the task of differing guidance among Federal agencies. Dr. Allen responded that the need for harmonization among Federal regulators is recognized. The panel will seek to assist by offering an independent view of priorities. However, Ms. Bonham said, this is not something the report is going to resolve. In some cases, there may be good reasons for the diversity of approaches.

Bioethical issues. Dr. Joffe, who reviewed the panel's completed report on bioethical issues, noted that the term "democratic deliberation" is used in its statement of guiding principles. He asked what the panel meant by the term. Ms. Bonham said the phrase captures a lot of ideas. Many individual processes are aimed at engaging the community and gauging acceptance of the research approach. The panel did not intend to embrace a particular process as much as to emphasize that processes to ensure engagement and to educate people in a variety of settings were both an opportunity and an obligation for researchers.

A SACHRP member observed that the committee's approach to synthetic technologies might suggest a way of addressing other emerging technologies. He asked whether the panel had considered operationalizing its findings for broader application. Ms. Bonham said the Commission has begun to consider issues related to genome sequencing, but it has not gone far enough in its deliberations to answer.

Dr. Bierer thanked Ms. Bonham for her presentation, adding that the panel's deliberations are clearly complementary to SACHRP's work.

Subpart A Subcommittee (SAS) and Subcommittee on Harmonization (SOH): PCSBI Discussion

Daniel Nelson, M.S., CIP, SAS Co-chair; David Borasky, M.P.H., CIP, SAS Co-chair; David Forster, J.D., SOH Co-chair; Mark Barnes, J.D., SOH Co-chair

SAS and SOH collaborated to develop a response from SACHRP to the Request for Information (RFI) from the Presidential Commission for the Study of Bioethical Issues (PCSBI). The response as initially presented is **Attachment A** of these minutes. The response was discussed section by section. After initial discussion and revisions, SAS and SOH were asked to address remaining concerns in a new draft

to be presented the following day. The final version approved on the second day of SACHRP is shown as **Attachment B.** In the interests of clarity and continuity, the discussions of the comments that occurred on both days have been combined in the summary of the discussion below.

Introduction. SACHRP members suggested a variety of changes to improve readability and clarity. SACHRP also:

- Removed the list of agencies that promulgate regulations or issue guidance,
- Clarified the issues that have arisen since regulations for human subjects protection were introduced (third paragraph) and removed the reference to the Health Insurance Portability and Accountability Act (HIPAA) in favor of a specific reference to "differences in interpretation of identifiability,"
- Removed language that referred to the Human Subjects Research Subcommittee of the Committee of Science in the Office of Science and Technology as "ineffective," noting simply that it had "no authority to make changes to the regulations and issue guidance."

Harmonization. Changes were made to correct statements or clarify meanings. Significant changes included:

- Noting that the Environmental Protection Agency (EPA) regulates products as well as FDA (first paragraph),
- Observing that state law is "sometimes inconsistent" in regard to research (first paragraph),
- Deleting a statement about the administrative scope of FDA and OHRP as unnecessary (second paragraph),
- Clarifying and correcting an example of additional requirements related to the Department of Veterans Affairs (VA) (second paragraph), and
- Adding an example from EPA (second paragraph) as suggested by Dr. Lux.

SACHRP also broadened the reference to interstate commerce power as the basis for federal jurisdiction in systemic reform, adding the words "or other applicable basis for federal jurisdiction" (third paragraph). Members observed that some states, such as Maryland, have succeeded in plugging the gaps in existing regulations while others, such as New York, wrote regulations for genetic testing too early, resulting in confusion. Mr. Barnes stressed that the need was for a national scheme that plugs holes and is comprehensible to everyone, including research subjects.

Alternatives to Local IRB Review. Only two changes were made. The words "for scientific validity and rigor" were added to clarify why it matters that a protocol be implemented consistently in multi-site studies. Also, the assertion that various concerns "prevent" widespread sharing of protocol reviews was felt to be overstated; the term "discourage" was selected instead.

HIPAA. A reference to the Family Educational Rights and Privacy Act (FERPA) was added.

Minimal Risk Research. SACHRP made changes to eliminate redundancy and to make the statement about the need to re-examine exemption categories more concise. The more specific term "minimal risk" replaced the term "lower risk." Since minimal risk issues described are of particular concern in social science, behavioral research, and educational research, a statement was added to that effect and

the section on Social Science, Behavioral and Educational Research was moved to follow Minimal Risk Research on the final version.

Banking and Secondary Uses of Identifiable Data and Biomaterials. References to biomaterials were changed uniformly to biospecimens. Language was added to point to the issues associated with consent for the use of specimens for which identifiers have been removed, and which therefore would not ordinarily be considered human subjects research (second paragraph). Dr. Joffe commented that addressing the issue and "plugging the hole" will require regulatory action. Additional wording was added in the third paragraph to highlight issues related to close families and "discrete and insular communities" in regard to biospecimens taken from these groups. The terms "discrete and insular" were added to avoid the "slippery slope" of allowing communities to define themselves. SACHRP considered giving examples of possible repercussions for families and communities, such as changes in insurance rates or eligibility and job discrimination, but decided this was not needed.

Dr. Bierer observed that the issue of harm to communities and related considerations is an emerging topic, and regulations say little about this. The committee agreed that these concerns should be considered in formulating regulations and guidance in this area. SACHRP might consider taking up this topic at a future meeting.

Informed Consent. A SACHRP member observed that the flexibility envisioned does not require a regulatory change. The real issue is the shift in focus from forms to the process of consent. Language was added to emphasize that everyone involved needs to participate in such a shift.

Education. No substantive changes were discussed or made. Public service announcements (PSAs) were added to educational efforts.

International Research. Dr. Allen suggested adding language to the effect that "PCSBI is encouraged to specifically examine additional standards to protect vulnerable populations involved in federally supported research," such as those who are socially and economically disadvantaged. A member observed that while "equivalent standards" of protection are required, most other countries do not have regulations to protect children; there is no concept of "assent," for example. Mr. Barnes suggested that the term "vulnerable" was a regulatory term and should not be used in this context. A paragraph was added to emphasize the importance of protecting "populations that may be uniquely burdened or harmed by participation in research," which includes several examples.

Financial Conflicts of Interest. A SACHRP member raised the question of whether language should read "a national approach to conflict of interest" or an "international approach." Since an international approach could not be mandated, the "national approach" was retained.

Social Science, Behavioral and Educational Research (SBER). Members discussed how best to describe the distinction between SBER and other research. SBER might be described as nonclinical or nonbiomedical. A member noted that a recent clinical study used reports from teachers about the effects of medications on children. Increasingly, he said, the line between clinical and nonclinical research is blurring. Members also stressed that while it is often taken for granted that clinical research is higher risk than nonclinical research, nonclinical research may have significant long-term consequences. Members decided to distinguish between "biomedical human research" and "SBER."

The initial draft of the final paragraph was revised to avoid possible confusion resulting from introducing the topic of exemptions. Members also agreed that this section should follow the one on Minimal Risk Research.

Sharing Individual Test Results with Participants. Dr. Joffe prepared an additional section for review to address this topic. Changes include:

- Clarifying that the Clinical Laboratories Improvements Act (CLIA) provides protections designed to ensure quality as well as barriers to sharing results.
- The word "impracticable" replaced the term "costly," since there are other barriers not of a financial nature that could make return of results difficult.
- SACHRP members raised the issue of who is to decide what research findings are potentially actionable and ought to be returned to research participants. A sentence was added at the end to clarify the need for such a mechanism. Members voted separately on this provision, deciding to include it with a vote of 6 to 3, with one abstention.

Third Parties in Research. A section was added pointing to the importance of third parties who are not intended as subjects but participate in the research and may have identifiable data collected about them. A member commented that a guidebook developed by OHRP for IRBs may contain a reference to "secondary subjects." One member was concerned about the potential for "mission creep" if these persons are treated as subjects.

Evidence-based Protections. A section was added on the importance of research to enhance the evidence base for human subject protection. The section calls for "increased" Federal support; a member noted that some support does exist, but it is insufficient.

ACTION

Following revisions, the final letter was approved unanimously.

Subpart A Subcommittee (SAS) Report

Daniel Nelson, M.S., CIP, SAS Co-chair; David Borasky, M.P.H., CIP, SAS Co-chair

SAS Co-Chairs reviewed their subcommittee's charge, membership, and accomplishments.

Recommendations Regarding Research Consent Forms

Co-Chairs explained that SAS has focused recently on issues related to informed consent. SAS is interested in making the process and forms associated with informed consent more purposeful and useful to research subjects.

Attachment C shows the draft recommendations as originally presented by SAS.

Attachment D shows the recommendations as approved, unanimously, by SACHRP.

SAS maintains an ongoing focus on shortening, clarifying and repackaging consent documents to

facilitate research participants' understanding. Co-Chairs reported that SAS is currently considering issues related to use of the "short form" for consent. It is also considering issues related to informed consent in internet-based research and awaiting a reading from legal counsel regarding state laws that have a bearing on informed consent in these instances. Specific recommendations regarding electronic signatures have been drafted and area also awaiting the advice of counsel.

Mr. Borasky reviewed the elements of informed consent as described in the regulations, then offered clarifications that SAS felt would be useful to the field.

1. §46.116(a)(1). Explanation of purposes and duration of the research

The following are key discussion points in regard to what *must* be included:

- SACHRP members wanted to highlight the first example, regarding randomization, in order to highlight the "therapeutic misconception."
- Members opted to use the term "biomedical" instead of "clinical" because it was more precise.
- The example of a survey of risk-taking behaviors by adolescents in a drug treatment program was changed to adolescents in a driver's education program in order to avoid introducing unrelated issues.
- An ex officio wanted to add a general introduction to consent forms for all research before breaking the discussion down into biomedical vs. nonbiomedical research. Members opted to keep the presentation as is.

The following are key discussion points in regard to what does *not* have to be included:

- Members observed that many times it is advisable and appropriate to include information that is not technically required. A revision made this explicit.
- Even though it is not essential to describe what would be happening in an individual's treatment plan without the research, it is very important. The revisions state that this type of information can be offered in different ways (e.g., in an appendix, in educational materials, or in a conversation with the doctor) rather than including in the consent form.

2. §46.116(a)(2). Description of reasonably foreseeable risks or discomforts

The following are key discussion points in regard to what *must* be included:

- The reference to benefits was removed. SACHRP decided to separate out the discussion of risks from the discussion of benefits.
- A member observed that what constitutes a "significant" risk will vary among subjects.

The following are key discussion points in regard to what does *not* have to be included:

- Again, the reference to benefits was removed.
- The statement was rewritten to clarify the regulatory requirement and to focus on the communication of risks.

3. §46.116(a)(3). Description of reasonably expected benefits

The following are key discussion points in regard to what *must* be included:

- The reference to clinical care was removed, since the discussion is not limited to a biomedical context.
- References to risk were removed to focus on benefits.

The following are key discussion points in regard to what does *not* have to be included:

- Dr. Menikoff observed that people often agree to participate in studies thinking there are benefits when in fact there are none. When this is the case, it is important to be clear there are no benefits.
- Dr. Menikoff noted that even though it is not what an IRB thinks of when it considers benefits, a possible subject may well consider payment a benefit.
- Dr. Joffe said statements about benefits should be as specific as possible. It is not helpful to say "you may or may not benefit." Instead, a form might say, "Although it is unlikely that you will benefit from participating in this research, there is some possibility that…." People should know how likely or unlikely it is that they will benefit.

4. §46.116(a)(4). Disclosure of alternatives

The following are key discussion points in regard to what *must* be included:

- A SACHRP member observed that even off-label uses of devices may be an evidence-based standard of care.
- Dr. Joffe observed that the standard of care may differ for each procedure included in the intervention may differ among study sites and subjects.

The following are key discussion points in regard to what does *not* have to be included:

- Ms. Krivacic observed that in some studies there really are no alternatives to participation that need to be described, especially as it relates to healthy volunteer Phase I studies. She agreed that the best approach is to make IRBs comfortable leaving this out when there is nothing to say.

5. §46.116(a)(5). Maintaining confidentiality

The following are key discussion points in regard to what *must* be included:

- Members decided that "when appropriate" was somewhat preferable to "when applicable" to qualify the statement, "consent forms should explain that research records will be kept confidential."

The following are key discussion points in regard to what does *not* have to be included:

- No discussion.

6. §46.116(a)(6). Compensation and medical treatment

The following are key discussion points in regard to what *must* be included:

- No discussion.

The following are key discussion points in regard to what does *not* have to be included:

- SACHRP agreed that the example of the pro forma disclaimer about embarrassing questions was not a helpful example and should be dropped.
- Members stressed that when a required element is not relevant or applicable, IRBs do not need to document a waiver of the element in their minutes. They agreed to add a statement to this effect in the introduction to these recommendations as well as in this section.

7. §46.116(a)(7). Contact information

SACHRP members discussed whether a documented waiver of contact information was necessary in the case of a survey. A member observed that in a nonexempt telephone survey, it might be appropriate to give the subject a telephone number to write down (although the subject might well ask why). SACHRP agreed that although providing contact information is clearly not always necessary, a waiver by the IRB is apparently required by the regulations and should be documented. They added a statement to this effect.

8. §46.116(a)(8). Voluntary participation

Again, SACHRP determined that not providing a statement that participation is voluntary would require a documented waiver by the IRB.

9. §46.116(b). Additional elements

There was no discussion.

ACTION

Revised recommendations were approved unanimously.

Work in Progress

Co-Chairs reported that SAS is considering appropriate use of the short form for consent. It is also exploring issues involving consent in Internet-based research and waiting for advice from counsel regarding State laws that may have a bearing on this. Recommendations have been drafted regarding electronic consent and also on hold pending input from legal counsel. SAS maintains an ongoing focus on shortening, clarifying, and/or repackaging consent documents to facilitate participant understanding.

Topics for Panel Discussion

The Chair invited members to consider possible topics for panel discussion. She observed that new members are interested in a variety of areas, including access to trials, globalization, and equity in participation.

Public Comment

Public comment was invited, but none was offered.

Wednesday, July 20, 2011

Remarks

Barbara Bierer, M.D., SACHRP Chair

A new version of the proposed letter to PCSBI was reviewed. Further changes were made and have been described as part of the earlier discussion in the interest of clarity. The letter was approved unanimously. The final letter appears as **Attachment B** of this report.

Report of Subcommittee on Harmonization (SOH)

David Forster, J.D., SOH Co-chair; Mark Barnes, J.D., SOH Co-chair

Co-Chairs reviewed the charge, membership, and completed activities of the committee. SOH brought forward the following items for consideration:

- A recommendation regarding the definition of a Minor Change in Research. Co-Chairs noted that significant differences exist among OCR, FDA, and OHRP. This issue has been discussed at SACHRP intermittently since March 4, 2009.

- Recommendations regarding the application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects. Suggestions made at the March, 2011 SACHRP meeting have been included.

- A recommendation regarding HIPAA Accounting of Disclosures and Access Reports. SOH would like to support an HHS proposal to exempt research disclosures from the Accounting Requirement. SOH also presented a statement of concerns related to new requirements related to report access.

- SOH additions to the Subpart A Subcommittee (SAS) FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens. The subcommittee expanded some HIPAA commentary and added an FDA component. Previous FAQ content was approved by SACHRP in July and October, 2009, and March, July, and October 2010.

Minor Change in Research

SACHRP reviewed a recommendation regarding a harmonized definition of a minor change in research. Co-Chairs explained that the recommendation addresses the issue of what constitutes a minor change of

research that can be approved through an expedited process. The recommendation includes changes suggested by SACHRP at its March, 2011 meeting. The final document, with changes, appears as **Attachment E** of these minutes.

Co-Chairs explained that the definitions of a "minor change" given in FDA and OHRP guidance are sufficiently different to cause confusion. SOH proposes that a single definition be issued as joint guidance from both FDA and OHRP:

- *Minor changes in approved research that can be approved through expedited review procedures are minor changes that neither increase risk nor materially decrease benefit.*

Discussion

Dr. Joffe suggested that the analysis of what constitutes a minor change includes considerations that don't involve risks or benefits to the subject. A change might affect the scientific value of the research, altering the social benefit piece of the equation. Mr. Barnes suggested that changes that don't "hurt anyone" don't require review. Other SACHRP members differed, however. The definition was amended to add the words, "nor materially decrease scientific merit." The word "minor" was also removed from the definition to avoid defining the terms with the same word.

Other changes include:

- Specifying that in each of the situations given as examples, the determination as to whether the change is minor should be made by an experienced reviewer who could decide that the matter requires review by the full board.

- Citing a specific amount of blood to be drawn in the second example.

- Clarifying the nature of the situation described in example 9 and adding guidance to the effect that IRBs should develop criteria for assessing whether a proposed new investigator for a multi-site study is "equally qualified."

- Clarifying that example 10 does not involve an invasive procedure, but strictly an observational one.

- Adding an example illustrating a change that decreases risk for subjects.

ACTION

The revised document, as it appears in **Attachment E** of these minutes, was approved unanimously.

Early Processes in Research

Two draft recommendations regarding early processes in research were presented. Co-Chairs observed that there are substantial differences among the Office of Civil Rights, FDA, and OHRP on issues that arise at the beginning of research. SOH incorporated recommendations from the SACHRP meeting on March 9, 2011 in the revised recommendations presented for approval. **Attachment F** shows the recommendations as presented, with further changes made as a result of the discussion.

ACTION

The recommendations were approved unanimously and appear as Attachment F of these minutes.

Proposed Comments on HIPAA Notice of Proposed Rulemaking

SOH presented draft comments on a Notice of Proposed Rulemaking (NPR) on Accounting of Disclosures and Access Reports pertinent to HIPAA. The proposed changes may be reviewed at the following site: http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/hitechnprm.html

Christine Heide of the Office of Civil Rights (OCR) reviewed key features of the NPR and explained the rationale for revisions. She observed that many of SACHRP's suggestions for easing burdens on researchers would be reflected in the new rules. SOH agreed that the proposal to exempt research from the requirement to account for disclosures under the HIPAA Privacy Rule deserved SACHRP support and gratitude. It is consistent with a recommendation submitted by SACHRP on September 7, 2004. However, SOH found that one of the proposed changes, related to subjects' access to their Electronic Medical Records, would be complex and potentially burdensome without benefitting research subjects.

Discussion

Introduction. No changes were suggested to the introduction.

Accounting Requirement: Exemption for Research. A SACHRP member asked for clarification of what residual rights subjects would have under HIPAA. Ms. Heide explained the individual would have the right to know their record was accessed but not the right to know why. Mr. Barnes said without the exemption, entities conducting research would have to maintain a proactive compliance system that would track every disclosure. The fact that the number of requests might be limited would not decrease the burden.

Access Reports. Mr. Barnes explained that SOH's concern regarding this proposal is that it is burdensome and complex, while offering uncertain benefits to subjects. Researchers would be compelled to respond to requests for information on who has accessed electronic medical records (EMRs) for any subject. In addition to reviewing their own audit trails and records, researchers would have to approach external vendors and subcontractors and ask them for their access records as well. Complexities include determining which of these entities should be considered business associates and what record sets are involved.

Representing OCR, Ms. Heide explained that under the HI TECH Act the individual has the right to receive access logs maintained by a business entity. The "designated record set" referred to is the same set of records to which individuals already have the right of access, and covered entities should already know that the subject has a right to see these records. Currently, agreements with business associates should specify that the associate will assist the covered entity in accessing any records needed to comply with HIPAA. She added that disclosure of information to an outside entity for research purposes would not make that entity a business associate.

Dr. Allen commented that this is an area that "keeps the lawyers busy"; it has a "huge impact" on the research enterprise. Acknowledging the need for balance, Ms. Heide expressed openness to suggestions for complying with the statutory requirements without placing unnecessary burdens on researchers.

Mr. Barnes noted that the printout for an access record might be huge, encompassing hundred of instances of access. He asked whether business entities would be required to answer queries about who accessed the information in each case. Ms. Heide said this is not a requirement. She acknowledged that the amount of information involved could be "voluminous," potentially encompassing over 3 years worth of information. Individuals could make requests for access records over a smaller amount of time.

Ms. Heide clarified that requests could encompass any data bases used to make decisions about an individual's treatment or billing. Mr. Barnes observed that determining what would and would not be included in the data set is far from straightforward and determining what affiliates were involved would pose an additional burden.

Dr. Ross asked how many people seek this type of information. Ms. Heide said the only available information on this point is anecdotal, but such requests appear to be limited. It is possible that subjects will not use the mechanism very much because it does not give them the right to find out specifically who has accessed their information. Also, there is no requirement that the purpose of the disclosure be captured. The access report would say that a nurse viewed the record, but it would not include the fact that she then provided this information to public health authority.

Dr. Joffe asked whether the concern around this proposal is that creating the information to comply is impracticable or that responding to requests will be burdensome. Dr. Bierer said that both were concerns. A SACHRP member observed that several large metropolitan areas are already engaged in developing large data bases that will extract partially identifiable data in order to aggregate records in order to advance human health. Ms. Heide suggested that an access log should automatically track direct entry to such a system.

Dr. Ross said she could envision people wanting to know this type of information and assess the amount of access that is occurring. Ms. Krivacic agreed that many patients are wary of where information is going and for what purpose and how that may affect their health privacy concerns. Dr. Bierer felt strongly that the rule should not require institutions to include research uses and disclosures in any requested reports. Dr. Chadwick observed that "the bottom line is cost": "I can fully staff a HIPAA office or I can hire a couple more registered nurses."

Summary. SACHRP articulated four specific recommendations in order to clarify the course of action it believes OCR should pursue.

Recommendation One:

Covered entities [should] not be required to disclose access for research purposes, as part of the electronic access report requirement;

Recommendation Two:

The Office for Civil Rights clarify that institutions have discretion, for purposes of the electronic access report, to define what electronic databases are intended primarily for research use and thus lie outside the "designated record set," with a presumption of validity as to explicit institutional decisions in this regard; and

Recommendation Three:

The Office for Civil Rights clarify that institutions have discretion, for purposes of the electronic access report requirement, to designate that "business associates" engaged for mixed research and other purposes may omit access for research purposes in responding to requests for electronic record access reports.

Recommendation Four:

In recognition of the public desire for greater transparency in unconsented uses and disclosures of identifiable data for research purposes, the Office for Civil Rights should open a dialogue with OHRP and other relevant agencies about possible guidelines for public access to information relating to waivers of informed consent and HIPAA authorizations that are granted by IRBs and/or privacy boards.

ACTION

The section of the comments dealing with exemption for research proved controversial, but it was approved with minor changes after a vote of 7 to 3. Specific recommendations were approved with the following votes:

Recommendation 1: 7 to 3
Recommendation 2: 7 to 3
Recommendation 3: 7 to 2, with one abstention
Recommendation 4: 9 to 1

SACHRP then approved a motion to move the comments forward by a vote of 7 to 3. The final comments appear as **Attachment G** of these minutes.

FAQs on Informed Consent and Research Use of Biospecimens

Co-Chairs reviewed additions and changes to FAQs originally developed by SAS. Many FAQs were

found to be approvable without discussion or revisions. Comments were made on the following sections.

Glossary and concepts. The statement that the FDA would not consider most research on specimens to be a "clinical investigation" was removed at the request of the ex officio representative for the agency, who observed that some products involve combinations.

FAQ 1. A qualifying phrase was added to "FDA issues" at the request of the FDA ex officio member in order to clarify the meaning.

FAQ 3. Changes were made to correct the citations to OHRP guidance.

FAQ 4. It was observed that OCR is considering changes in this area. OHRP and OCR will confer when OHRP addresses the FAQs to ensure the assumptions about OCR's position are accurate.

ACTION

The final FAQs were approved unanimously by SACHRP and appear as **Attachment H** of these minutes. The Chair expressed appreciation for the dedicated work of ex officios, which made it possible to complete the FAQs.

Future Topics

SOH presented a variety of future topics it plans to address. Examples include the distinctions between "innovative care," research, and clinical investigation; engaging the community in research; consent issues; the unequal application of Subparts B, C, and D across agencies; harmonization in international research; incapacitated adults; safety issues; exculpatory language; procedural issues, including the possible need for a single new agency to oversee all human subjects research in the U.S.; research misconduct (the subject of a panel at this meeting); and differences in FDA and OHRP guidance on local attitudes.

Research Integrity Panel

Barbara Bierer, M.D., SACHRP Chair; Kristina Borror, Ph.D., Director of Division of Compliance, OHRP; John Dahlberg, Ph.D., Director of the Division of Investigative Oversight, Office of Research Integrity

The panel was charged with discussing issues surrounding scientific misconduct and fraud. Speakers were asked to explore both internal agency processes and compliance mechanisms. In addition, they were asked to address IRB and institutional mechanisms for responding to allegations of misconduct and fraud and to consider investigator perspectives on the issue.

Mr. Barnes introduced the topic as part of the earlier presentation by SOH. He noted that when incidents of research misconduct occur, they may be violations of the Common Rule, of the FDA's rules and

procedures, or of the Misconduct Standards enforced by the Office of Research Integrity. Each type of violation triggers its own requirements for reporting, standards of proof, and guidelines for disclosures. Issues include how to coordinate investigation by different agencies operating under different requirements. Questions posed include:

- Do any abuses of human subjects give rise to research misconduct violations under the purview of the Office of Research Integrity?
- Are there research misconduct violations that are also clear violations of human subjects research standards?
- Can research misconduct issues arise in FDA enforcement actions?

Mr. Barnes also summarized the FDA's proposed new rule regarding falsification of data, illustrating the complexity of the topic with several examples of cases that might be violations that would result in action by OHRP, FDA, or the Office of Research Integrity (ORI). Under the new rule, sponsors would be required to report to the appropriate FDA center information indicating that any person "has, *or may have*, engaged in the falsification of data" (emphasis added). Falsification of data is defined as "creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred." Examples include:

- "Creating data that were never obtained …forging the signature on an informed consent form," or
- "Altering data by re placing original data with something different that does not accurately reflect study conduct or results."

The required time frame for reporting is: "Promptly, but no later than 45 calendar days after the sponsor becomes aware of the information." Reports must contain the name of the person accused of falsifying data and may be made directly by FDA, without knowledge of or action by institution or sponsor.

Remarks by Kristina Borror

Dr. Borror explained that for-cause compliance oversight cases are usually initiated by information provided by internal whistle blowers, subjects, family members, and advocacy groups. In such cases, OHRP will determine whether or not it has jurisdiction and, if so, make a written inquiry to appropriate institutional officials. It will then review the institution's report and relevant IRB documents, collecting additional information as needed through correspondence, telephone interviews, and site visits before issuing final determinations.

OHRP is most apt to be involved in cases involving falsification of human subject signatures on informed consent documents, particularly if consent was not obtained at all prior to subjects' involvement in the research; instances in which eligibility criteria were falsified or fabricated such that subjects were inappropriately involved in research; and falsification or fabrication of safety tests. She explained that OHRP refers scientific misconduct issues to ORI as appropriate, and vice versa.

Remarks by John Dahlberg

Dr. Dahlberg explained that the Office of Research Integrity (ORI) is charged with promoting the integrity of PHS-supported extramural and intramural research programs, responding effectively to

allegations of research misconduct, and promoting research integrity. Its jurisdiction includes every institution that holds a Federal-wide Assurance (FWA). Usually, complaints originate in the lab where the research was conducted.

Research misconduct includes fabrication, falsification, and plagiarism:

- *Fabrication* is making up data or results and recording or reporting them.
- *Falsification* is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
- *Plagiarism* is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

Research misconduct does not include honest error or differences of opinion (42 CFR Part 93.103). ORI's working procedures do not allow it to discuss any case until it has been closed, regardless of whether the institution's own investigation concludes that misconduct occurs. To raise institutional awareness of what constitutes scientific misconduct and encourage institutional vigilance, ORI has begun to offer "boot camps" for Research Integrity Officers (RIOs) at institutions. When ORI concludes that misconduct has occurred, an adversarial legal process ensues. To date, ORI has not lost a case.

Dr. Dahlberg highlighted key differences between ORI and OHRP. ORI makes findings against individuals, while OHRP (generally) makes findings against institutions. Also, ORI's records are kept in a Privacy Act System of Records, while OHRP's are publically available. He added that it is rare for ORI to conduct compliance reviews against institutions.

Discussion

A SACHRP member asked whether ORI has jurisdiction to handle issues related to FDA-regulated research. Dr. Dahlberg said that FDA has better authority to expedite a response. FDA investigators can shut down a research activity within 24 hours. ORI and FDA have collaborated to investigate some allegations of misconduct. Usually, when OHRP receives a complaint involving FDA-sponsored research, it refers the matter to FDA; however, the agencies may collaborate when appropriate.

A SACHRP member asked for clarification of what happens when a whistleblower "goes public." Mr. Dahlberg responded that ORI is responsible for protecting the identity of the whistleblower and follows the guidelines posted on the ORI web site. However, the institution is also responsible for protecting these individuals. See 42 U.S.C. § 289b(e), which may be viewed at: http://ori.hhs.gov/policies/regulations_statutory.shtml Mr. Barnes said that he has heard or seen reports of retaliation against individuals engaged in fact finding; this could include IRB members.

Dr. Borror clarified, in response to a SACHRP member's question, that OHRP cannot issue a final determination against an individual. Its relationship is with the institution sponsoring the research and its authority derives from the assurance.

Members asked about how Federal entities that may become involved in cases of scientific misconduct comply with their varied responsibilities. Dr. Borror said that while potential for conflict exists, overlap

in investigations is fairly rare. Mr. Dahlberg agreed. He observed that IRBs may view some scientific misconduct as protocol deviation. Dr. Borror added that OHRP has reported instances of falsification of information in granted applications to the office of the Inspector General (IG_ within HHS.

Examples. SACHRP reviewed the examples provided by Mr. Barnes, seeking to understand the roles and likely action that OHRP, ORI, and FDA would take in each instance.

Example 1

- Researcher systematically varies protocol from what was presented to and approved by IRB, and publishes results; later analysis reveals that results were rendered unreliable by the non-compliance, and publication is withdrawn/
- Noncompliance could be lack of testing or measurement at defined points, or coercion of subjects so intense as to adulterate survey results.
- Is it research misconduct?

Discussion:

FDA would certainly come down hard on the research sponsor in this case. Members and speakers agreed this could be considered misconduct.

Example 2

- Researcher falsifies informed consent forms in a study in which informed consent has been described in acute detail in research protocol approved by the IRB, even though subjects enrolled in the study were otherwise treated appropriately.
- In publication, the human subjects section describes the elaborate informed consent process, but with gross inaccuracy; IRB discovers this serious deviation, and demands that researcher abandon data.
- Study that was paid for with significant federal grant funds is now worthless.
- Is it research misconduct?

Discussion:

Falsified signatures are certainly a human subjects protection issue. From an ORI perspective, Dr. Dahlberg said, the false description of the research definitely constitutes misconduct. The fact that the inaccurate description was published raises it to a level that would concern ORI. Dr. Bierer added that if the issues were limited to the falsification of signatures and dates on consent forms, the issue likely would be handled within OHRP.

Example 3

- Researcher fabricates research data on 50 subjects; enrollment was reported as 100 but there were actually 50 who enrolled and completed a complicated, lengthy protocol.
- The protocol had no direct benefit for those 50 subjects who actually completed the study.
- Fabricated data on 50 fictitious subjects were combined with actual data on another 50 true subjects, and are published.
- This is fabrication of data and depriving subjects of their time and trouble, with only a false promise

of scientific benefit for society or any specific population.
- Is this research misconduct also a human subjects violation?

Discussion:

An OHRP spokesperson remarked that had the study been conducted the way the IRB approved it, there would be no problem; also, "nothing in the regulations prohibits people from wasting their time." Dr. Dahlberg agreed this would be an ORI concern.

Dr. Bierer observed that the IRB would be likely to see this as falling within their jurisdiction, and this type of case is frequently reported to the IRB. Once the IRB begins to investigate, however, data cannot be properly sequestered for an ORI investigation. Dr. Dahlberg commented the investigator could destroy the data. Dr. Borror gave an example in which an investigator claimed that consent forms were destroyed in a fire.

An ex officio said an incident like the one described would result in a major investigation for FD and would be viewed as "extremely serious."

Example 4

- Researcher believes that human subjects data that appear to be outliers in an otherwise consistent data set were actually inaccurately measured, and so he or she "adjusts" the outlier data to what he or she believes are more correct values.
- The data are aggregated from both the true and false values, but later analysis reveals researcher falsification.
- Have subjects been cheated of the scientific benefits to society promised at enrollment?
- Is this research misconduct a violation of human subjects research standards?

Discussion:

An FDA spokesperson said this would be a major issue for FDA. However, it was viewed as less of a concern from a human subject protection standpoint. Mr. Barnes said that if subjects have incurred significant risk, he would expect them to feel their rights were violated.

Dr. Joffe asked for clarification of the appropriate route that should be taken from an institutional viewpoint if there is scientific misconduct and the study underway should be shut down. Dr. Bierer said the research integrity officer should be informed and the data should be sequestered. The Office of Research Integrity can then discuss the matter with the IRB and with the Institutional Official (IO). The IO has the authority to suspend the study (termed an "administrative suspension") and does not have to inform OHRP why this was done. Dr. Borror confirmed this was accurate.

Example 5

- Researcher enrolls subjects who are not clinically eligible for a study and either falsifies enrollment records or creates accurate enrollment records, but in presentations to FDA and other publications of study results represents, falsely, that the subject population was defined by certain eligibility and ineligibility criteria. This was a demonstrably false statement, both in FDA submission and in

publication of study results.
- Is this FDA violation also research misconduct and a violation of human subjects research standards?

Discussion:

OHRP, ORI, and FDA would all have an interest in this case. FDA would pursue a criminal action based on a false report to the Government. Records submitted are required to be "current, accurate, and complete."

A SACHRP member asked whether the study would fall within the jurisdiction of ORI if Public Health Services funds were used to provide the infrastructure needed to conduct the study, but the specific study were not government funded. Dr. Dahlberg said this would fall under its jurisdiction if "core support" has been provided.

Example 6
- Researcher fails to report serious and unexpected adverse events, and/or injuries to subjects that could have been avoided;
- Adverse events and/or injuries in turn were not reported in FDA submissions, and were not reported in publications;
- Publications and FDA submissions indicate, in fact, that few or no serious adverse events occurred during the study
- Is this FDA violation also research misconduct and a violation of human subjects research standards?

Discussion:

OHRP would be involved because of the harm to human subjects. ORI would also be involved because of the false statements.

Next steps. SACHRP then turned its attention to possible next steps by the advisory committee. Members noted with concern that OHRP does not have a ready mechanism to keep an individual investigator from continuing to flout requirements of the Common Rule at a different institution from the one investigated. There is no apparent way to take action to exclude a "bad actor." OHRP can terminate approval for a study, but its actions have no legal bearing. Dr. Borror said OHRP could conceivably recommend to the Secretary that institutions or individuals be barred from research, debarred from their professional organizations, or that peer groups be informed about their misconduct, but it has never done so.

A member noted that a 3rd edition of a relevant study by the National Academy of Sciences is now available: *On Being a Scientist: A Guide to Responsible Conduct in Research*. It is available at: http://www.nap.edu/catalog.php?record_id=12192

SACHRP did not identify specific follow-up activities for the committee in this area.

Public Comment

Public comment was invited, but none was offered.

Wrap-up Discussion and Adjourn

The Chair adjourned the meeting

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Attachment A.
Comments Regarding the PCSBI, as Presented

Subpart A and Harmonization Subcommittee Comments Regarding the PCSBI
Request for Comments on Human Subjects Protections in Scientific Studies

The Secretary's Advisory Committee on Human Research Protections (SACHRP) is charged with providing the Secretary, HHS, with advice and recommendations on issues relating to human research protections, with the dual aim of improving the protection of human subjects and the quality of protection programs and of decreasing regulatory burdens that do not meaningfully contribute to the protection of such subjects. The protection and promotion of scientifically rigorous and ethically sensitive research in the public interest is our collective concern.

In consideration of our charge, the Subpart A Subcommittee and Subcommittee for Harmonization of SACHRP have considered the *Request for Comments on Human Subjects Protections in Scientific Studies* emanating from the Presidential Commission for the Study of Bioethical Issues ("the Commission"). We summarize herein the major topics that have been discussed in our deliberations, and recommend that these comments should be considered by SACHRP and forwarded to the Commission through the Secretary, HHS.

SACHRP has previously considered a number of the areas mentioned below, and substantive and detailed recommendations have been forwarded to the Secretary in the past. That said, much of SACHRP's work to date has focused on subpart A of 45 CFR Part 46, the "Common Rule" and its additional subparts (B, C and D), and more recently on the overlap and dissonance between the regulations espoused by OHRP and other agencies (e.g., FDA, OCR). We find that the basic framework of the regulations in 45 CFR Part 46, coupled with the bedrock principles of the Belmont Report, have served the regulated community – and the human subjects that it serves – well over the past decades. We note, however, that only a portion of studies is governed by these regulations, and the Request for Comments by the Commission provided us with the opportunity to comment on the patchwork system of regulatory oversight, and on certain specific issues within. Further, we are sensitive to the fact that few if any regulations or guidance—promulgated by OHRP, FDA, VA, DOD, ED, CMS, DHS, OCR, or others—speak to compelling issues that have emerged since the current regulations have been introduced. These issues include HIPAA and privacy of identifiable data, future research uses of data and tissues that are identified to specific human subjects, and significant inconsistencies between FDA and HHS regulations and guidance, as in the availability of waivers of the consent process for minimal risk research. Further, the fact that human subjects research is increasingly international, prompting considerations of the globalization of research, and increasingly involving vulnerable subjects—because vulnerability is often dynamic—has not been adequately addressed in the current regulatory framework.

We would strongly encourage the Commission to recognize, and consider a solution for, a basic structural deficiency in the organization of regulatory oversight of human subject research at the federal level, in that there is presently no public forum for all the federal agencies that fund and regulate human research to share issues and perspectives, and – to the greatest extent possible – to harmonize or reconcile their regulations and guidance in this area. Although SACHRP

performs this function for HHS, and the Common Rule agencies have ex-officio members on SACHRP, there is no standing analog to SACHRP for the many other federal offices and agencies that routinely promulgate and enforce human research regulations. Until just this year, the Committee of Science in the Office of Science and Technology convened the Human Subjects Research Subcommittee, which met regularly for decades and was co-chaired by OHRP and NSF. Unfortunately this subcommittee was ineffective because it had no authority to make changes to the regulations and issue guidance.

The lack of federal-wide coordination has resulted in confusing, complex, and, not infrequently, inconsistent welter of regulations and guidance documents. Researchers and research institutions incur significant transaction costs in seeking to comply with these disparate requirements without, in our judgment, yielding any research processes that are superior in terms of protection of human subjects. An alternative worth exploring would, in our judgment, be the establishing of a new public advisory committee working under, for example, the Office of Science and Technology Policy, which would have authority to make recommendations for all the Common Rule agencies, similar to the way in which SACHRP is structured within HHS.

The purpose of this committee would not be to recommend steps that each federal agency or office might take in regard to its own regulation of human subjects research, but rather to make, on a continuing basis, recommendations for how agencies and offices can adopt common, consistent, and effective standards for this research. What seems needed at this point is not an advisory committee that would sustain each agency in any unique aspects of its regulations and interpretations, but an advisory committee that would seek to steer all the agencies into a common, harmonious approach to this heavily regulated area of academic and industrial activity. To make such an advisory committee effective, its charter could require federal offices and agencies to respond meaningfully to the committee's formal recommendations within a set period of time, and in case of failures to adopt its recommendations, for elevation of these recommendations directly to the Secretarial or agency director level.

We offer these comments, and more specific comments below, for SACHRP's consideration, and respectfully request that these be forwarded to the Presidential Commission for the Study of Bioethical Issues.

1. Harmonization

The current legal framework for protection of human subjects is composed of an overlapping and non-uniform set of regulations and other requirements. The basic reason for this patchwork of regulatory provisions is that each federal agency has own authority to write regulations and to promulgate additional regulations or guidance to the "Common Rule" (subpart A of 45 CFR 46). Further, the triggers for applicability of the existing regulatory structure are either federal funding from a federal agency that is a signatory to the "Common Rule," or involvement of a product regulated by FDA. Other research falls within cognizant state law jurisdictions. The result of this patchwork framework is that there are gaps in oversight for certain research and overlaps in regulations for other research. These overlaps have led to differences in application, interpretation and implementation of the regulations. The President's Commission should

consider recommending a legislative solution that would close the gap in oversight and harmonize the overlapping regulations governing human subjects protections.

By way of explanation, the two main federal agencies charged with protection of human subject protections are the Office of Human Research Protections (OHRP), which administers the 45 CFR 46 (HHS regulations), and the Food and Drug Administration (FDA), which administers the Federal Food, Drug and Cosmetic Act and the implementing regulations at Part 21 of the Code of Federal Regulations. The HHS regulations apply to all human subject research that is funded by HHS, whereas the FDA regulations apply to all human subject research that involves an FDA regulated test article (e.g., a food, cosmetic, dietary supplement, drug or medical device). Research funded by one of the other federal agencies is subject to that agency's codification of the "Common Rule," for example 38 CFR 16 and 17 for VA. Thus, research that does not involve federal funding from a signatory to the "Common Rule" or an FDA regulated article often will not be subject to any federal oversight, and some research that involves federal funding and an FDA regulated article will be subject to both sets of regulatory requirements. To make this scheme more complicated, multiple federal agencies (e.g., VA, DOD, ED) have their own regulations that superimpose additional requirements. For example, the VA requires compensation for research related injuries and had required protections for adults who are unable to consent, while other agencies do not. The Department of Navy requires a separate FWA addendum with training requirements (type and scope) that differ from and expand upon the OHRP requirements. Similarly, HHS, FDA, and ED require additional protections for children in research (subpart D), but the other agencies do not.

True systemic reform would demand a critical look at integrating, harmonizing and simplifying this regulatory system. One possible solution, which has been introduced as a Congressional bill and was proposed by the National Bioethics Advisory Commission, is to create a single federal regulatory agency or office for oversight of research involving human subjects; another solution would be to expand the legislative authority of an existing regulatory entity (e.g., OHRP) with oversight authority for all human subject research (presumably through the interstate commerce power), regardless of whether it involves federal funding or an FDA regulated article. The requirements should preempt state laws in this field. Such legislation should also harmonize existing federal requirements governing human subject protections, while maintaining the appropriate distinctions in the regulatory framework for FDA and HHS that are essential to fulfilling their respective legislative mandates.

2. Alternatives to local IRB review for multi-site research

The current system of protections was largely established 40 years ago, when research was conducted much differently than it is today, and is predicated on local review by IRBs at individual institutions. Redundant review by multiple IRBs has been identified as a hindrance to the efficient and effective conduct of research in today's environment, and may be of questionable benefit in multi-site scenarios, because the protocol must be conducted consistently across all sites. Further, subject protections might be lessened when multiple IRBs review a protocol and do not have complete study-wide data, such as for data and safety monitoring.

There is nothing in the current regulations to prohibit IRBs from sharing IRB reviews. However, the complexity of current agreements and concerns over institutional liability, accountability, and jurisdiction prevent their widespread use. Alternative models exist and their use should be explored and expanded. Effective review models that have mechanisms to account for local issues, address institutional liability concerns, and address other barriers to their use should be encouraged. Prior SACHRP recommendations have supported these efforts, and led to national conferences in 2005 and 2006 that explored related issues (summary reports available at: www.aamc.org/initiatives/clinicalresearch/irbreview/).

3. HIPAA

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) has had various negative impacts on human subjects research, often without demonstrable benefit in further protecting the subjects of that research. SACHRP has previously developed several recommendations for changes in HIPAA (see Secretarial Letters dated Sept 27, 2004 and July 15, 2009) that focus on decreasing regulatory burden without decreasing human subject protection. HHS has recently proposed some regulatory changes to HIPAA that would ease some HIPAA burdens on research, and while SACHRP has been supportive of these recent proposals, SACHRP would encourage full implementation of its own past recommendations in this area, in addition to adoption of the recommendations of the 2009 Institute of Medicine committee on HIPAA and research.

In addition, the Presidential Commission should examine whether a comprehensive national data privacy scheme would provide better privacy protections to U.S. citizens and promote global harmonization of standards. Most countries have comprehensive data protection schemes that are patterned after the EU Data Protection Directive. These comprehensive schemes govern all aspects of data protection including, but not limited to, health related information, and are administered by data protection authorities that have broad enforcement powers. The U.S., on the other hand, is one of the few countries with sector-specific rules governing data privacy (e.g., HIPAA, drug and alcohol abuse treatment regulations, state regulations on information relating to genetic testing, HIV and mental health treatment). The use of personal information outside of one of these sector-specific legislative schemes is not regulated. The Commission should examine whether the adoption of a comprehensive scheme would provide better protections and promote harmonization with international standards for data protection.

4. Minimal Risk Research

IRBs today are required to apply the same criteria for approval of (a) research involving high or moderate risk, and (b) research involving little to no risk. For example, data analysis when identifiers are present is an example of research that engenders confusion and discord over the level of oversight needed. As a result, there is an imbalance in the time that IRBs spend reviewing minimal risk research, resulting in less time and resources available for higher and moderate risk studies, where closer review and more exacting attention are merited. There should

be a reevaluation as to how minimal risk research is reviewed, including the criteria for approval of that research and how it is monitored in an ongoing fashion. In addition, there is potential for more minimal risk research to be accommodated under the categories for exemption, if determination and verification of the risk level of a proposed study were to qualify some research for exemption. Alternatively, simplified criteria for approval and continuing review could be developed for lower-risk studies, including greater flexibility for review of minimal risk research and relaxation of continuing review requirements, thus relying more heavily on investigators to signal any problems in research through their reporting of unanticipated problems. Overall, the processes for review and approval of this type of research could be reconsidered and revised, with a view toward allocating an increased share of IRB time and attention to higher risk studies, thus reducing time and attention focused on research with lower risk to subjects.

5. Banking and Secondary Uses of Identifiable Data and Biomaterials

In large, population-based studies, as well as in clinical trials of drugs, devices and biotechnology agents, massive amounts of health data, including data relating to past and present family and medical history, are routinely collected; these data are often preserved after a study ends and placed either into a unique database or aggregated into larger databases with data from other studies. Further, with increasing frequency, biospecimens collected for immediate study purposes are preserved after the study ends, and are placed into biobanks or biospecimen repositories, and thus preserved for future research uses, the nature and contours of which are presently unknown, and to a large extent, unknowable. Similarly, in academic medical centers both in the U.S. and abroad, treatment data and biomaterials collected in the course of standard of care treatment are now often preserved long after any period of required retention has ended, in order to allow future researchers to use these data and biomaterials for future, presently unspecified studies. These practices of data and biomaterials preservation coincide, not unexpectedly, with increasingly frequent federally-mandated requirements in many types of biomedical and behavioral research, which require that data and biomaterials collected in federally funded studies be placed into large databases or repositories maintained by federal agencies or entities they fund to perform these functions.

With these data banking and tissue banking practices increasing in frequency and scope (a phenomenon seemingly attributable to the increasing scientific value of the uses of these data and tissue banks and the promise of precision or personalized medicine), IRBs, research institutions, and sponsors are struggling with what data and tissues are appropriate to share or to request, how to share or request them, what level of review is required to support this sharing, and what future research uses, if any, may not be appropriate. While some case law has addressed the issues of ownership and control of specimens once they have been obtained, and of data, once they have been collected, there is a need for greater regulatory clarity and predictability. Further, complex and often ill-drafted state laws relating to genetic testing (and also, in some cases, privacy of medical information) further cloud the issues, and confuse the legalities of trans-state research.

In sum, it is critical for progress in science and medicine that these data and tissues be banked, shared and used in responsible and accountable ways, by responsible and accountable parties,

with reasonable protections for subjects' privacy and welfare. The legality and ethics of practices in this area need swift clarification, with consistency of regulation and guidance among FDA, OHRP, other federal offices and agencies, and, if possible, the state jurisdictions as well.

6. Informed Consent

Consent documents have been transformed from tools of individual (subject) protection and information sharing into tools of regulatory compliance documentation and investigator, sponsor and institutional protection. These forms have become increasingly lengthy and complex, describing every conceivable risk and tending to a level of detail that often obscures the information needed for subjects to make an informed choice. We encourage a shift in focus from the *form* to the *process* of consent. This could include the use of pre-consent education tools, with ongoing education throughout the duration of the study, and exit interviews. Forms must be simplified and alternative formats (both written documents and use of other technologies such as computer-assisted and video formats) should be encouraged. The consent process, including the forms employed in that process, must be restored to its intended role as a tool for protecting research subjects.

7. Education

Education regarding research and research participation is critically needed for all stakeholders including institutional leadership, IRBs, investigators and research staff, policymakers, sponsors, research subjects and the general public. This will be especially important as changes to human subjects protection requirements are considered. Currently, unless funding support for a researcher's salary or project falls under certain categories of NIH or NSF programs, educational requirements -- whether for responsible conduct of research, in general, or for human subjects protections in particular – do not apply. Educational efforts should include public campaigns, PSAs, community outreach and creation of a model curriculum. An improved understanding of the processes of research will promote transparency. An informed public is more likely to consider research participation in advance of being approached for possible study enrollment and to be more knowledgeable about their options, rights, and the requirements of participation, resulting in greater protections and higher quality research results.

8. International Research

The increased globalization of clinical research has highlighted the inadequate resources and oversight authority by federal agencies for international research. OHRP and FDA have too few resources and potentially inadequate legislative authority to provide adequate monitoring and oversight of international research. For instance, foreign institutions that have obtained Federal Wide Assurances receive little in the way of guidance, and foreign IRBs that review FDA-regulated research are not required to register with the FDA. The Presidential Commission should review the legislative authority and resources allocated to FDA and OHRP to ensure they are adequate for those agencies to operate effectively in a global environment.

In addition, the "Common Rule" allows for the recognition of international standards that provide protections to human subjects that are at least equivalent to those of subpart A of 45 CFR 46. However, there have been no determinations of equivalent protections, even as research has globalized and several countries have developed robust human subjects protection and regulatory mechanisms, consistent with their own national laws and cultural values, and requested that OHRP deem their systems of protection to be equivalent. At the same time, FDA accepts foreign data developed in studies that are performed in compliance with foreign laws and standards if they are completed before the FDA application filing; the FDA thus tacitly accepts an equivalent standard (e.g., ICH and CIOMS) in its own approval process, in significant contrast to OHRP's current stance on these "equivalence" issues. The lack of determinations of "equivalence" – and of acceptable methods to determine "equivalence" – has led to circumstances in which U.S.-based researchers and research institutions must insist on foreign entities' and foreign researchers' strict adherence to what can seem, to them, confusing and even impenetrable U.S. regulations and guidance documents. The solution is for the equivalent standard regulation to be implemented, as recommended by the Equivalent Protections Working Group, the National Bioethics Advisory Commission, and others.

Finally, guidance for U.S.-based IRBs that review multinational research is lacking. Current standards do not clearly enable non-local IRBs to judge whether they have sufficient knowledge of local context, or when local practices in areas such as legally effective consent may be considered acceptable under U.S. regulations.

9. Financial Conflicts of Interest

Financial conflict of interest regulations in human subject research originate from several set of regulations including those of FDA, PHS and NSF, and the Common Rule prohibition on conflicts of interest among IRB members. In these different sets of regulations and corresponding guidance documents, there is significant inconsistency in approach, procedure, and definition of cognizable financial interests. This inconsistency would be exacerbated by adoption of the proposed PHS revisions to that set of regulations. Indeed, during the comment period on those proposed regulations, SACHRP elaborated on the ways in which the proposed regulations would widen the gulf between the FDA and PHS approaches to financial conflicts of interest. These inconsistencies were also noted by SACHRP's predecessor committee, the National Human Research Protections Advisory Committee (NHRPAC), in a 2001 report to HHS. Recent heightened attention to the issues of investigators' financial interests in human subjects research has also led to a number of states enacting their own laws governing these issues, thus leading to further complexity of the legal regimes applicable to this area of activity. Viewed globally, there is even less uniformity, as PHS regulations are rarely enforced in foreign institutions that receive NIH funds directly or as subrecipients.

Interests of research subjects and the research enterprise as a whole would be better served if there were a coherent and consistent national approach to conflict of interest in human subjects research, with uniform standards for disclosure of financial interests that may affect such

research, and with common procedural approaches and norms for the management of identified conflicts of interest.

10. Social Science, Behavioral and Educational Research (SBER)

A distinction is often drawn between biomedical or "clinical" human research and non-clinical human research, with the term "SBER" being used as a general expression for human research that is non-clinical in nature. The types of research subsumed under this shorthand abbreviation are broad, and include a range of methods/techniques as well as a range of scientific fields. Nevertheless some regulatory and subject protection issues regularly emerge in discussion of SBER.

Regarding research methods and techniques, SBER often makes use of surveys, interviews, review of existing records/data, observations of public behaviors, etc. These are the same methods and techniques that non-regulated professions such as journalism, market "researchers" and pollsters use – generally without abuse of subjects, public outrage or mistrust. These methods are also used in quality assurance activities that the biomedical field employs routinely without the "protection" of regulatory oversight.

Regarding scientific approaches, fields such as anthropology, ethnography, and community participatory research often have striking differences from clinical research. IRBs are accustomed to structured protocols for clinical studies, but SBER protocols may include only a general overview with a brief outline of procedures, and the focus of the research develops over the course of time in cooperation with communities and participants. Consent forms thus may be more difficult to review because specifics are unknown in advance.

It has been long and loudly argued that the burden imposed on researchers and IRBs by human subjects research oversight in SBER seems out of proportion to the potential harms to research subjects, which are rarely physical or irreversible. Delineation of high and low risk research is, however, an exacting task, and these categories are not invariably correlated with clinical and non-clinical research. Indeed, the Tuskegee Syphilis Study that directly resulted in the current human research regulations was an observational study, not clinical research. The Milgram Study, Wichita Jury Study, and Zimbardo Prison Study, to name a few examples, all resulted in great concern about subject harms, and yet none was a clinical study.

As stated above in the minimal risk section, a solution may be for the IRB to focus on making the determination whether a SBER project presents no more than minimal risk to subjects; if so, the IRB should be allowed to "exempt" the study from further requirements or review. This step would require a regulatory change.

The following proposed addition to this draft was prepared by SACHRP member Steve Joffe:

Sharing individual research test results with participants

Imaging, genomic, proteomic and other technologies increasingly permit the performance of sophisticated tests and assays on specimens obtained from human research participants, or on the participants themselves. These technologies, such as whole-genome sequencing, are increasingly high-throughput, i.e., they permit simultaneous collection of thousands or even millions of data points. Although the vast majority of these data points will lack validated clinical implications, the result of a test may occasionally have clinical or perhaps personal meaning for the participant

The ability to perform high-throughput testing in the research context presents investigators and IRBs with a conundrum. Responsible investigators and IRBs conducting or overseeing such studies seek to minimize risk to participants, maximize benefit, enhance partnership, and demonstrate respect for participant autonomy. It is difficult, however, for investigators employing high-throughput research tools to simultaneously achieve all these goals. On the one hand, a broad policy of sharing research results risks physical, psychological or financial harms as a result of actions taken in response to results of uncertain clinical meaning. On the other hand, such a policy respects the autonomy of participants who desire their results and demonstrates a commitment to partnership with participants. In addition, results of tests performed in the research context may occasionally have significant and actionable implications for participants, as in the incidental detection of a cancer predisposition mutation for which actions to mitigate risk are available. Many observers have argued that policies regarding the handling of research results should make it possible--or indeed should require--that investigators make such results available to participants. The requirements of the Clinical Laboratories Improvements Act (CLIA) create an additional barrier to sharing such results with participants, whether motivated by a desire to benefit participants or to respect their autonomy and foster partnership. As currently interpreted by CMS, only results that have been obtained in a CLIA-certified laboratory may be returned to individuals. Much research testing, however, occurs in non-CLIA-certified laboratories, in part because the specialized testing performed in many research studies is not yet available in CLIA-certified laboratories. Given the increasing use of genomic and other high-throughput technologies, federal guidance regarding the return of research test results to individual participants is urgently needed.

Attachment B.
Comments Regarding the PCSBI, as Approved

Subpart A and Harmonization Subcommittee Comments Regarding the PCSBI
Request for Comments on Human Subjects Protections in Scientific Studies

The Secretary's Advisory Committee on Human Research Protections (SACHRP) is charged with providing the Secretary, HHS, with advice and recommendations on issues relating to human research protections, with the dual aims of improving the protection of human subjects and the quality of protection programs, and of decreasing regulatory burdens that do not meaningfully contribute to the protection of such subjects. The protection and promotion of scientifically rigorous and ethically sensitive research in the public interest is our collective concern.

In consideration of our charge, SACHRP **has** considered the *Request for Comments on Human Subjects Protections in Scientific Studies* emanating from the Presidential Commission for the Study of Bioethical Issues ("the Commission"). We summarize herein the major topics that have been discussed in our deliberations, and recommend that these comments **be** forwarded to the Commission through the Secretary, HHS.

SACHRP has previously considered a number of the areas mentioned below, and substantive and detailed recommendations have been forwarded to the Secretary in the past. That said, much of SACHRP's work to date has focused on subpart A of 45 CFR Part 46, the "Common Rule" and its additional subparts (B, C and D), and more recently on the overlap and dissonance between the regulations espoused by OHRP and other agencies (e.g., FDA, OCR). We find that the basic framework of the regulations in 45 CFR Part 46, coupled with the bedrock principles of the Belmont Report, have served the regulated community – and the human subjects that it serves – well over the past decades. We note, however, that only a portion of studies is governed by these regulations, and the Request for Comments by the Commission provided us with the opportunity to comment on the patchwork system of regulatory oversight, and on certain specific issues within. **There are** compelling issues that have emerged since the regulations **for human subjects protections were** introduced. These issues include **differences in interpretations of identifiability**, future research uses of data and tissues that are identified to specific human subjects, and significant inconsistencies between FDA and HHS regulations and guidance, as in the availability of waivers of the consent process for minimal risk research. Further, the fact that human subjects research is increasingly international, prompting considerations of the globalization of research, and increasingly involving vulnerable subjects—because vulnerability is often dynamic—has not been adequately addressed in the current regulatory framework.

We would strongly encourage the Commission to recognize, and consider a solution for, a basic structural deficiency in the organization of regulatory oversight of human subject research at the federal level, in that there is presently no public forum for all the federal agencies that fund and regulate human research to share issues and perspectives, and – to the greatest extent possible – to harmonize or reconcile their regulations and guidance in this area. Although SACHRP performs this function for HHS, and the Common Rule agencies have ex-officio members on SACHRP, there is no standing analog to SACHRP for the many other federal offices and

agencies that routinely promulgate and enforce human research regulations. Until just this year, the Committee of Science in the Office of Science and Technology convened the Human Subjects Research Subcommittee, which met regularly for decades and was co-chaired by OHRP and NSF. Unfortunately this subcommittee had no authority to make changes to the regulations and issue guidance.

The lack of federal-wide coordination has resulted in a confusing, complex, and, not infrequently, inconsistent welter of regulations and guidance documents. Researchers and research institutions incur significant transaction costs in seeking to comply with these disparate requirements without, in our judgment, yielding any research processes that are superior in terms of protection of human subjects. An alternative worth exploring would, in our judgment, be the establishing of a new public advisory committee working under, for example, the Office of Science and Technology Policy, which would have authority to make recommendations for all the Common Rule agencies, similar to the way in which SACHRP is structured within HHS.

The purpose of this committee would not be to recommend steps that each federal agency or office might take in regard to its own regulation of human subjects research, but rather to make, on a continuing basis, recommendations for how agencies and offices can adopt common, consistent, and effective standards for this research. What seems needed at this point is not an advisory committee that would sustain each agency in any unique aspects of its regulations and interpretations, but an advisory committee that would seek to steer all the agencies into a common, harmonious approach to this heavily regulated area of academic and industrial activity. To make such an advisory committee effective, its charter could require federal offices and agencies to respond meaningfully to the committee's formal recommendations within a set period of time, and in case of failures to adopt its recommendations, for elevation of these recommendations directly to the Secretarial or agency director level.

We offer these comments, and more specific comments below, for SACHRP's consideration, and respectfully request that these be forwarded to the Presidential Commission for the Study of Bioethical Issues.

1. Harmonization

The current legal framework for protection of human subjects is composed of an overlapping and non-uniform set of regulations and other requirements. The basic reason for this patchwork of regulatory provisions is that each federal agency has own authority to write regulations and to promulgate additional regulations or guidance to the "Common Rule" (subpart A of 45 CFR 46). Further, the triggers for applicability of the existing regulatory structure are either federal funding from a federal agency that is a signatory to the "Common Rule," or involvement of a product regulated by FDA **or EPA**. Other research falls within **sometimes inconsistent** state law jurisdictions. The result of this patchwork **structure** is that there are gaps in oversight for certain research and overlaps in regulations for other research. These **gaps and** overlaps have led to differences in application, interpretation and implementation of the regulations. The President's Commission should consider recommending a legislative solution that would close

the gap in oversight and harmonize the overlapping regulations governing human subjects protections.

The HHS regulations apply to all human subject research that is funded by HHS, whereas the FDA regulations apply to all human subject research that involves an FDA regulated test article (e.g., a food, cosmetic, dietary supplement, drug or medical device). Research funded by one of the other federal agencies is subject to that agency's codification of the "Common Rule," for example 38 CFR 16 and 17 for VA. Thus, research that does not involve federal funding from a signatory to the "Common Rule" or an FDA regulated article often will not be subject to any federal oversight, and some research that involves federal funding and an FDA regulated article will be subject to both sets of regulatory requirements. To make this scheme more complicated, multiple federal agencies (e.g., VA, DOD, ED) have their own regulations that superimpose additional requirements. For example, the VA requires **its medical facilities to provide necessary medical treatment to a research subject injured as a result of participation in a VA research study** , while **most** other agencies do not. The Department of Navy requires a separate FWA addendum with training requirements (type and scope) that differ from and expand upon the OHRP requirements. Similarly, HHS, FDA, ED, **and other agencies** require additional protections for children in research (subpart D), but **some** agencies do not. **Another agency, EPA, has additional protections and prohibitions for children and pregnant women that diverge significantly from those of any other department or agency.**

True systemic reform would demand a critical look at integrating, harmonizing and simplifying this regulatory system. One possible solution, which has been introduced as a Congressional bill and was proposed by the National Bioethics Advisory Commission, is to create a single federal regulatory agency or office for oversight of research involving human subjects; another solution would be to expand the legislative authority of an existing regulatory entity (e.g., OHRP) with oversight authority for all human subject research (presumably through the interstate commerce power **or other applicable basis for federal jurisdiction), even if it does not** involve federal funding or an FDA regulated article.

Such legislation should also harmonize existing federal requirements governing human subject protections, while maintaining the appropriate distinctions in the regulatory framework for FDA and HHS that are essential to fulfilling their respective legislative mandates. **The federal requirements should preempt all state laws in this field. When state laws offer additional protections for human subjects and those protections are reasonable, effective, and efficient, those should be considered for adoption in the national research regulations.**

2. Alternatives to local IRB review for multi-site research

The current system of protections was largely established 40 years ago, when research was conducted much differently than it is today, and is predicated on local review by IRBs at individual institutions. Redundant review by multiple IRBs has been identified as a hindrance to the efficient and effective conduct of research in today's environment, and may be of questionable benefit in multi-site scenarios, because the protocol must be conducted consistently across all sites **for scientific validity and rigor.** Further, subject protections might be lessened

when multiple IRBs review a protocol and do not have complete study-wide data, such as for data and safety monitoring.

There is nothing in the current regulations to prohibit IRBs from sharing IRB reviews. However, the complexity of current agreements and concerns over institutional liability, accountability, and jurisdiction **discourage** their widespread use. Alternative models exist and their use should be explored and expanded. Effective review models that have mechanisms to account for local issues, address institutional liability concerns, and address other barriers to their use should be encouraged. Prior SACHRP recommendations have supported these efforts, and led to national conferences in 2005 and 2006 that explored related issues (summary reports available at: www.aamc.org/initiatives/clinicalresearch/irbreview/).

3. HIPAA

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) has had various negative impacts on human subjects research, often without demonstrable benefit in further protecting the subjects of that research. SACHRP has previously developed several recommendations for changes in HIPAA (see Secretarial Letters dated Sept 27, 2004 and July 15, 2009) that focus on decreasing regulatory burden without decreasing human subject protection. HHS has recently proposed some regulatory changes to HIPAA that would ease some HIPAA burdens on research, and while SACHRP has been supportive of these recent proposals, SACHRP would encourage full implementation of its own past recommendations in this area, in addition to adoption of the recommendations of the 2009 Institute of Medicine committee on HIPAA and research.

In addition, the Presidential Commission should examine whether a comprehensive national data privacy scheme would provide better privacy protections to U.S. citizens and promote global harmonization of standards. Most countries have comprehensive data protection schemes that are patterned after the EU Data Protection Directive. These comprehensive schemes govern all aspects of data protection including, but not limited to, health related information, and are administered by data protection authorities that have broad enforcement powers. The U.S., on the other hand, is one of the few countries with sector-specific rules governing data privacy (e.g., HIPAA, **the Family Educational Rights and Privacy Act** [**FERPA],** drug and alcohol abuse treatment regulations, state regulations on information relating to genetic testing, HIV and mental health treatment). The use of personal information outside of one of these sector-specific legislative schemes is not regulated. The Commission should examine whether the adoption of a comprehensive scheme would provide better protections and promote harmonization with international standards for data protection.

4. Minimal Risk Research

IRBs today are required to apply the same criteria for approval of (a) research involving high or moderate risk, and (b) research involving little to no risk. For example, data analysis when identifiers are present is an example of research that engenders confusion and discord over the

level of oversight needed. As a result, there is an imbalance in the time that IRBs spend reviewing minimal risk research, resulting in less time and resources available for higher and moderate risk studies, where closer review and more exacting attention are merited. **The existing categories for exemption should be examined to determine if additional types of research could be accommodated within current categories or within new or revised categories.** Simplified criteria for approval and continuing review could be developed for **minimal risk** studies, including greater flexibility for **initial** review and relaxation of continuing review requirements, thus relying more heavily on investigators to signal any problems in research through their reporting of unanticipated problems. Overall, the processes for review and approval of this type of research could be reconsidered and revised, with a view toward allocating an increased share of IRB time and attention to higher risk studies, thus reducing time and attention focused on research with lower risk to subjects. **These issues occur with particular frequency in social science, behavioral and educational research as detailed in the section that follows.**

The following section was moved here from an original position as 10.

5. Social Science, Behavioral and Educational Research (SBER)

~~A distinction is often drawn between biomedical or "clinical" human research and non-clinical human research, with the term "SBER" being used as a general expression for human research that is non-clinical in nature. The types of research subsumed under this shorthand abbreviation are broad, and include a range of methods/techniques as well as a range of scientific fields. Nevertheless some regulatory and subject protection issues regularly emerge in discussion of SBER.~~

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Regarding research methods and techniques, SBER often makes use of surveys, interviews, review of existing records/data, observations of public behaviors, etc. These are the same methods and techniques that non-regulated professions such as journalism, market research and public polling use – generally without abuse of subjects, public outrage or mistrust. These methods are also used in quality assurance activities that the biomedical field employs routinely without the "protection" of regulatory oversight.

Regarding scientific approaches, fields such as anthropology, ethnography, and community participatory research often have striking differences from clinical research. IRBs are accustomed to structured protocols for clinical studies, but SBER protocols may include only a general overview with a brief outline of procedures, and the focus of the research develops over the course of time in cooperation with communities and participants. Consent forms and study plans (protocols) thus may be more difficult to review because specifics are unknown in advance.

It has been long and loudly argued that the burden imposed on researchers and IRBs by human subjects research oversight in SBER seems out of proportion to the potential harms to research subjects, which are rarely physical or irreversible. Delineation of high and low risk research is, however, an exacting task, and these categories are not invariably correlated with clinical and non-clinical research. Indeed, the Milgram Study, Wichita Jury Study, and Zimbardo Prison Study, to name a few examples, all resulted in great concern about subject harms, and yet none was a clinical study.

As stated above in the minimal risk section, a solution may be for the IRB to focus on making the determination whether a SBER project presents no more than minimal risk to subjects; if so, the IRB should be allowed to ~~**"exempt" the study from further requirements or review**~~ **determine that the study does not require further review.** This step would require a regulatory change.

6. Banking and Secondary Uses of Identifiable Data and Biospecimens

In large, population-based studies, as well as in clinical trials of drugs, devices and biotechnology agents, massive amounts of health data, including data relating to past and present family and medical history, are routinely collected; these data are often preserved after a study ends and placed either into a unique database or aggregated into larger databases with data from other studies. Further, with increasing frequency, biospecimens collected for immediate study purposes are preserved after the study ends, and are placed into biobanks or biospecimen repositories, and thus preserved for future research uses, the nature and contours of which are presently unknown, and to a large extent, unknowable. Similarly, in academic medical centers both in the U.S. and abroad, treatment data and **biospecimens** collected in the course of standard of care treatment are now often preserved long after any period of required retention has ended, in order to allow future researchers to use these data and **biospecimens** for future, presently unspecified studies. These practices of data and **biospecimens** preservation coincide, not unexpectedly, with increasingly frequent federally-mandated requirements in many types of biomedical and behavioral research, which require that data and **biospecimens** collected in federally funded studies be placed into large databases or repositories maintained by federal agencies or entities they fund to perform these functions.

With these data banking and tissue banking practices increasing in frequency and scope (a phenomenon seemingly attributable to the increasing scientific value of the uses of these data and tissue banks and the promise of precision or personalized medicine), IRBs, research institutions, and sponsors are struggling with what data and tissues are appropriate to share or to request, how to share or request them, what level of review is required to support this sharing, and what future research uses, if any, may not be appropriate. **For example, current regulations are inadequate to address whether and when subsequent uses of biospecimens (particularly when individual identifiers are removed) must be compatible with the original terms of consent under which they were obtained and how this would be determined.** While some case law has addressed the issues of ownership and control of specimens once they have been obtained, and of data, once they have been collected, there is a need for greater regulatory clarity and predictability. Further, complex and often ill-drafted state laws relating to

genetic testing (and also, in some cases, privacy of medical information) further cloud the issues, and confuse the legalities of trans-state research.

In sum, it is critical for progress in science and medicine that these data and tissues be banked, shared and used in responsible and accountable ways, by responsible and accountable parties, with **appropriate** protections for **the** privacy, **rights** and welfare **of subjects. Concerns have also been raised about the effect of research use of databases and biorepositories on close families and discrete and insular communities; these concerns should be considered in formulating regulations and guidance in this area.** The legality and ethics of practices in this area need swift clarification, with consistency of regulation and guidance among FDA, OHRP, other federal offices and agencies, and, if possible, the state jurisdictions as well.

7. Informed Consent

Consent documents have been transformed from tools of individual (subject) protection and information sharing into tools of regulatory compliance documentation and investigator, sponsor and institutional protection. These forms have become increasingly lengthy and complex, describing every conceivable risk and tending to a level of detail that often obscures the information needed for subjects to make an informed choice. We encourage **the PCSBI to examine how to best facilitate** a shift in focus **on the part of all parties involved in the human research enterprise** from the *form* to the *process* of consent. This could include the use of pre-consent education tools, with ongoing education throughout the duration of the study, and exit interviews. Forms must be simplified and alternative formats (both written documents and use of other technologies such as computer-assisted and video formats) should be encouraged. The consent process, including the forms employed in that process, must be restored to its intended role as a tool for protecting research subjects.

8. Education

Education regarding research and research participation is critically **important** for all stakeholders including institutional leadership, IRBs, investigators and research staff, policymakers, sponsors, research subjects and the general public. This will be especially **vital** as changes to human subjects protection requirements are considered. Currently, unless funding support for a researcher's salary or project falls under certain categories of NIH or NSF programs, educational requirements -- whether for responsible conduct of research, in general, or for human subjects protections in particular – do not apply. Educational efforts should include public campaigns, **public service announcements** , community outreach and creation of a model curriculum. An improved understanding of the processes of research will promote transparency. An informed public is more likely to consider research participation in advance of being approached for possible study enrollment and to be more knowledgeable about their options, rights, and the requirements of participation, resulting in greater protections and higher quality research results.

9. International Research

The increased globalization of clinical research has highlighted the inadequate resources and oversight authority by federal agencies for international research. OHRP and FDA have too few resources and potentially inadequate legislative authority to provide adequate monitoring and oversight of international research. For instance, foreign institutions that have obtained Federal Wide Assurances receive little in the way of guidance, and foreign IRBs that review FDA-regulated research are not required to register with the FDA. The Presidential Commission should review the legislative authority and resources allocated to FDA and OHRP to ensure they are adequate for those agencies to operate effectively in a global environment.

In addition, the "Common Rule" allows for the recognition of international standards that provide protections to human subjects that are at least equivalent to those of subpart A of 45 CFR 46. However, there have been no determinations of equivalent protections, even as research has globalized and several countries have developed robust human subjects protection and regulatory mechanisms, consistent with their own national laws and cultural values, and requested that OHRP deem their systems of protection to be equivalent. At the same time, FDA accepts foreign data developed in studies that are performed in compliance with foreign laws and standards if they are completed before the FDA application filing; the FDA thus tacitly accepts an equivalent standard (e.g., ICH and CIOMS) in its own approval process, in significant contrast to OHRP's current stance on these "equivalence" issues. The lack of determinations of "equivalence" – and of acceptable methods to determine "equivalence" – has led to circumstances in which U.S.-based researchers and research institutions must insist on foreign entities' and foreign researchers' strict adherence to what can seem, to them, confusing and even impenetrable U.S. regulations and guidance documents. The solution is for the equivalent standard regulation to be implemented, as recommended by the Equivalent Protections Working Group, the National Bioethics Advisory Commission, and others.

When addressing federal and international standards for protecting the rights and welfare of participants in scientific studies, the PCSBI is encouraged to specifically examine the standards to protect populations that may be uniquely burdened or harmed by participation in research such as children, the mentally ill, severely socially and economically disadvantaged, displaced persons and others.

Finally, guidance for U.S.-based IRBs that review multinational research is lacking. Current standards do not clearly enable non-local IRBs to judge whether they have sufficient knowledge of local context, or when local practices in areas such as legally effective consent may be considered acceptable under U.S. regulations.

10. Financial Conflicts of Interest

Financial conflict of interest regulations in human subject research originate from several set of regulations including those of FDA, PHS and NSF, and the Common Rule prohibition on conflicts of interest among IRB members. In these different sets of regulations and corresponding guidance documents, there is significant inconsistency in approach, procedure, and definition of cognizable financial interests. This inconsistency would be exacerbated by

adoption of the proposed PHS revisions to that set of regulations. Indeed, during the comment period on those proposed regulations, SACHRP elaborated on the ways in which the proposed regulations would widen the gulf between the FDA and PHS approaches to financial conflicts of interest. These inconsistencies were also noted by SACHRP's predecessor committee, the National Human Research Protections Advisory Committee (NHRPAC), in a 2001 report to HHS. Recent heightened attention to the issues of investigators' financial interests in human subjects research has also led to a number of states enacting their own laws governing these issues, thus leading to further complexity of the legal regimes applicable to this area of activity. Viewed globally, there is even less uniformity, as PHS regulations are rarely enforced in foreign institutions that receive NIH funds directly or as subrecipients.

Interests of research subjects and the research enterprise as a whole would be better served if there were a coherent and consistent national approach to conflict of interest in human subjects research, with uniform standards for disclosure of financial interests that may affect such research, and with common procedural approaches and norms for the management of identified conflicts of interest.

11. Sharing individual research test results with participants

Imaging, genomic, proteomic and other technologies increasingly permit the performance of sophisticated tests and assays on specimens obtained from human research participants, or on the participants themselves. These technologies, such as whole-genome sequencing, are increasingly high-throughput, i.e., they permit simultaneous collection of thousands or even millions of data points. Although the vast majority of these data points will lack validated clinical implications, the result of a test may occasionally have clinical or perhaps personal meaning for the participant

The ability to perform high-throughput testing in the research context presents investigators and IRBs with a conundrum. Responsible investigators and IRBs conducting or overseeing such studies seek to minimize risk to participants, maximize benefit, enhance partnership, and demonstrate respect for participant autonomy. It is difficult, however, for investigators employing high-throughput research tools to simultaneously achieve all these goals. On the one hand, a broad policy of sharing research results risks physical, psychological or financial harms as a result of actions taken in response to results of uncertain clinical meaning. **There is also concern that the requirement of returning research results, with appropriate education and counseling, will be impracticable for some research studies**. On the other hand, such a policy respects the autonomy of participants who desire their results and demonstrates a commitment to partnership with participants. In addition, results of tests performed in the research context may occasionally have significant and actionable implications for participants, as in the incidental detection of a cancer predisposition mutation for which actions to mitigate risk are available. Many observers have argued that policies regarding the handling of research results should make it possible--or indeed should require--that investigators make such results available to participants. The requirements of the Clinical Laboratories Improvements Act (CLIA) create an additional barrier **as well as a protection** to sharing such results with participants, whether motivated by a desire to benefit participants or to respect their autonomy and foster partnership. As currently interpreted by CMS, only results that have been obtained in a CLIA-certified laboratory may be returned to individuals. Much research testing, however, occurs in non-CLIA-

certified laboratories, in part because the specialized testing performed in many research studies is not yet available in CLIA-certified laboratories. Given the increasing use of genomic and other high-throughput technologies, federal guidance is urgently required regarding whether, when, and how research results should be returned to individual participants, **as well as how this is reflected in the informed consent process. In addition, if results may be returned in some instances, the development of a mechanism for recommending which results should be considered for return, such as an advisory panel housed within the National Institutes of Health or other appropriate agency, would greatly assist the research community in addressing this challenging issue.**

12. Third Parties in Research

Human subjects research increasingly involves persons who, although perhaps not originally intended as research subjects, nevertheless participate in the conduct of research and have identifiable data about them collected as part of the research. These "third parties" to research can often become research subjects themselves (e.g., educational research on students but involving teachers, health research on patients but involving medical providers, research on individuals that involves data collection on family members). There is a current lack of clarity on whether and when and under what circumstances these "third parties" may become research subjects themselves, and guidance on this issue is needed.

13. Evidence-based Protections

There is an inadequate evidence base to inform regulation and best practices in many areas of human subjects protections. Increased federal support for research to enhance this evidence base is essential to facilitate improvements in human subjects research regulations and practices.

The Presidential Commission is urged to use its broad charge and trans-agency scope to contemplate appropriate revisions and harmonization of human research protection statutes and regulatory standards that are necessary to keep pace with the evolving advances in the conduct of human subjects research.

Attachment C.
Recommendations Regarding Research Consent Forms, As Presented

DRAFT RECOMMENDATIONS FROM SUBPART A SUBCOMMITTEE (SAS) FOR CONSIDERATION BY SACHRP ON JULY 19, 2011

Guidance on Applying the Regulatory Requirements for Research Consent Forms: What Should and Should Not be Included?

Consent forms must convey basic elements of information as required by federal regulations. It is essential that consent disclosures be tailored to the research at hand and focus on the information that prospective participants need to make an informed decision. Conversely,

standard disclaimers or statements without meaningful content may not help subjects and should be discouraged. To assist in focusing and simplifying consent forms, we offer the following clarifications concerning what federal regulations do and do not require.

§46.116(a)(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental

1. What has to be included?

a. Consent forms for clinical research should identify and describe procedures that are experimental or that are performed solely for research purposes. In other words, consent forms should focus on *things that would happen because the person participates in research* that otherwise would not happen as part of his or her clinical care.

Examples:

- Undergoing (or potential randomization to) an experimental intervention (e.g., drug, device, procedure)
- Taking *extra* blood or tissue during a procedure needed for clinical care
- As part of a clinical trial, the researcher will access and use specimens/data that were originally collected for clinical purposes

A special example of something that would happen because the person takes part in research that otherwise would not happen is when research participation places *constraints* on the person's clinical care.

- Example: In a trial of a new chemotherapy agent, the research protocol prescribes the dose and schedule for adjuvant radiation therapy that must be followed. Even though this prescription reflects "standard of care," research participation constrains adjustments to the radiation dose or schedule that the participant's physician might otherwise recommend.

Such constraints should be described in consent forms (including the risks) as a consequence of research participation.

b. Similarly, consent forms for non-clinical research (e.g., social/behavioral studies) should identify and describe procedures that are experimental or that are performed solely for research purposes. In other words, consent forms should focus on *activities that would happen because the person participates in research.*

- Example: Survey of risk-taking behaviors by adolescents who are already enrolled in a drug treatment program. In this case, the consent form would describe the purpose and procedures of the survey research rather than details of the treatment program.

2. What does *not* have to be included?

a. When there are no experimental procedures a statement to that effect is not required.

b. Activities that would occur as part of the person's clinical care (if he or she was not participating in research) do not need to be described in consent forms.

- Removing this kind of information represents a potential opportunity to shorten/simplify consent forms.
- Consent forms may refer to an appendix or educational materials that contain this information, or state "your doctor will tell you more about the procedures needed for your clinical care."

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§46.116(a)(2) A description of any reasonably foreseeable risks or discomforts to the subject

§46.116(a)(3) A description of any benefits to the subject or to others which may reasonably be expected from the research

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1. What has to be included?

a. Consent forms should identify reasonably foreseeable risks and benefits, not all possible risks and benefits.

- Consent forms should address risks/benefits arising from research participation (not from things that would happen anyway as part of the person's clinical care).

b. IRBs and investigators have a responsibility to review information regarding potential risks and to assess relatedness, severity, and likelihood. Risk statements in consent forms should be simplified such that the information included is understandable and relevant to the subject population. Detailed descriptions of all potential risks are counterproductive if they do not provide potential subjects with useful information and may inadvertently distract subjects from relevant data.

- Example: In a previous study, a single subject experienced a tonic clonic seizure. First the IRB must determine whether this is a reasonably foreseeable risk about which potential subjects should be aware. If so, the consent form might simply state "There is a small risk of seizures" rather than providing a long description of the circumstances of the single subject.

The investigator may choose to provide additional information placing this risk in context during discussions with prospective participants.

2. What does *not* have to be included?

- When there are no reasonably foreseeable risks and/or benefits to participants, consent forms may include statements to this effect but such statements are not required. However when research participation involves greater than minimal risk but no reasonably foreseeable benefits, consent forms should alert prospective participants to not expect direct benefit. Including this statement may help minimize the presumption of benefit/therapeutic misconception.

§46.116(a)(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

1. What has to be included?

- Consent forms should identify appropriate alternatives to the research intervention. For example, in research on pain management following tooth extraction, the consent form might provide information about standard analgesics available outside of any research study.

2. What does *not* have to be included?

- When the only alternative to research participation is not to participate, it is not necessary to include a statement to this effect. "Not participating" is already fully addressed in sections of the form emphasizing that participation is voluntary; see §46.116(a)(8).

§46.116(a)(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

1. What has to be included?

- When applicable, consent forms should explain that research records will be kept confidential. General descriptions of the measures that will be taken to protect confidentiality can be described when it helps inform the prospective participant's decision.

- Absolute confidentiality should not be guaranteed. Participants should be informed of limits to confidentiality, including circumstances under which confidentiality will not be maintained (e.g., legal requirements, mandated reporting).

2. What does *not* have to be included?

- Detailed technical descriptions of the measures in place to maintain confidentiality (e.g. encrypted FTP sites, locked file cabinets) are not likely helpful to subjects, under most circumstances.

§46.116(a)(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

1. What has to be included?

- For research involving *more than minimal risk*, consent forms should provide explanations about the availability of compensation and medical treatment, consistent with sponsor and institutional policies.

2. What does *not* have to be included?

- For research involving *no more than minimal risk*, these explanations are not required and may be unnecessarily alarming, particularly when the risks do not involve physical injury. For example, a pro forma disclaimer that "some survey questions may be embarrassing…" may not be warranted or helpful.

§46.116(a)(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

- Providing contact information for each of these circumstances is appropriate for all study types where informed consent is required.

§46.116(a)(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

- Including these statements is appropriate for all study types where informed consent is required.

§46.116(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- **A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable**
- **Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent**
- **Any additional costs to the subject that may result from participation in the research**
- **The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject**
- **A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject**
- **The approximate number of subjects involved in the study**

1. **What has to be included?**
   a. It is up to the IRB to determine in a particular instance whether some or all of the above additional elements must be included in the consent form for a particular study. The IRB should make this determination based on the nature of the research and its knowledge of the local research context (from "Informed Consent-FAQs" http://answers.hhs.gov/ohrp/categories/1566)
   b. In general:
      - Several of these elements may be most appropriate for clinical trials but may be less applicable to other kinds of studies.
      - When determining whether to include any particular element, a key consideration is the relevance of the information to a prospective participant's decision about whether to take part.
2. **What does *not* have to be included?**
   - These additional elements are particularly susceptible to automatic inclusion of boilerplate language in every consent form. Removing information that is not applicable to a particular study represents an important opportunity to shorten and/or simplify consent forms.

Attachment D.
Recommendations Regarding Research Consent Forms, As Approved

Guidance on Applying the Regulatory Requirements for Research Consent Forms: What Should and Should Not be Included?

Consent forms must convey basic elements of information as required by federal regulations. It is essential that consent disclosures be tailored to the research at hand and focus on the information that prospective participants need to make an informed decision. Conversely, standard disclaimers or statements without meaningful content may not help subjects and should be discouraged. To assist in focusing and simplifying consent forms, we offer the following clarifications concerning what federal regulations do and do not require. **In cases where a required element is not relevant or applicable, IRBs do not need to document a waiver of the element in their minutes. It is the responsibility of the person seeking consent to ensure that the process includes sufficient detail to enable each potential subject to make an informed and voluntary decision.**

§46.116(a)(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental

1. **What has to be included? Consent forms for research should identify and describe procedures that are experimental or that are performed solely for research purposes.**

   a. Consent forms **for biomedical research** should focus on *things that would happen because the person participates in research* that otherwise would not happen as part of his or her clinical care.

      Examples:

      - **Having treatment randomly selected rather than determined by medical practice**
      - Undergoing an experimental intervention (e.g., drug, device, procedure)
      - Taking *extra* blood or tissue during a procedure needed for clinical care
      - As part of **the** clinical trial, the researcher will access and use specimens/data that were originally collected for clinical purposes

   A special example of something that would happen because the person takes part in research that otherwise would not happen is when research participation places *constraints* on the person's clinical care.

      - Example: In a trial of a new chemotherapy agent, the research protocol prescribes the dose and schedule for adjuvant radiation therapy that must be followed. Even though this prescription reflects "standard of care," research participation constrains adjustments to the radiation dose or schedule that the participant's physician might otherwise recommend.

Such constraints should be described in consent forms (including the risks) as a consequence of research participation.

b. Similarly, consent forms for non-**biomedical** research (e.g., social/behavioral studies) should identify and describe procedures that are experimental or that are performed solely for research purposes. In other words, consent forms should focus on *activities that would happen because the person participates in research.*

   - Example: Survey of risk-taking behaviors by adolescents who are already enrolled in a **driver's education program** . In this case, the consent form would describe the purpose and procedures of the survey research rather than details of the **educational** program.

2. What does *not* have to be included?

a. **Activities that would occur if he or she were <u>not</u> participating in research do not need to be described in consent forms.**

   - **Removing this kind of information represents a potential opportunity to shorten/simplify consent forms.**
   - **Consent forms may refer to an appendix or educational materials that contain this information, or state "your doctor will tell you more about the procedures needed for your clinical care."**.

b. **While there may be circumstances where it may be relevant or appropriate to note that there are no experimental procedures, a statement to that effect is not required by the regulations and consequently no requirement to document that in the minutes of the IRB meeting**

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§46.116(a)(2) A description of any reasonably foreseeable risks or discomforts to the subject

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- ***NOTE: This section on risks and the one that follows on benefits were originally combined. SACHRP determined they should be presented separately as they appear here.***

1. What has to be included?

a. Consent forms should identify reasonably foreseeable risks, not all possible risks.

   - Consent forms should address risks arising from research participation (not from things that would happen anyway).

b. IRBs and investigators have a responsibility to review information regarding potential risks and to assess relatedness, severity, and likelihood. Risk statements in consent forms

should be simplified such that the information included is understandable and relevant to the subject population. Detailed descriptions of all potential risks are counterproductive if they do not provide potential subjects with useful information and may inadvertently distract subjects from relevant data.

- Example: In a previous study, a single subject experienced a tonic clonic seizure. First the IRB must determine whether this is a reasonably foreseeable risk about which potential subjects should be aware. If so, the consent form might simply state "There is a small risk of seizures" rather than providing a long description of the circumstances of the single subject.

The investigator may choose to provide additional information placing this risk in context during discussions with prospective participants.

2. What does *not* have to be included?

- When there are no reasonably foreseeable risks and to participants, consent forms may include statements to this effect but such statements are not required **by the regulations.**

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§46.116(a)(3) A description of any benefits to the subject or to others which may reasonably be expected from the research

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1. What has to be included?

a. Consent forms should identify reasonably expected benefits, not all theoretical benefits.

- Consent forms should address benefits arising from research participation (not from things that would happen anyway ~~as part of the person's clinical care~~).

b. When research participation involves greater than minimal risk but no reasonably foreseeable benefits, consent forms should alert prospective participants that there is no anticipated benefit to them. Including this statement may help minimize the presumption of benefit or therapeutic misconception.

~~IRBs and investigators have a responsibility to review information regarding potential risks and to assess relatedness, severity, and likelihood. Risk statements in consent forms should be simplified such that the information included is understandable and relevant to the subject population. Detailed descriptions of all potential risks are counterproductive if they do not provide potential subjects with useful information and may inadvertently distract subjects from relevant data.~~

- ~~Example: In a previous study, a single subject experienced a tonic clonic seizure. First the IRB must determine whether this is a reasonably foreseeable risk about which potential subjects should be aware. If so, the consent form might simply~~

~~state "There is a small risk of seizures" rather than providing a long description of the circumstances of the single subject.~~

~~The investigator may choose to provide additional information placing this risk in context during discussions with prospective participants.~~

2. What does *not* have to be included?

- ~~o~~ When there are no reasonably expected benefits to participants, consent forms may include statements to this effect but such statements are not required **by the regulations.** ~~However when research participation involves greater than minimal risk but no reasonably foreseeable benefits, consent forms should alert prospective participants to not expect direct benefit. Including this statement may help minimize the presumption of benefit/therapeutic misconception.~~
- o **A statement that individuals "may or may not benefit from participation" confers no useful information and may in fact be misleading in some circumstances. Investigators and IRBs should strive to describe as accurately as possible the nature and likelihood of any anticipated benefits.**

§46.116(a)(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

1. What has to be included?

- Consent forms should identify appropriate alternatives to the research intervention. For example, in research on pain management following tooth extraction, the consent form might provide information about standard analgesics available outside of any research study.

2. What does *not* have to be included?

- When the only alternative to research participation is not to participate, it is not necessary to include a statement to this effect. "Not participating" is already fully addressed in sections of the form emphasizing that participation is voluntary; see §46.116(a)(8).

§46.116(a)(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

1. What has to be included?

- When **appropriate,** consent forms should explain that research records will be kept confidential. General descriptions of the measures that will be taken to protect

confidentiality can be described when it helps inform the prospective participant's decision.

- Absolute confidentiality should not be guaranteed. Participants should be informed of limits to confidentiality, including circumstances under which confidentiality will not be maintained (e.g., legal requirements, mandated reporting).

2. What does *not* have to be included?

- Detailed technical descriptions of the measures in place to maintain confidentiality (e.g. encrypted FTP sites, locked file cabinets) are not likely helpful to subjects, under most circumstances.

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§46.116(a)(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

---

1. What has to be included?

- For research involving *more than minimal risk,* consent forms should provide explanations about the availability of compensation and medical treatment, consistent with sponsor and institutional policies.

2. What does *not* have to be included?

- For research involving *no more than minimal risk*, these explanations are not required and may be unnecessarily alarming, particularly when the risks do not involve physical injury. **IRBs are not required to document in their minutes that this statement is not required.**

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§46.116(a)(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

---

- Providing contact information for each of these circumstances is appropriate for all study types where informed consent is required **unless the IRB approves and documents a waiver of that element.**

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§46.116(a)(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

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- Including these statements is appropriate for all study types where informed consent is required **unless the IRB approves and documents a waiver of that element.**

§46.116(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- **A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable**
- **Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent**
- **Any additional costs to the subject that may result from participation in the research**
- **The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject**
- **A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject**
- **The approximate number of subjects involved in the study**

1. **What has to be included?**

   a. It is up to the IRB to determine in a particular instance whether some or all of the above additional elements must be included in the consent form for a particular study. The IRB should make this determination based on the nature of the research and its knowledge of the local research context (from "Informed Consent-FAQs" http://answers.hhs.gov/ohrp/categories/1566)

   b. In general:

      - Several of these elements may be most appropriate for clinical trials **and** may be less applicable to other kinds of studies.
      - When determining whether to include any particular element, a key consideration is the **likely** relevance of the information to prospective **participants'** decision**s** about whether to take part.

2. **What does *not* have to be included?**

   - These additional elements are particularly susceptible to automatic inclusion of boilerplate language in every consent form. Removing information that is not applicable to a particular study represents an important opportunity to shorten and/or simplify consent forms.

Appendix E.
Recommendation Regarding Definition of a Minor Change in Research, As Approved

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear :

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services human subjects protection regulations at 45 CFR part 46. This letter represents the xxx in a series of recommendations from SACHRP.

SACHRP Recommendation regarding definition of a minor change in research under 45 CFR 46 and 21 CFR 56

The Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations both have sections addressing expedited review (45 CFR 46.110; 21 CFR 56.110). IRBs may use expedited review to approve certain kinds of research involving no more than minimal risk, and minor changes in approved research. Expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. Expedited review greatly reduces the administrative burden on IRB members and staff, and allows for more efficient review of research.

Although the regulatory language regarding expedited review of a minor change in research is identical in the HHS and FDA regulations, OHRP and FDA have provided differing guidance regarding the definition of a minor change. The guidance documents from each agency are included below in Appendix I. FDA in the preamble comment to the regulations and in the FDA Information Sheets has taken the approach that changes that result in increased risk to human subjects are not minor. OHRP, on the other hand, has taken the approach that changes in research that would materially affect the assessment of risks and benefits are not minor. In its September 29, 2008 letter to CTEP, OHRP re-emphasized that approach as it relates to new or modified risk information, and also added the concept that a minor change in research is one that does not affect any of the determinations for IRB criteria at 45 CFR 46.111. OHRP stated that IRBs can consider "whether the new or modified risk information adversely impacts the overall risk-benefit relationship for the subjects of the research and therefore may significantly alter the prior determinations of the IRBs required for approval of research under HHS regulations at 45 CFR 46.111 (in particular, the determinations under 45 CFR 46.111(a)(1) and (2))."

SACHRP makes the following recommendations regarding the definition of a minor change in research under the HHS and FDA regulations:

OHRP and FDA should issue a single joint guidance on this issue so that IRBs have a single source of information regarding the agencies' viewpoint on this issue. This will reduce administrative burden on IRBs and ease compliance requirements. Currently, it appears that in some cases a change in research may not be a minor change in research under the FDA interpretation but still be considered a minor change in research under the OHRP interpretation.

The joint guidance, regardless of where it is located, should include a formal statement that it is FDA guidance as well as OHRP guidance. This will ensure that institutions, IRBs, and FDA employees are aware that it represents formal FDA guidance.

SACHRP recommends the following definition of a minor change in approved research that can be reviewed through the expedited review process:

> Minor changes in approved research that can be approved through expedited review procedures are ~~minor~~ changes that neither materially increase risk, nor materially decrease benefit, **nor materially decrease scientific merit.**

Commentary: This approach is similar to existing FDA and OHRP guidance. This approach has several advantages. It is familiar to IRBs. Also, if issued in a joint guidance document then IRBs would have the benefit of knowing the expectations of both agencies.

~~Finally,~~ SACHRP recommends that the joint guidance provide examples of the kinds of changes that qualify as minor changes in approved research. It is very helpful when guidance provides examples as well as a definition. The types of examples that would be helpful to IRBs include the following, **all of which should be assessed by an experienced reviewer, who would, of course, have the option of referring the change to full board review:**

1. Adding a new procedure to a research study, when that procedure is on the expedited list and involves no more than minor risk.

2. Adding a new minimal risk procedure to a research study, when that procedure is <u>not</u> on the expedited list. Two examples are low dose radiation procedures and drawing 3-5 blood draws **of less than 550 ml** from an in-dwelling catheter. It is SACHRP's understanding that this represents OHRP's current position.

3. A minor change to research that is not on the expedited list, but does not involve the addition of a procedure. Examples include many types of changes to research, such as:
   - Change in the equally qualified individuals who will do statistical analysis.
   - Change in consent form wording that does not increase risk or decrease benefit. For example, changing "nausea" to "nausea and stomach upset," or fixing a run-on sentence or a comma.
   - Replacing old case report forms with essentially equivalent new case report forms, and the change is noted in a revised protocol.
   - Changing the order of questions in a psychology study questionnaire.
   - Adding the word "approximately" to the table of the lab test schedule.

4. The guidance should also address the point from section E of the current OHRP "Guidance on IRB Approval of Research with Conditions," which states that "Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research." These administrative changes to the protocol need to be clearly distinguished from administrative changes to the consent form, which always need at least expedited review.

5. A new media advertisement that is submitted after the research is approved, such as a new newspaper or radio advertisement.

6. A statistically small change to the number of subjects an investigator will enroll. For instance, in a single site study, a change from 100 to 105 subjects, or in multi-center study, and change from 20 subjects to 30 subjects at one site in a study involving 1,000 subjects. Minor decreases in the number of subjects would also qualify for expedited review.

7. A change in equally qualified study personnel (study coordinator, nurse, technician, transcriptionist for anthropology study), e.g., a person leaves the institution and is replaced.

8. A change in equally qualified principal investigators. For example, when a principal investigator leaves the institution and a new principal investigator takes over.

~~9.~~ Adding a new equally qualified investigator at a new site for a multi-site study, **overseen by a central IRB. The IRB should have established criteria for this in its SOPs, such as familiarity with the investigator and the sponsor.** ~~This is a central/independent IRB issue which FDA has addressed in e-mails.~~

10. In a coronary stent study, an amendment to extend **the observational** follow up from 12 to 60 months.

11. **Deletion from the protocol of a research biopsy that, without impairing scientific merit, materially decreases risk for study subjects.**

Finally, the guidance should note that changes to research that were initially approved through expedited review will qualify for expedited review unless the change increases the overall risk level of the research to more than minimal risk.

In summary, joint OHRP and FDA guidance addressing these issues will greatly aid the regulated community, and particularly IRBs, in reducing burden and ensuring compliance.

Attachment F. Recommendations Regarding Early Processes in Research, As Approved

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear :

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services human subjects protection regulations at 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

SACHRP Recommendation regarding application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects

The Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations regarding research do not specifically address activities that are conducted prior to the subject's providing consent to participate in research. FDA and the Office for Human Research Protections (OHRP) have addressed this issue through guidance. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and related guidance addresses activities conducted prior to the subject's providing authorization to participate in research. The Department of Education (ED) Family Educational Rights and Privacy Act (FERPA) regulations also specifically address access to and release of private information from education records for specific purposes, including research.

FDA addresses these issues predominately in two sections of the FDA Information Sheets:

Recruiting Study Subjects
http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm (Attached as Appendix 1).

Screening Tests Prior to Study Enrollment
http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm (Attached as Appendix 2).

OHRP addressed this issue in 2004 with the issuance of joint guidance documents with FDA and the Office for Civil Rights (OCR) regarding implementation of the HIPAA Privacy Rule. In that guidance, OHRP recommended that IRBs approve a waiver of consent under 45 CFR 46.116(d) for all activities conducted prior to consent.

An example is the guidance entitled "Clinical Research and the HIPAA Privacy Rule," online at http://privacyruleandresearch.nih.gov/clin_research.asp. The relevant FAQ is attached as Appendix 3.

Based on this background, SACHRP makes two recommendations regarding application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects.

First Recommendation:

SACHRP recommends that OHRP abandon the guidance that IRBs approve a waiver of consent under 45 CFR 46.116(d) for all activities conducted prior to consent, as exemplified in the guidance entitled "Clinical Research and the HIPAA Privacy Rule." There are several difficulties with this guidance.

- IRB approval of a waiver of informed consent does not serve any practical purpose in protecting the rights and welfare of human subjects. It is often necessary for investigators to identify potential subjects to recruit for research through either records' review or contact by e-mail, phone calls, or direct contact. There are many ethical issues involved in these activities. However, requiring a waiver of consent under 45 CFR 46.116(d) does not address these ethical issues. Rather, it is a pro forma determination that does not in itself provide any protection of subjects.

- Consideration of a waiver of consent under 45 CFR 46.116(d) involves analysis of whether the research is minimal risk. The criterion at 45 CFR 46.116(d)(1) is that "the research involves no more than minimal risk to the subjects." Much research is not minimal risk. Therefore, in order to apply this finding to all research that involves identification of human subjects using identifiable private information prior to consent, there must be an interpretation that the recruitment activity being considered for the waiver of consent is minimal risk, rather than the research as a whole. If this approach is not used, recruitment involving the use of identifiable private information would not be possible for research that involves more than minimal risk. Alternatively, if OHRP chooses to continue to recommend that IRBs waive consent under 45 CFR 46.116(d) for recruitment activities, then OHRP should issue guidance on the use of this waiver, and specifically address when the research as a whole has to be minimal risk, or when some "subsection" of the research can be determined to be minimal risk. Note: Consideration of subsections of research in other situations (e.g., exempt determinations) has generally been discouraged in OHRP guidance.

- Much research is regulated by both HHS and FDA, or HHS and ED. The FDA regulations do not include the 45 CFR 46.116(d) waiver of consent provisions. Thus, it is theoretically not compliant with FDA regulations, or at least awkward, to apply 45 CFR 46.116(d) to FDA regulated research. FERPA regulations (34 CFR 99.31) provide specific permission for access to education records without consent under certain conditions.

Because of these difficult interpretation issues, SACHRP recommends that OHRP abandon this approach to requirements for recruitment activities. When researchers intend to obtain informed consent to a study, then their activities incident to obtaining such consent (e.g., identifying and contacting the individuals for consent) should not be regarded as a separate research activity requiring a waiver of consent. Rather, OHRP should regard this extremely common situation as one overall research project and should not bifurcate it. It should be sufficient for an IRB to review these preparatory activities as an integral part of the overall project, ensure that access to identifiable information is appropriate as proposed and that any risks are minimized, and focus on the proposed consent process and its documentation. In other studies in which the researchers do *not* intend to obtain informed consent (e.g., medical record reviews), the researchers' preparatory activities to identify participants and their work to obtain and review records should similarly be regarded as one overall project and the IRB should consider whether a waiver of consent is permissible. This approach has several advantages: (1) it respects OHRP's jurisdiction over preparatory activities to identify participants for studies; (2) it serves a harmonization goal (since both OCR, with respect to researchers that are part of a HIPAA covered entity, and FDA permit researchers to contact individuals for consent without requiring a prior consent or waiver thereof); and (3) it is a sound, workable policy that allows IRBs to review a study as a whole and focus on the proposed informed consent process and its documentation.

Alternatively, OHRP may wish to consider utilizing the 45 CFR 46.101(i) secretarial waiver. This section of the regulations states, "Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy." OHRP could waive the applicability of the consent requirements to recruitment activities, and instead of requiring consent or a waiver of consent, adopt the FDA guidance statements regarding the ethical standards for recruitment activities.

Second Recommendation:

SACHRP recommends that OHRP and FDA should take the necessary steps to issue a single joint guidance on recruitment of subjects so that IRBs have a single source of information regarding the agencies' viewpoint on this issue. This will reduce administrative burden on IRBs and ease compliance requirements. SACHRP recommends that OHRP should adopt the FDA approach to this issue as exemplified in FDA's guidance and take steps necessary to interpret the Common Rule so that this is possible. The joint guidance should clearly indicate that it applies equally to social, behavioral, and educational research, as well as medical research. The regulatory criterion for equitable selection of subjects should be addressed in the guidance. To the extent possible, OHRP, FDA, and OCR should also consider what activities must be performed due to the HIPAA Privacy Rule, and to what extent harmonization of interpretation can be implemented. Finally, OHRP and FDA should consider whether it would be useful to note in the guidance that other laws and regulations addressing recruitment activities might apply to the research, such as FERPA.

Attachment G. SACHRP Comments Regarding HIPAA/HITECH Notice of Proposed Rulemaking, As Approved

Re: *HIPAA/HITECH Notice of Proposed Rulemaking on Accounting of Disclosures and Access Reports*, RIN 0991-AB62

Ladies and Gentlemen:

Pursuant to its federal charter, the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) provides expert advice and recommendations on human subjects research protection issues to the Secretary of the United States Department of Health and Human Services (HHS). Shortly after its creation in 2003, SACHRP began developing recommendations on significant topics in research, including the protection of the privacy of research subjects. Consistent with its longstanding interest in and recommendations relating to this issue, SACHRP submits the following comments in response to the Notice of Proposed Rulemaking (NPRM) published on May 31, 2011 (76 Fed. Reg. 31426) pursuant to the Health Information Technology for Economic and Clinical Health Act (HITECH) and the Health Insurance Portability and Accountability Act (HIPAA). SACHRP's comments address two HHS proposals: (1) exempting research from the requirement to account for disclosures under the HIPAA Privacy Rule ("Accounting Requirement"), and (2) requiring, as a new regulatory measure, access reports, for which there must be electronic tracking of every person's access to electronic information in a designated record set at covered entities and business associates, with very limited exceptions ("Access Reports").

Accounting Requirement: Exemption for Research

SACHRP strongly supports the HHS proposal to exempt research disclosures from the Accounting Requirement. As the NPRM notes, this proposal would implement a recommendation that SACHRP submitted to the Secretary in 2004. See SACHRP Chair Letter to HHS Secretary on HIPAA, Sept. 27, 2004, and Appendix A. (http://www.hhs.gov/ohrp/sachrp/hipaalettertosecy090104.html; http://www.hhs.gov/ohrp/sachrp/appendixa.html). SACHRP's primary rationale for its 2004 recommendation was that strong protections already are in place for research conducted pursuant to a waiver of authorization (i.e., the research that currently is subject to the Accounting Requirement). This research may proceed only with a waiver of authorization approved by a privacy board or institutional review board (IRB), in accordance with several strict regulatory criteria. (Many of the same studies also undergo IRB scrutiny to determine if the Common Rule's separate criteria for a waiver of consent are met.) Given this high level of oversight and the specificity of researchers' commitments to protect individuals in these studies, SACHRP indicated in 2004 that the accounting requirement was unnecessary and overly burdensome to the research community.

SACHRP's rationale for its 2004 recommendation is even more compelling today. The federal government is investing over a billion dollars in comparative effectiveness research, an area of study that often requires waivers of individual authorization. Recent HHS policies also

provide significant incentives for covered entities to conduct retrospective patient safety and benchmarking studies to improve the quality and safety of patient care. The HHS proposal to exempt research from the Accounting Requirement allows the research community to pursue and expand these critical areas of work without attendant administrative burden.

SACHRP further notes that in a 2009 report, prepared at the conclusions of a lengthy committee study, the Institute of Medicine similarly concluded that the Accounting Requirement unduly burdens research without materially adding privacy protection. **See** *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research, Institute of Medicine of the National Academies* (2009).

Access Reports

The NPRM's new regulatory proposal for Access Reports would require covered entities and business associates to report to individuals, upon request, every access to their electronic information that is part of a designated record set (i.e., any health information relied upon for treatment or billing purposes, among other activities). This requirement would have an expansive reach: it would seem to include all electronic health record systems within a covered entity, of which there can be several at any one covered entity, such as those systems for main hospital or clinical records, labs, billing, and other services. The requirement would also include all electronic research forms, systems, or databases, and business associates' electronic records, provided that the electronic information includes a designated record set. More specifically under the NPRM, upon an individual's request, a covered entity would need to aggregate all logs of access into the individual's electronic information over three years, contact all business associates for their own records of internal access to and disclosure of the individual's designed record set information, and provide an understandable report to individuals within 30 days, unless an extension is approved.

SACHRP is concerned that this proposal would pose several significant**ly burdensome** challenges to the research enterprise. First, researchers are increasingly using electronic health records and other electronic information about a patient's care to facilitate research. These systems are critical to advancing research for many reasons: for example, they allow for more precise review and design of research questions, more tailored enrollment, more valuable longitudinal data, and more readily available sources of data, both for studies of widespread conditions and critical studies of rare diseases. Such research is not possible without accurate health information, which is increasingly found in electronic designated record sets. While covered entities likely would have records of electronic access to provide to individuals, if individuals had questions about the reports, covered entities that tried to respond would need to track down numerous protocols and research teams' membership, which would be extremely time-intensive. Further, the required Access Reports might be confusing even to individuals who had authorized their participation in research, but who do not understand the listings in the Access Report or the connection of those listings to the research in which they voluntarily enrolled. Similarly, for studies conducted under waivers of authorization and waivers of consent, in accordance with highly specific regulatory criteria and oversight, these Access Reports could lead individuals to have questions or concerns for research institutions even when the institutions have fully complied with privacy board and IRB review requirements. In sum, with so many

multiple entries for completely valid, expressly authorized or clearly permitted research uses of the electronic medical record, the **informational** value to research subjects of making these entries available in an Access Report is not clear.

A second set of concerns is based on the fact that many researchers in covered entities access and record electronic designated record set information in multiple places. For example, cancer patients' participation in clinical trials is extremely common and often extends to multiple research studies. Researchers typically need to access information in electronic health record systems for the clinical trials, and they often record trial data in the electronic medical record, in electronic case report forms, and in electronic databases. It would seem that all of these sets of electronic information would contain information relied upon for treatment or billing purposes, and therefore would qualify as electronic designated record sets. It would be quite difficult for covered entities to identify all the applicable electronic designated record sets containing a given individual's information, and preparing the Access Report (which includes all other types of non-research access at the covered entities and by its business associates) would therefore be extremely time-consuming and burdensome. Moreover, the Access Report would contain potentially duplicative information, in that researchers would have required access to multiple electronic systems containing somewhat similar information (e.g., medical record, updated case report forms, and other databases) for purposes of even a single clinical trial.

A third area of concern is that the NPRM proposes that, in order to generate an Access Report for a requesting individual, a covered entity must contact all of its business associates that have electronic designated record set information. While, to date, business associate relationships have not been common for research activities, some relationships already exist and more seem likely in the near future, as covered entities outsource functions due to expertise deficits and staff budget constraints. For example, some researchers within covered entities have hired information technology (IT) vendors to facilitate data collection, analysis, and storage in large survey studies. Researchers also hire outside consultants to assist in recruiting patient-participants for studies, and these consultants could maintain electronic designated record set information. SACHRP therefore is concerned about the significant burden that would be imposed on covered entities to identify and contact every business associate that may have electronic designated record set information for a given study, for reasons including but not limited to research.

Fourth, the primary interest of a research subject in seeking an Access Report presumably would be to ascertain any unauthorized uses or disclosures of his or her electronic medical record. Yet other requirements of the Privacy and Security Rules already offer significant protection against such unauthorized uses and disclosures, and moreover require notification to a patient if unauthorized access to an electronic record occurs. Indeed, in the breach notification provisions, HHS has already determined the specific circumstances of unauthorized access in which notification to a patient must occur. Requiring an Access Report therefore seems unnecessary and overly burdensome on research institutions, without meaningfully adding protection beyond what already exists in the breach notification requirements and in the various requirements for IRB and privacy board approval of waivers of authorizations.

Summary

In summary, SACHRP supports the HHS proposal to exempt research from the Accounting Requirement. At the same time, SACHRP has serious concerns about the new proposed Access Report requirement for reasons including, but not limited to, its negative effects on the research enterprise and its uncertain value to the overall interests of research subjects. **SACHRP would recommend, instead, as follows:**

- **Recommendation One:**
    - **Covered entities *not be required* to disclose access for research purposes, as part of the electronic access report requirement;**
- **Recommendation Two:**
    - **The Office for Civil Rights clarify that institutions have discretion, for purposes of the electronic access report, to define what electronic databases are intended primarily for research use and thus lie outside the "designated record set," with a presumption of validity as to explicit institutional decisions in this regard; and**
- **Recommendation Three:**
    - **The Office for Civil Rights clarify that institutions have discretion, for purposes of the electronic access report requirement, to designate that "business associates" engaged for mixed research and other purposes may omit access for research purposes in responding to requests for electronic record access reports.**
- **Recommendation Four:**

In recognition of the public desire for greater transparency in unconsented uses and disclosures of identifiable data for research purposes, the Office for Civil Rights should open a dialogue with OHRP and other relevant agencies about possible guidelines for public access to information relating to waivers of informed consent and HIPAA authorizations that are granted by IRBs and/or privacy boards. The Secretary should note that these recommendations in their entirety were endorsed by a majority of seven of the ten members of SACHRP who were present, while three other SACHRP members expressed their opposition, based on their commitment to increased access by individuals to information about research uses and disclosures of their protected health information.

SACHRP appreciates the consideration that has been given to its prior recommendations and the opportunity to comment on this NPRM.

Attachment H. SOH Additions to FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens, As Approved

Preface

The collection and use of human specimens have become essential to biomedical research. These biospecimens include blood and other tissues, some collected originally for clinical lab tests, some removed during surgeries, and some obtained specifically for research. While there is no accurate catalog of the number or locations of specimens, there are reasonable estimates that billions of specimens are now stored in laboratories, repositories and "tissue banks" across the country. Coupled with associated clinical data and the power of bioinformatics, these specimens represent an invaluable resource for current and future research on human health and disease.

At the same time, there are significant ethical, legal and social policy implications relating to the collection, storage and use of biospecimens. Institutions, investigators, institutional review boards (IRBs), funding agencies and the public are struggling with issues like informed consent, ownership, stewardship, genetic testing, and future uses that are often unspecified at the time specimens are first obtained. The ethical tensions that frequently exist between the needs of science and the rights of individuals are present in research involving specimens, and there is much inconsistency and uncertainty as to how they should be used responsibly. The research community would benefit from federal-level guidance.

The HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) has considered a number of unanswered questions relating to informed consent and research use of biospecimens. Upon request by SACHRP, the Subpart A Subcommittee of SACHRP deliberated on these issues and presented their recommendations to SACHRP for further discussion and approval, over the course of several meetings in 2009 and 2010. The finalized recommendations take the form of a series of "Frequently Asked Questions" (FAQs), each presented as a commonly encountered scenario and a suggested response that addresses regulatory and ethical issues. The goal was to provide a framework for IRBs, institutions and investigators to consider individual research scenarios without prescribing the final outcome, recognizing that those decisions will always be case-specific.

It is hoped that these compiled FAQs and recommendations constitute a product that the Office for Human Research Protections, the Office for Civil Rights, and the Food and Drug Administration and others can use to provide much-needed guidance in this area.

I. Glossary and concepts

1. CODED[1] means:

(1) Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and

[1] OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens, issued August 10, 2004; updated October 16, 2008

(2) A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

2. HONEST BROKER means:

A neutral intermediary (person or system) between the individual whose tissue and data are being studied, and the researcher. The honest broker collects and collates pertinent information regarding the tissue source, replaces identifiers with a code, and releases only coded information to the researcher.

3. LIMITED DATA SET:

As defined by HIPAA, limited data sets are data sets stripped of certain direct identifiers that are specified in the Privacy Rule. They are not de-identified information under the Privacy Rule.

A limited data set is protected health information that excludes the following direct identifiers of the individual or of relatives, employers, or household members of the individual: (1) names; (2) postal address information, other than town or city, state, and ZIP code; (3) telephone numbers; (4) fax numbers; (5) e-mail addresses; (6) social security numbers; (7) medical record numbers; (8) health plan beneficiary numbers; (9) account numbers; (10) certificate/license numbers; (11) vehicle identifiers and serial numbers, including license plate numbers; (12) device identifiers and serial numbers; (13) web URLs; (14) Internet Protocol (IP) address numbers; (15) biometric identifiers, including fingerprints and voiceprints; and (16) full-face photographic images and any comparable images.

Importantly, unlike de-identified data, protected health information in limited data sets *may include the following*: city, state and ZIP codes; all elements of dates (such as admission and discharge dates); and unique codes or identifiers not listed as direct identifiers.

Recognizing that institutions, IRBs and investigators are frequently faced with applying both the Common Rule and the HIPAA Privacy Rule, 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).

4. When is research with specimens not Human Subjects Research?[2]

OHRP does not consider research involving only coded private information or specimens to involve *human subjects* if the following conditions are both met:

(1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

(2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example, there are agreements, IRB-approved policies and procedures, or legal requirements in place that prohibit the release of the key to the code to the investigators under any circumstances until the individuals are deceased.

5. **How are studies with specimens addressed under the FDA regulations?**
?

Certain research studies involving medical devices and tissue specimens will qualify as clinical investigations under the FDA regulations. **Most commonly, devices that are tested using tissue samples are In Vitro Diagnostic (IVD) devices.** Under the definition of a human subject in FDA device regulation 21 CFR 812.3(p), "Subject means a human who participates in an investigation, either as an individual on whom or *on whose specimen* an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease." Thus, if tissues are used to establish the safety and effectiveness of a device, then the FDA regulations apply. Under the FDA regulations, IRB review (21 **CFR** Part 56) is always required, and consent of the subject (**21 CFR Part 50) i**s usually required. Consent may be waived in certain emergency situations under 21 CFR 50.23 and 50.24. FDA **applies** enforcement discretion to certain clinical investigations of IVDs, as described in the guidance document "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." This guidance allows research with tissues without consent if seven conditions are met. The most important condition for the purposes of these FAQs is that "The specimens are not individually identifiable, i.e., the identity of the subject is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor. If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems." The guidance uses essentially the same definition of "coded" that OHRP uses in its coded data guidance: "coded means that: 1) a number, letter, symbol, or combination thereof (i.e., the code) has replaced identifying information (such as name or social security number) that would enable the investigator or any other individuals associated with the investigation, including the sponsor to readily ascertain the identity of the individual to whom the specimen pertains; and 2) a key to decipher the code exists, enabling linkage of the identifying information to the specimen."

II. Related SACHRP Recommendations

1. Recommendation on Compatibility of Secondary Use with Consent.

The determination of whether a proposed secondary research use is compatible with the original consent will be context-specific based on a range of considerations. If the original consent form specifically prohibited the proposed research activity, it is presumed the research is not

allowable. If the consent does not prohibit the proposed use, IRBs should consider several questions to determine compatibility:

- What is the nature of the proposed secondary research?
- Could it reasonably be understood to fall within the scope of research that was described in the original consent form?
- Does the new research use impose new or significantly greater risks (including privacy risks) not described in the initial consent form?
- Are there known concerns of the study population(s) about the proposed new use?

2. 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. Persons 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."

III. Frequently Asked Questions (FAQs)

FAQ #1

Tissue biopsies were obtained for clinical diagnostic purposes, which have now been satisfied. The patients did not provide consent for the research use of the tissue specimens. The hospital pathology department is willing to provide a portion of the remaining biopsy specimens to an investigator who will perform research assays. In order to allow matching with relevant clinical information, the specimens will be provided with identifiers such that the investigator can readily ascertain the identity of subjects.

Is consent of the patient from whom the biopsy was taken (or waiver of consent) required for the secondary research use?

Response – HHS Common Rule Issues. Yes. Under this scenario, informed consent of the subjects should either be obtained or waived under 45 CFR 46.116(d) because the samples are identifiable to the recipient investigator.

HIPAA Issues. Assuming the hospital is a HIPAA covered entity, the use or disclosure of patient identifiers for the research purpose would also require a HIPAA authorization from the patient or an IRB or Privacy Board waiver of the authorization requirement. If the research could be performed using only information about the patient that constitutes a limited data set, the hospital could disclose the limited data set to the researcher after the researcher has signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4).

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required and informed consent of the subjects for the secondary use must be obtained unless the subjects provided consent addressing the elements required under 21 CFR 50.25 at the time of tissue collection, **which would adequately address the secondary use activities.**

FAQ #2

Tissue biopsies were obtained for clinical diagnostic purposes, which have now been satisfied. The hospital pathology department is willing to provide a portion of the remaining biopsy specimens to an investigator who will perform research assays. The specimens will be coded such that the investigator will not be able to readily ascertain the identity of individuals.

Is consent of the patient from whom the biopsy was taken (or waiver of consent) required for the secondary research use?

Response– HHS Common Rule Issues. No. Under this scenario, neither consent nor waiver is required, because the activity is not considered to be research involving human subjects.

HIPAA Issues. If the information associated with the specimen is de-identified in accordance with the HIPAA Privacy Rule, neither authorization nor an IRB or Privacy Board waiver of the authorization is required, because de-identified information would no longer be considered protected health information.

Note, however, that information associated with the specimen that is not individually identifiable per OHRP guidance (i.e., coded) may not necessarily be de-identified for HIPAA Privacy Rule purposes. For example, the coded information may not be considered to be de-identified under the Privacy Rule if the code is derived from a patient identifier or certain data elements, such as dates of service or zip codes, remain with the information. Thus, the use or disclosure of the information for research may still require a form of HIPAA permission, such as a HIPAA authorization, IRB or Privacy Board waiver of authorization, or, if the information constitutes a "limited data set," a data use agreement with the recipient of the information.

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable."

FAQ #3

Blood samples were obtained for research purposes, with informed consent of the subjects, and the original study has been completed. The samples remain under the control of the original investigator. Another investigator wants to use a portion of the remaining samples to perform research completely unrelated to the original study.

If the original consent stated that "…your sample will only be used for research on colon cancer," but the secondary user is interested in studying Alzheimer's disease, can the samples still be used if provided to the secondary user in a coded fashion?

Response– HHS Common Rule Issues. The use of de-identified samples, **or coded samples for which the requirements of OHRP's guidance on Research Involving Coded Private Information or Biological Specimens to preserve the samples' anonymity are met,** is not research involving human subjects under 45 CFR 46. In the case where secondary use of tissue samples **involves** tissues that are de-identified, coded, or anonymized and are not readily identifiable, the samples are no longer subject to human subject **research** regulations. Thus, **the use of such samples without individual informed consent to the secondary use** is not itself a regulatory violation. Nevertheless, the original investigator and his/her institution have made **representations to** the subjects about use of their specimens **through the original consent form**, and have an obligation to honor **these representations**.

Institutions should establish mechanisms to determine whether secondary uses are compatible with the original informed consent; this could involve consultation with the IRB that approved the original research, or review by some other body designated for these purposes. Coding **and/or de-identification** should not be used as a means to circumvent the original terms of consent. This is ethically problematic, even if the original project is over and the secondary use is no longer considered to be research involving human subjects. **To the extent secondary uses on de-identified or coded specimens are contemplated, the original informed consent should alert participants to that possibility so that they can evaluate it as part of their enrollment decision.**

Response– HHS Common Rule Issues. The secondary use of de-identified or coded samples is not research involving human subjects under 45 CFR 46. In the case where secondary use of tissue samples is not compatible with the original consent for tissues that are de-identified, coded, or anonymized and are not readily identifiable, the samples are no longer subject to human subject regulations. Thus, there is no regulatory violation. Nevertheless, the original investigator and his/her institution have made an agreement with the subjects about use of their specimens, and have an obligation to honor that agreement.

Institutions should establish mechanisms to determine whether secondary uses are compatible with the original informed consent; this could involve consultation with the IRB that approved the original research, or review by some other body designated for these purposes. Coding should not be used as a means to circumvent the original terms of consent. This is ethically problematic, even if the original project is over and the secondary use is no longer considered to be research involving human subjects.

HIPAA Issues. Assuming the original investigator is in a HIPAA covered entity, the disclosure of direct identifiers for the new research purpose would require a study-specific HIPAA authorization from the subject or an IRB or Privacy Board waiver of the authorization requirement. If the research could be performed using only information about the subject that constitutes a limited data set, the original investigator could disclose the limited data set to the researcher after the researcher has signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4).

FDA Issues. If tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." However, FDA agrees with the considerations described above regarding the ethical obligation to the subjects.

FAQ #4

It is increasingly common to collect and store specimens for future unspecified research. How broad can this consent be without requiring investigators to obtain additional consent for specific uses? Alternatively, how specific must this consent be to allow for future use of biospecimens?

Response– HHS Common Rule Issues. There is a tension between the desire to be as specific as possible when informing subjects of what will be done, and the reality that specifics of future research are, by definition, not known at the time of consent.

Many institutions and IRBs have found it prudent to include some general language in the consent form sufficient to give subjects a reasonable idea of the types of research that might be conducted in the future and the associated risks, but without placing unreasonable restrictions on what the research might be. Thus, subjects can be informed that future studies may involve genetic research, drug development, or searching for links between genes and environmental factors like diet or lifestyle, or between genes and diseases. While examples might be given of

specific diseases (e.g., cancer, diabetes, heart disease), being overly specific or restrictive in this regard may result in problems later, when investigators propose other uses. IRBs and investigators should consider the downstream implications before promising subjects that "your specimens will only be used for research on XYZ."

Future uses of identifiable specimens should be reviewed by the IRB, which should determine whether the research is compatible with original terms of consent, whether additional consent may be required, or whether consent may be waived.

Alternatively, the creation of a repository with an oversight committee and "honest broker" mechanisms that distribute specimens to investigators in coded fashion can remove subsequent uses from IRB review, to the extent they no longer constitute human subjects research. In these cases, special attention should be given upfront to ensure that the repository (which is human subjects research and does require IRB approval) is established with policies and procedures to effectively manage subsequent uses in keeping with what the IRB approved.

HIPAA Issues. This scenario raises a number of HIPAA-related issues for institutions that are covered entities under the HIPAA Privacy Rule.

While consent under 45 CFR 46 can be broader than a specific research study, an authorization under the HIPAA Privacy Rule must be study-specific. How specific must that authorization be? How can health information associated with specimens be used and disclosed from a research repository when specific research uses are unknown at the time the information is collected? There are two separate activities to consider when a HIPAA covered entity is collecting and storing identifiable health information in a research repository for future unspecified research:
(A) A covered entity's use or disclosure of protected health information (PHI) to create the repository; and
(B) The release of PHI from the repository for a future research purpose.

There are a number of ways health information can move into and out of a research repository, including those established for future unspecified research. In this scenario, it is assumed that the repository will contain PHI and that authorization will be obtained to disclose PHI to the repository. With reference to the two separate activities in this scenario:

(A) An authorization for research use and disclosure of PHI under the HIPAA Privacy Rule must be study-specific. However, the authorization may state that the purpose of the authorization is to create a research repository or database.
(B) Health information can then be subsequently used and disclosed from the research repository in one of several ways:

1. With study-specific authorization
2. With an IRB or Privacy Board waiver of the authorization requirement
3. Preparatory to research (with certain representations)
4. Use of a HIPAA De-identified Dataset*
5. Use of a Limited Data Set (with data use agreement)
6. Research solely on decedents (with certain representations)

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. If the tissues are identifiable, then subjects must provide consent for the secondary use and that consent must cover the elements of consent in 21 CFR 50.25. If the original consent met the requirements of 21 CFR 50.25, then that consent would be sufficient to meet FDA requirements. If the original consent did not meet those requirements, then the subjects must provide consent specifically for the use to test the IVD. Finally, it may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable."

Other than the use of tissues for testing IVDs, FDA has no regulations that apply to the collection of tissues or their **storage**. It is worth noting that when non-governmental organizations (NGOs) and pharmaceutical sponsors collect and store specimens for future unspecified research, without the involvement of federal funding, it is also often the case that the HHS regulations and HIPAA do not apply.

FAQ #5

When can informed consent be waived for use of previously-collected human specimens and data (e.g., when does such research meet "minimal risk" criteria, what does "practicability" mean with regard to the informed consent waiver criteria)?

Response– HHS Common Rule Issues. The criteria for waiver of consent under 45 CFR 46.116(d) include that the research involves no more than minimal risk; the waiver would not adversely affect the rights and welfare of subjects; the research could not practicably be carried out without the waiver; and whenever appropriate, the subjects will be provided with pertinent information after participation.

Points to consider in applying these criteria include the nature of the research; the protections in place to maintain privacy and confidentiality (e.g., coding, limited/controlled access, honest broker mechanisms); the change in level of risk, if any; the ability to locate or contact subjects; risk of introducing bias into the research; 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 proposed secondary use, based on the nature of original collection.

HIPAA Issues. The concept of waiver of informed consent is not a HIPAA concept. As set forth in more detail in 45 CFR 164.512(i)(2), the HIPAA authorization requirement can be waived by an IRB or privacy board when (1) the research use or disclosure involves no more than minimal risk to the individual's privacy; (2) the research could not practicably be conducted without the waiver; and (3) the research could not practicably be conducted without use or disclosure of the protected health information.

FDA Issues. FDA regulations do not include the waiver of consent found at 45 CFR 46.116(d). Therefore, the use of this waiver for FDA regulated studies is not possible. If the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the

FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." If the tissues are identifiable, then consent addressing the elements under 21 CFR 50.25 is required.

FAQ #6

Blood samples were obtained for research purposes, with informed consent of the subjects, and the original study has been completed. The samples remain under the control of the original investigator. Another investigator wants to use a portion of the remaining samples to perform research unrelated to the original study.

If the sample is identifiable to the secondary user, is this considered to be human subjects research under the purview of the IRB? If so, what are the consent considerations?

Response– HHS Common Rule Issues. Yes. This is human subjects research under the purview of the IRB. The IRB should consider whether the secondary use is compatible with the original terms of consent given by the subjects.

HIPAA Issues. A HIPAA authorization for research must be research-study specific. Thus, assuming a HIPAA covered entity is involved, a new HIPAA authorization would be required for the subsequent unrelated research use or disclosure, or another form of HIPAA permission obtained (e.g., waiver of authorization). If the research could be performed using only information about the subject that constitutes a limited data set, the original investigator could disclose the limited data set to the new investigator after the new investigator has signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4).

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. Because the subjects are identifiable to the secondary user, the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable" is not applicable. Consent addressing the elements under 21 CFR 50.25 is required, either at the time of the original collection of the blood samples, or at the time of the use of the specimens for the IVD testing.

FAQ #7

Identifiable blood samples were obtained for research purposes, with informed consent of the subjects, and the original study has been completed. The samples remain under the control of the original investigator, who now wants to collaborate with another investigator to perform research unrelated to the original study.

If the original consent was silent on the question of subsequent uses, is informed consent (or waiver of consent) required before the identifiable sample can be used for other purposes?

Response– HHS Common Rule Issues. Yes. Under these circumstances, the IRB should consider the original terms of consent, and determine whether a waiver might be appropriate or whether additional consent is required.

The criteria for waiver of consent under 45 CFR 46.116(d) include that the research involves no more than minimal risk; the waiver would not adversely affect the rights and welfare of subjects; the research could not practicably be carried out without the waiver; and whenever appropriate, the subjects will be provided with pertinent information after participation.

Points to consider in applying these criteria include the nature of the research; the protections in place to maintain privacy and confidentiality (e.g., coding, limited/controlled access, honest broker mechanisms); the change in level of risk, if any; the ability to locate or contact subjects; risk of introducing bias into the research ; 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 proposed secondary use, based on the nature of original collection.

HIPAA Issues. A HIPAA authorization for research must be research-study specific. Thus, assuming a HIPAA covered entity is involved, a new HIPAA authorization would be required for the subsequent unrelated research use or disclosure, or another form of HIPAA permission obtained (e.g., waiver of authorization). If the research could be performed using only information about the subject that constitutes a limited data set, the original investigator could disclose the limited data set to the new investigator after the new investigator has signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4).

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. Because the subjects are identifiable to the secondary user, the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable" is not applicable. Consent addressing the elements under 21 CFR 50.25 is required.

FAQ #8

Patients undergoing surgery provide consent to donate any excess tissue (i.e., beyond that needed for clinical purposes) to a tissue bank. The creation of the bank has been reviewed and approved by the IRB, meaning the IRB has approved the policies and procedures under which the bank will be managed, the control of specimens, and the types of research to be conducted, etc. The consent form makes it clear that the specimens and associated clinical data will be used for research, but does not specify or limit that use.

If the bank employs an "honest broker" mechanism, so that specimens and any associated data are coded so that the recipient investigator cannot readily ascertain the identity before being given to investigators, is this subsequent use considered to be human subjects research under the purview of the IRB?

Response– HHS Common Rule Issues. No, the subsequent research use is not considered to be research involving human subjects and IRB review is not required. However, there should be mechanisms in place to ensure that proposed research uses are compatible with the original consent.

HIPAA Issues. A HIPAA authorization for research must be research-study specific. Thus, assuming a HIPAA covered entity is involved and the information is not considered fully de-

identified under the HIPAA Privacy Rule, a new HIPAA authorization would be required for the subsequent unrelated research use or disclosure, or another form of HIPAA permission obtained (e.g., waiver of authorization, data use agreement if use or disclosure of a limited data set).

However, if the information associated with the specimens is de-identified in accordance with the HIPAA Privacy Rule, neither authorization nor waiver of authorization is required, because it would no longer be considered protected health information. The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. For example, an encrypted individual identifier (e.g., a social security number) would not meet the conditions for use as a re-identification code for de-identified health information because it is derived from individually identified information. In addition, the covered entity may not (1) use or disclose the code or other means of record identification for any other purpose, or (2) disclose its method of re-identifying the information.

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." If the seven conditions are not met, then consent addressing the elements under 21 CFR 50.25 is required.

FAQ #9

Patients undergoing surgery provide consent to donate any excess tissue (i.e., beyond that needed for clinical purposes) to a tissue bank. The creation of the bank is reviewed as human subjects research and approved by the IRB. The consent form makes it clear that the specimens and associated clinical data will be used for research, but does not specify or limit that use.

If specimens are provided to the researchers with clinical information that allows the researcher to readily ascertain the identity of the subjects, do those researchers need separate IRB approval of the proposed research use of the specimens and data?

Response– HHS Common Rule Issues. Yes, the provision of identifiable information with the specimen means the research to be conducted with the specimen is a separate human subjects research protocol and separate IRB approval would be required.

FDA Issues. If the tissues are used to test an FDA regulated IVD, then separate IRB review is required.

FAQ #10

Patients undergoing surgery provide consent to donate any excess tissue (i.e., beyond that needed for clinical purposes) to a tissue bank. The creation of the bank is reviewed and approved by the IRB. The consent form makes it clear that the specimens and associated clinical data will be used for research, but does not specify or limit that use.

If specimens are provided to the researchers with clinical information that allows the researcher to readily ascertain the identity of the subjects, is a new consent from the patient/subject [or IRB waiver of informed consent] required?

Response– HHS Common Rule Issues. Yes, a new consent from the subjects is required unless the IRB determines that the original consent was adequate to allow the subsequent research use, or the IRB determines a waiver is appropriate.

The criteria for waiver of consent under 45 CFR 46.116(d) include that the research involves no more than minimal risk; the waiver would not adversely affect the rights and welfare of subjects; the research could not practicably be carried out without the waiver; and whenever appropriate, the subjects will be provided with pertinent information after participation.

Points to consider in applying these criteria include the nature of the research; the protections in place to maintain privacy and confidentiality (e.g., coding, limited/controlled access, honest broker mechanisms); the change in level of risk, if any; the ability to locate or contact subjects; risk of introducing bias into the research ; 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 proposed secondary use, based on the nature of original collection.

HIPAA Issues. A covered entity's use or disclosure of protected health information to create a research database or repository, and use or disclosure of protected health information from the database or repository for a future research purpose, are each considered a separate research activity under the Privacy Rule. A HIPAA authorization for research must be research-study specific. Thus, assuming a HIPAA covered entity is involved, a new HIPAA authorization would be required for a future research use or disclosure of protected health information from the repository, or another form of HIPAA permission would need to apply or be obtained (e.g., waiver of authorization). If the research could be performed using only information about the subject that constitutes a limited data set, the tissue bank could use, or could disclose to the researcher, the limited data set after the researcher and the tissue bank have signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4)

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. Consent addressing the elements under 21 CFR 50.25 is required. If the original consent met the requirements of 21 CFR 50.25, that would be sufficient. If not, subjects must provide consent prior to the use of the tissues to test the IVD.

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 newly obtained 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 consent for research obtained from the patients?

Response– HHS Common Rule Issues. Generally no. 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.

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.

HIPAA Issues. A covered entity's use or disclosure of protected health information to create a research database or repository is considered a separate research activity under the HIPAA Privacy Rule. Assuming the academic medical center is a HIPAA covered entity, the disclosure or use of direct identifiers for the purpose of creating the database would require a HIPAA authorization from the subject or an IRB or Privacy Board waiver of the authorization requirement. If the specimens could be included in the database using only information about the subject that constitutes a limited data set, the specimens could be included in the database after the academic medical center and the database have signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4).

FDA Issues. FDA regulations do not cover the specimen banking. However, if the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." If the seven conditions are not met, then consent addressing the elements under 21 CFR 50.25 is required.

FAQ #12

A research participant agrees to allow extra blood to be stored for future research purposes. Blood samples will be stored in a repository with identifiers. The participant later changes his/her mind. Is this allowed, once tissue has been stored?

Response– HHS Common Rule Issues. Yes. Subjects have the right to withdraw from research, and this extends to withdrawing their specimens from future research. Subjects should be informed upfront about the procedures for withdrawing specimens from a repository. The obligation to honor subjects' requests to withdraw does not extend to retrieving specimens already distributed to secondary users. Analyses already completed will generally not be destroyed or removed from datasets. These practical limitations to withdrawal should be disclosed to subjects as part of the consent process.

HIPAA Issues. With respect to HIPAA authorizations, the HIPAA Privacy Rule provides an individual with the right to revoke an authorization in writing, except to the extent the covered entity has already acted in reliance on the authorization. For example, a covered entity is not required to retrieve information that it disclosed from its repository to a researcher under a valid authorization before receiving the revocation. Thus, if a covered entity obtained an individual's authorization to disclose identifiable health information from its repository to a researcher, then the covered entity is not required to seek the return of the information from the researcher. Further, the reliance exception would permit the continued use or disclosure of PHI by a covered entity already obtained pursuant to the authorization to the extent necessary to protect the integrity of the research (e.g., to account for the subject's withdrawal from a research repository). However, the reliance exception would not permit a covered entity to continue disclosing additional PHI to a researcher or to use for its own research purposes information not already gathered at the time an individual withdraws his or her Authorization.

FDA Issues. The FDA regulations do not cover the specimen banking. If the tissues were used in an FDA regulated clinical investigation to test an IVD, then the subjects have the right to withdraw from research, and no future use of the specimens can be made. Please refer to the FDA guidance "Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials" for information on the withdrawal of data.

FAQ #13

A research subject agrees to allow extra blood to be stored with identifiers for future research purposes. The individual later changes his/her mind and requests that the specimen be destroyed. The lead investigator who manages the repository proposes to the IRB that, rather than losing valuable specimens, all identifiers and coding be permanently removed, so that it would be impossible for anyone ever to link to this subject's identity; doing so would mean that any subsequent uses are not human subjects research, per OHRP guidance.

Is this an acceptable approach?

Response– HHS Common Rule Issues. While it is true that permanently stripping a specimen of all identifiers or codes would mean that subsequent uses are not considered to be human subjects research, doing this after the fact would not be acceptable, if done solely to avoid withdrawing specimens on request. If the specimen is identifiable at the time of the request, failing to follow through when it is possible to do so would violate the ethical principle of respect for persons, and possibly the terms of original consent.

HIPAA Issues. Assuming the removal of identifiers and coding is sufficient to cause the specimen to be de-identified in compliance with 45 CFR 164.514(b), the HIPAA Privacy Rule would permit such de-identification of the sample. Permission to de-identify under the HIPAA Privacy Rule would not cure the issues identified above under the HHS Common Rule.

FDA Issues. FDA regulations do not cover specimen banking.

FAQ #14

An investigator collected specimens from a large number of cancer patients and stored them with identifiers. Some of the patient-subjects are now deceased.

Is research using the specimens of those subjects who died still considered to be human subjects research, and under the oversight of an IRB?

Response– HHS Common Rule Issues. No. 45 CFR 46.102 defines a human subject as a "living individual." However, deceased individuals would still have protections under the HIPAA Privacy Rule.

HIPAA Issues. The Privacy Rule generally protects the Protected Health Information of decedents in the same manner as that of living individuals. However, in the research context, the Privacy Rule allows the use or disclosure of decedent information without the authorization of a personal representative and without waiver of authorization by an IRB or Privacy Board if the covered entity receives representations from the researcher that the decedents' protected health information is necessary for the research and is being sought solely for research on decedents (and not related living individuals) and, upon request of the covered entity, receives documentation of the deaths of the individuals.

FDA Issues. No. Under FDA's regulations, "human subject" means "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient." (See 21 CFR 50.3(g); similar language is found at 21 CFR 312.3 and 812.3(p).) FDA has interpreted its regulations as applicable only to research involving living human subjects. Since the individuals referenced are deceased, research involving those tissues does not meet FDA's definition of a clinical investigation involving human subjects. See FAQ # 114 in the FDA guidance document "Exception from Informed Consent Requirements for Emergency Research."

FAQ #15

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

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

Response– HHS Common Rule Issues. In most cases, specimens compiled at an institution, in the course of research or medical practice at the institution, will belong to the institution, not to the investigator. These issues are an institutional responsibility, and involve multiple components across the institution, including legal counsel, sponsored or grant programs administration, the technology transfer office, and the IRB, as appropriate. The first determination is whether, and if so, how the institution will release the specimens to the new institution. 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 the new 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. If specimens are transferred without identifiers, subsequent uses would not be considered to be research involving human subjects under 45 CFR 46.

HIPAA Issues. If the institution is a HIPAA covered entity and the specimens are to be transferred along with information that constitutes protected health information, then the institution needs to consider whether the transfer of information from it to another entity was encompassed in the original HIPAA authorization or in any IRB or Privacy Board waiver of the authorization requirement that the institution may have obtained. If the specimens could be transferred along with only information about the subject that constitutes a limited data set, the specimens could be transferred after the transferring institution and the receiving institution have signed a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4). If the specimens could be transferred after having been de-identified in a manner that complies with 45 CFR 164.514(b), the HIPAA Privacy Rule would not govern the transfer.

FDA issues. If the specimens are being or have been used in FDA regulated clinical investigations of IVDs, then FDA and the sponsor have to be notified if there is a change in ownership or location.

FAQ #16

A clinical trial is funded by an industry sponsor or other entity and the contract provides for specimens to be transferred to the sponsor or other entity.

What factors should be considered in such an arrangement?

Response– HHS Common Rule and HIPAA Issues. This arrangement requires coordination of the provisions of the protocol, informed consent form, HIPAA authorization, and clinical trial or other sponsorship agreement. The protocol should describe the specific specimens and data to be transferred to the sponsor, and this transfer of identified specimens should be disclosed to the research subject in the informed consent form, at least in general terms. (Presumably, the disclosure to the sponsor of the identifiable data that are to accompany those specimens has been permitted by the study's HIPAA authorization, which may or may not have been combined with the informed consent.) The best informed consent practice in such an arrangement is to inform the research subject whether there are "downstream" restrictions on the recipient of the specimens for their future use. In situations in which there are no contractual provisions that

limit the recipient sponsor's downstream uses of the specimens, the subjects therefore should be informed of this, in the same manner that they are informed that once personal data have been disclosed to a sponsor that is not a HIPAA covered entity, there is essentially no HIPAA-imposed limit on the sponsor's future uses of those data. If a research site or researcher seeks to limit downstream uses by a recipient sponsor of specimens or data, then this can usually be accomplished by seeking to negotiate, in the clinical trial or other sponsorship agreement, specific limits on future uses by the sponsor of the transferred specimens and data.

FAQ #17

The protocol for a clinical trial stipulates that all samples should be destroyed after the study is completed. The consent form is silent on the disposition of samples after the study.

What should be done if there are 10,000 identifiable specimens and new scientific data emerges in the field that warrants further testing on the samples?

Response– HHS Common Rule Issues. The investigator could amend the protocol, describing the circumstances and seeking IRB approval to retain the specimens for additional research. The IRB should consider if this additional research is compatible with the original terms under which samples were obtained, and whether a waiver of informed consent is appropriate.

HIPAA Issues. The HIPAA Privacy Rule would govern protected health information accompanying the specimens, not the specimens themselves. Assuming the investigator is in a HIPAA covered entity, the disclosure or use of direct identifiers for additional research would also require a HIPAA authorization from the subject or an IRB or Privacy Board waiver of the authorization requirement. If the additional research could be performed using only information about the subject that constitutes a limited data set, the investigator could use and disclose the limited data set for the additional research in compliance with the terms of a data use agreement that complies with the requirements in 45 CFR 154.514(e)(4). If the additional research could be accomplished after the specimens have been de-identified in a manner that complies with 45 CFR 164.514(b), the HIPAA Privacy Rule would not govern the additional research.

FAQ #18

A tissue biopsy was obtained for clinical diagnostic purposes, which have now been satisfied. The hospital pathology department is willing to provide a portion of the remaining biopsy specimen to an investigator, who will perform research assays with no clinical relevance. If the specimen is coded and identifying information is removed so that the identity of the patient cannot be readily ascertained by the investigator before it is provided to them (so that it is de-identified for the purposes of HIPAA), is the investigator conducting human subjects research under the purview of an IRB?

Response– HHS Common Rule Issues. No, this is not research involving human subjects, because the recipient investigator will not be able to readily ascertain the identity of patients from whom specimens were obtained.

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." If the seven conditions are not met, then consent addressing the elements under 21 CFR 50.25 is required.

FAQ #19

A tissue biopsy was obtained for clinical diagnostic purposes, which have now been satisfied. The hospital pathology department is willing to send a portion of the remaining biopsy specimen to an investigator, who will perform research assays. If the specimen will be provided to the researcher in an identifiable manner, is this considered to be human subjects research under the purview of an IRB?

Response– HHS Common Rule Issues. Yes, this is human subjects research. Because investigators will receive a specimen with identifiable information, the research is non-exempt human subjects research that is nevertheless potentially eligible for expedited review**.**

FDA Issues. If the tissues are used to test an FDA regulated IVD, then this is a clinical investigations for which IRB review is required and consent addressing the elements under 21 CFR 50.25 is required.

FAQ #20

Many hospitals have a sentence on the standard admission form to the effect that "This is a teaching and research institution, and any specimens remaining after your care is complete may be used for teaching or research purposes." Is this sufficient to allow identifiable specimens to be used for research purposes, without any additional consent or waiver?

Response– HHS Common Rule Issues. No, an additional consent or waiver is required**.** If the information provided to prospective subjects were limited to the above statement, this would not be sufficient to meet the requirements of informed consent for research under 45 CFR 46. However, the IRB should review each protocol that proposes to use such specimens and, as part of that review, consider whether the criteria for a waiver of informed consent have been met at 45 CFR 46.116(d).

HIPAA Issues. This approach (single sentence on the hospital admission form) would also not be sufficient for HIPAA authorization purposes. In order to comply with the HIPAA Privacy Rule, an authorization must meet the requirements of 45 CFR 164.508(c).

FDA Issues. If the tissues are used to test an FDA regulated IVD, then IRB review is required and consent addressing the elements under 21 CFR 50.25 is required. The single sentence on the admission form would not meet this requirement.

FAQ #21

Many hospitals have a sentence on the standard admission form to the effect that "This is a teaching and research institution, and any specimens remaining after your care is complete may

be used for teaching or research purposes." Is this sufficient to allow identifiable specimens to be placed into a tissue bank, if they are coded and released to researchers through an honest broker mechanism?

Response– HHS Common Rule Issues. The plan to remove identifiers from the specimens and manage them through a bank might be factors the IRB considers when assessing the risks to subjects, but it doesn't change the fundamental answer above (FAQ #20). The creation of a bank containing identifiable specimens would be considered human subjects research and thus, subject to IRB review and informed consent. As above, the statement on the admission form would not be considered sufficient to meet the requirements of informed consent under 45 CFR 46. However, the IRB could consider whether the criteria for waiving or altering informed consent have been met at 45 CFR 46.116(d). The subsequent research use of specimens would not be considered human subjects research if the conditions of the OHRP guidance on coded private information or biological specimens have been met.

FDA Issues. FDA regulations do not apply to specimen banking. However, if the tissues are used to test an FDA regulated IVD, then IRB review is required. It may not be necessary to obtain informed consent of the subjects for the secondary use if the seven conditions are met in the FDA "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable." If the seven conditions are not met, then consent addressing the elements under 21 CFR 50.25 is required. The single sentence on the admission form would not meet this requirement.

FAQ #22

A 13-year-old child is enrolled by his/her parents in a tissue banking protocol that involves storage of specimens for future research. Is the child's assent required at the time of the original enrollment in the repository, in addition to parental permission?

Response– HHS Common Rule Issues. Yes, if the IRB determines that the children are capable of providing assent, taking into account the ages, maturity and psychological state of the subjects [45 CFR 46.408(a) and 46.116]. Given that most projects that store tissues for future unspecified research are not likely to hold out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, it is anticipated that affirmative agreement on the part of the child would generally be required.

HIPAA Issues. The HIPAA Privacy Rule follows state law with respect to when an individual is capable of signing an authorization on his own behalf and when a personal representative may act on the individual's behalf. Thus, state law would govern.

FDA Issues. Tissue banking in and of itself does not constitute an FDA regulated clinical investigation, and the FDA regulations would not apply.

FAQ #23

A child is enrolled by his/her parents in a tissue banking protocol that involves storage of specimens for future research. Should there be a process in place for the child to give consent for continued storage and use of specimens when he/she reaches the age of majority?

Response– HHS Common Rule Issues. In and of itself, the retention of specimens in a biobank is not considered to be research involving human subjects. However, ongoing use of such specimens (e.g., continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), or ongoing collection of identifiable information, is human subjects research. In these cases, it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects.

The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research. Such a waiver may be considered at the time of initial review or during a subsequent amendment. Factors that may make it impracticable to conduct the research, and therefore would support a waiver, include the number of subjects, length of time since first enrolled, and ability to locate subjects (see also FAQ #5).

HIPAA Issues. A valid HIPAA authorization signed by a parent, as the personal representative of a minor child in accordance with state law at the time the authorization is signed, remains valid until it expires or is revoked, even if such time extends beyond the child's age of majority. However, if the authorization expires on the date the minor reaches the age of majority, a new authorization would be required at that time for continued use or disclosure of protected health information (unless the continued use or disclosure is otherwise permitted by an IRB or Privacy Board waiver of the authorization requirement, as the use or disclosure of a limited data set after the signing of a data use that complies with the requirements in 45 CFR 154.514(e)(4), or as the use or disclosure of information that has been de-identified in a manner that complies with 45 CFR 164.514(b) so that the HIPAA Privacy Rule would not govern).

FDA Issues. FDA Issues. Tissue banking in and of itself does not constitute an FDA regulated clinical investigation, and the FDA regulations would not apply.

FAQ # 24
What issues should be addressed in the consent process with regard to sponsorship, ownership, control, access, commercialization and possession of stored specimens?

Response– HHS Common Rule Issues. Consent documents for such projects should disclose sponsorship and address issues including (but not limited to) disposition of samples, who will have access, how samples will be used, and the potential for commercialization, if any. Subjects should be informed to what extent, if any, they can expect to control or receive compensation from future commercial uses.

Some of these matters are subject to state laws, and consent documents should reflect that.

As with any part of the consent form, care should be taken to communicate these complicated issues in simple terms understandable to the subject

Secretary's Advisory Committee on Human Research Protections
July 19-20, 2011
Washington, D.C.

Certification of the Summary of Minutes

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

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Barbara Bierer, M.D., Chair Date