

SACHRP Minutes, October 4-5, 2011

Table of Contents

WELCOME: OPENING REMARKS	3
REPORT OF ISSUES	3
FACILITATING IRB REVIEW FOR SINGLE PATIENT TREATMENT: USE OF INVESTIGATIONAL DRUGS AND BIOLOGICS	3
ENHANCING PROTECTIONS FOR RESEARCH SUBJECTS AND REDUCING BURDEN, DELAY, AND AMBIGUITY FOR INVESTIGATORS	6
DISCUSSION OF INTRODUCTION	8
DISCUSSION OF SECTION 1: IRB REVIEW CHANGES	8
MINIMAL RISK	8
“EXCUSED” RESEARCH.....	9
MANDATORY AUDITING.....	11
EXPEDITED REVIEW	12
CRITERIA FOR IRB APPROVAL.....	13
CONTINUING REVIEW	13
REDUCING ADMINISTRATIVE BURDEN.....	13
APPEALS MECHANISM	13
ADDITIONAL REPORTING	14
DISCUSSION OF SECTION 2. MANDATORY REVIEW OF MULTI-SITE STUDIES BY SINGLE IRBS	14
DISCUSSION OF SECTION 3. INFORMED CONSENT	17
DISCUSSION OF SECTION 4. STRENGTHENING DATA PROTECTIONS TO MINIMIZE INFORMATION RISK	17
PUBLIC COMMENT	18
DISCUSSION OF SECTION 4. STRENGTHENING DATA PROTECTIONS TO MINIMIZE INFORMATION RISK (CONTINUED)	19
DISCUSSION OF SECTION 5. ADVERSE EVENT (AE) REPORTING	20
DISCUSSION OF SECTION 6. EXTENSION OF FEDERAL REGULATIONS	20
DISCUSSION OF SECTION 7. CLARIFYING AND HARMONIZING REGULATORY REQUIREMENTS AND AGENCY GUIDANCE	20
DISCUSSION OF SECTION 8. FUTURE USE OF BIOSPECIMENS	21
MINORITY REPORT.....	25
DISCUSSION OF SECTION 9. AREAS TO ADDRESS THAT WERE NOT INCLUDED IN THE ANPRM AS PROPOSED	27
REQUIREMENT TO ADDRESS INVESTIGATOR REGULATORY RESPONSIBILITIES IN THE COMMON RULE	27
PEDIATRICS	27
VULNERABLE SUBJECTS.....	28
INTERNATIONAL RESEARCH.....	28
INCURRED COST AND RESOURCE COMMITMENT	28
PUBLIC COMMENT	29
ATTACHMENT A. DRAFT OF SACHRP LETTER ON ANPRM AS PRESENTED AT THE OCTOBER, 2011 MEETING	29

ATTACHMENT B. FINAL SACHRP LETTER ON ANPRM29
ATTACHMENT C. FIRST DRAFT OF MINORITY REPORT ON BIOSPECIMENS30
ATTACHMENT D. FINAL VERSION OF ANPRM MINORITY REPORT ON BIOSPECIMENS.....32

Secretary's Advisory Committee on Human Research Protections
(SACHRP)
Tuesday, October 4, 2011 – Wednesday, October 5, 2011
Minutes

Voting SACHRP Members Present

Barbara Bierer (Chair), Albert J. Allen, Carl H. Coleman, Gary L. Chadwick, David G. Forster, Steven Joffe, Susan Krivacic, Suzanne M. Rivera, Lainie F. Ross, Stephen O. Sodeke

Tuesday, October 4, 2011

Welcome: Opening Remarks

Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed attendees to the 27th meeting of SACHRP.

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

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

Report of Issues

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

Dr. Menikoff reported that an Advanced Notice of Proposed Rulemaking (ANPRM) has been released. *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators* was published in the July 25 *Federal Register*. OHRP welcomes constructive comments. The ANPRM may be reviewed at this address:
<http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/html/2011-18792.htm>

Facilitating IRB Review for Single Patient Treatment: Use of Investigational Drugs and Biologics

Dominic Cirincione, J.D., M.P.P., Program Analyst, FDA Office of Special Health Issues;
Richard Klein, Patient Liaison Program Director, FDA Office of Special Health Issues

<p>Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.</p>
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Mr. Cirincione explained that the Office of Special Health Issues seeks feedback from patient advocacy groups and coordinates patient representative and consultant programs. FDA currently works with 150 patient representatives and consultants.

FDA may authorize “expanded access” to trials of investigational drugs or biologic products (21 C.F.R. 312.300 [2011]) to treat patients with serious or life-threatening diseases or conditions who have no satisfactory or comparable alternative therapy to diagnose, monitor, or treat the disease or condition. When this is done, FDA must ascertain that the following are true:

1. The patient has a serious or life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential benefit justifies the potential risk and that the risks are not unreasonable in light of the disease or condition to be treated; and
3. The provision of the investigational product will not interfere with the clinical investigation that could support marketing approval or otherwise compromise potential development.

Three population levels are eligible for Expanded Access. While the focus of the presentation to SACHRP is on individual patients, there are also provisions for intermediate-size patient populations (21 C.F.R. 312.315) and for widespread treatment use (21 C.F.R. 312.320). When widespread use is authorized, typically the protocol size is large and the manufacturer is also the sponsor of the trial.

FDA continues to hear from individual patients, caregivers, IRB members, and health care professionals that the administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under Expanded Access Protocols (EAPs), especially for single patient treatment access protocols. Usually the treating physician is the investigator but is not affiliated with an IRB; the physician must find an IRB to review the protocol. Typically, the cost of the review is borne by the patient. Comments submitted to the FDA on its Expanded Access Final Rule (74 Fed. Reg. 40900, 40920-21 [2009]) recommended that FDA standardize expanded access review for all IRBs, create a centralized IRB for small-to-medium expanded access protocols, and reduce or limit the scope of the IRB review to avoid delays and expenses.

FDA is considering whether to amend its regulations or take other appropriate actions to address concerns. The speakers posed several questions to SACHRP:

- What is the Committee’s experience with IRB reviews of expanded access protocols? How quickly are they reviewed? Is there a charge to the individual? Are EAPs able to be scheduled ahead of studies already on the calendar?
- Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
- If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
- What is the Committee’s opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?

DISCUSSION

The Chair asked how often FDA finds that the patient seeking access to the product can obtain it under another protocol. Mr. Cirincione responded that there are many barriers to taking advantage of other studies. The approach may not work for the individual, the study may not be geographically accessible, or the patient may not meet the eligibility criteria. FDA receives hundreds of requests, and many

callers identify the IRB review process as a barrier. The speaker confirmed that if a patient has access to a clinical trial in which results are compared to a placebo, FDA will deny any requests to receive the drug rather than the placebo.

Dr. Joffe commented that the issues surrounding Expanded Access appear to be basically clinical and do not seem to fit well with typical procedures for IRBs. He asked whether IRB review appears to be a “rubber stamp” or may substantively change what happens. Speakers responded that the IRB has a responsibility to ensure the patient understands the risks, but they were unaware of any instance in which an IRB turned down a request for Expanded Access for an individual. Mr. Forster said his IRB receives about twenty applications annually and has disapproved at least two. He added that Western IRB cuts the review rate in half for individuals and will waive the fee altogether if individuals are otherwise unable to afford it. He observed that the process is often complicated: the sponsor may want the IRB to review the request before shipping the product, it is difficult to get hold of busy physicians, and both the investigator and patient may need education on the process.

Dr. Less observed that regulations governing drugs and devices differ slightly in regard to Expanded Access. While access to a drug under an IND does require review by an IRB Board, an IRB Chair and an independent physician may approve “compassionate access” for a device.

Dr. Allen noted that while FDA does seek to make a possible treatment available to people in desperate straits, it still needs to be careful that it is not inappropriately encouraging experimental or off-label use of drugs or devices. While some SACHRP members felt that these cases were different from reviews of research protocols, Dr. Allen differed, noting that FDA still wants to learn something from these cases that may be useful and that there is an element of research. He stressed that whenever there is more than one patient involved, the full IRB should review the access request.

Areas of possible confusion. Mr. Forster observed that there is sometimes a fine line between emergency use and a situation that requires usual procedures. IRBs may be hesitant to approve emergency use for fear FDA will disagree. Also, the sponsor may decide not to give the product to the patient, even after the IRB has agreed that the patient may enter the trial. He pointed to a difference in guidance on the topic between FDA’s Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER), further adding to the confusion.

Dr. Bierer added that IRBs may not be aware that the procedure need not be used to allow off-label use of approved drugs or devices. IRBs also may receive requests for Expanded Access from people who do not meet the criteria for access to a trial. Finally, the differences in processing requests for individual access and access for a small group are not well understood.

Suggestions. SACHRP members had the following suggestions for addressing the problem:

- FDA could make the analyses the IRB would normally make.
- FDA could issue a guidance document on the responsibilities of each party in such cases.
- FDA could establish a contract with an IRB to provide reviews on an ongoing basis.
- IRB chairs or vice chairs could be trained to respond to requests on an expedited basis.
- Consider using FDA’s own IRB to handle such cases, since expertise is readily available.
- Consider the use of a central IRB, within or outside FDA, which would be better prepared to handle such cases.

- Review by an NIH IRB might be a good option, especially for people who lack access to a local IRB.

Dr. Rivera pointed out that expedited review may still not address the needs of people who are not near an IRB. At present, she said, IRBs tend to feel uncomfortable with the situation and do a cursory review. She also suggested, in regard to the consent process, that FDA use its enforcement authority to make sure it is not applying research standards to nonresearch scenarios. A SACHRP member noted that an IRB was recently cited for doing an expedited review of an individual's request for Expanded Access in a drug trial.

Mr. Klein observed that since FDA regulates the companies involved in these cases, it may be perceived as improper for FDA to handle access issues directly. The speakers said they might wish to talk to General Counsel about the issue.

Dr. Joffe suggested changing the regulations so that IRB review is not required. He questioned whether IRB review added anything worthwhile to the process. Mr. Klein noted, however, that informed consent is required by the Statute whenever an investigational drug is involved.

Mr. Forster cautioned that it was important that OHRP and FDA agree on whatever approach is taken.

Next steps. SACHRP asked the Subpart A Subcommittee (SAS) to consider issues related to Expanded Access. A focus point is whether or not human subject protection would be compromised by expedited review.

Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Daniel Nelson, M.S., CIP, Subcommittee on Subpart A (SAS) Co-Chair; David Borasky, M.P.H., CIP, SAS Co-Chair; David Forster, J.D., Subcommittee on Harmonization (SOH) Co-Chair; Mark Barnes, J.D., SOH Co-Chair

Dr. Bierer observed that the ANPRM from OHRP was released just after the last SACHRP meeting, and she has never seen a community more engaged in responding to an ANPRM than this one. Everyone appreciates the creativity and vision that was brought to the ANPRM, and there will be many sources of input to OHRP, of which SACHRP is one.

To prepare SACHRP's recommendations regarding the ANPRM, each of the two subcommittees discussed their initial responses by telephone, and then met together for a 2-day meeting to form a joint response. Many ex officios contributed to the discussion. After subcommittee Co-Chairs prepared a draft based on the discussion, it was circulated to all subcommittee members for comments, which the Chair then integrated.

Because SACHRP members who are not on subcommittees were not included in the process of preparing a draft letter, the Chair invited them to comment. She cautioned committee members to focus on content rather than "wordsmithing" and to offer alternative solutions when they are in disagreement with the option described in the ANPRM. Views were presented as follows:

- Dr. Ross's biggest concern was that biospecimens and clinical data are being held to different standards. She stated that biospecimens and clinical data were equally sensitive in terms of their implications for individuals and should be held to the same standards. She stated that biospecimens were equally sensitive in terms of their implications for individuals and should be held to the same standards.
- Dr. Sodeke agreed with Dr. Ross's position.
- Mr. Coleman felt the section on "excused research" was the strongest. He agreed that the type of research described in the ANPRM should not require IRB review.
- Dr. Rivera said the ANPRM showed excessive concern about deidentified biospecimens, given the many protections already in place. She suggested that reidentification of existing deidentified data should be prohibited. Given the many benefits derived from work with deidentified biospecimens, she felt concerns about reidentification were overblown and investigators deserved more trust. She also expressed reservations about the term "excused."
- Dr. Chadwick commended OHRP for developing the ANPRM and putting it on the table for discussion.
- Dr. Allen said the ANPRM seemed to place a good deal of emphasis on privacy but needed to pay more attention to other core principles of bioethics.
- Ms. Krivacic said patients support progress in research and treatments but do have concerns about the control of their data and health information, including biospecimens. They want biospecimens to be tested and used, but with an eye to unintended consequences for society and patients.
- Dr. Joffe particularly appreciated the push to reduce overregulation of minimal risk studies and the effort to encourage central review of multicenter studies. He was not sure how the role of the local IRB would be fulfilled in multicenter studies. He would like the letter to be more open to the direction chosen in the ANPRM.

Dr. Bierer asked Ms. Gorey to provide guidance on legal requirements related to the expression of minority opinions on advisory committees. Ms. Gorey said that while the Federal Advisory Committee Act encourages consensus opinions, minority views can also be conveyed. Dr. Menikoff said OHRP appreciated the diversity of views within SACHRP and wanted them all on the table. Dr. Bierer said it was important to reflect any strongly held minority opinions when recommendations are submitted to the Secretary. She added that members of SACHRP are not prohibited from submitting views on behalf of their institutions in addition to those expressed in the letter from SACHRP.

The Chair proposed to go through each section of the draft letter, take general comments, and vote on the revised section.

Tuesday and Wednesday, October 4-5, 2011

Recorder's note: In order to present SACHRP discussions clearly, the following presents the discussion of each section of the letter sequentially, combining discussions that occurred on each day of the meeting.

The complete text of SACHRP proposals and final recommendations are contained in Attachments A-D as follows:

- Attachment A. Draft of SACHRP Letter on ANPRM as Presented at the October, 2011 Meeting (see separate document);
- Attachment B. Final SACHRP Letter on ANPRM (see separate document);
- Attachment C. First Draft of Minority Report on Biospecimens
- Attachment D. Final Version of ANPRM Minority Report on Biospecimens

Note that Attachment A incorporates changes that were made just before the meeting but after the draft letter had been copied for reference at the meeting. These changes, like those made at the meeting, are in bold and cannot be distinguished in the draft.

Discussion of Introduction

The Introduction to the letter was approved without further changes.

Discussion of Section 1: IRB Review Changes

Minimal Risk

SACHRP reviewed draft language and made the following changes:

1. Added a more complete description of prior work on minimal risk by SACHRP in the second paragraph:

*SACHRP has previously **recommended an analytical framework for understanding, interpreting and applying the existing definition of minimal risk, and provided case examples to guide IRBs and investigators.***

2. Added an explanation of why risks encountered in the daily lives of subjects should not be used to determine minimal risk to the end of the third paragraph:

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

The proposed language was originally “unjust skewing of risks,” but was revised to clarify that the concern is not related to validity.

3. Added a reference to the need to provide guidance related to risk mitigation mechanisms IRBs should consider at the end of the section:

Guidance should address what risk mitigation mechanisms may be considered by IRBs when determining that proposed research is minimal risk.

SACHRP members noted that IRBs sometimes fail to take risk mitigation strategies into account. Dr. Rivera commented that risks might exceed those encountered in everyday life (for example, in a comparison between antibiotics).

“Excused” Research

Mr. Coleman thought the idea of empowering investigators to identify a study as “excused” was a good one, because having to go through a lengthy review process to determine that a study is in fact exempt defeats the purpose.

Investigator accountability. Mr. Coleman was concerned that one of the examples given in the letter to illustrate whether or not a study can be excused may be construed as implying that any research that asks a question about mood or mental status invariably requires review, which would be overkill. Dr. Ross pointed out that if a respondent said he or she were suicidal and the protocol’s plan was to analyze responses in three months, this would obviously be problematic. She was not sure that all social science protocols should be assumed to be expeditable; nor did she feel that investigators should be self-monitoring in regard to unexpected results. Mr. Coleman questioned the wisdom of always looking to IRBs to resolve such problems, but Dr. Ross asserted that health care providers do a poor job of self-regulation in a clinical setting and would likely do a poor job in a research setting as well. Dr. Allen shared Dr. Ross’s concerns, arguing that a high standard of accountability is expected from Federally funded studies.

Dr. Chadwick argued for trusting investigators and giving them clear guidance on expectations they can follow independently. He did not support the idea that audits can be used to monitor what is being done. Another SACHRP member rejoined that not all investigators are responsible enough to carry out this responsibility. Dr. Bierer said members of her IRB have been “appalled” at studies the investigator believes should not require IRB review and emphasize the need for interaction with investigators, which offers an opportunity for education. Another SACHRP member cited the example of an investigator who asserted that he or she was not keeping identifiers, “only social security numbers.”

Studies that can be excused. Mr. Barnes said subcommittee members were unanimous in the belief that minimal risk (MR) studies should not have to go through the full IRB process. He noted that 95 percent of behavioral research is less than MR. At the same time, he acknowledged that some behavioral studies do have high risk for individuals. Examples include asking about sexual behaviors in cultures in which the answer can be stigmatizing or considered criminal.

Dr. Rivera was concerned about the use of terms such as “very sensitive topics.” Instead, she said, language should refer to reasonably foreseeable risks and the likelihood of harm. She could imagine a

case in which one person conceivably might have a bad reaction to something, but in which this is so unlikely that it should not be a focus. Individuals can choose not to participate.

Dr. Joffe proposed the concept of “registered” as opposed to “excused” studies. If the investigator is proposing to do something that fits an allowed category, the investigator would register the study with the IRB by filing a brief description, which the IRB would have five days to review. IRBs would need training to carry out this responsibility. The waiting period and the concept of “registering” rather than “excusing” a study give this proposal a different “flavor,” he suggested. Mr. Coleman liked the idea of registration and a waiting period, noting that an IRB would have the opportunity to decide it needs to review a study. Dr. Bierer was concerned that a list of eligible types of studies inevitably becomes the only ones eligible for registration, and IRBs will take the most conservative position possible.

Dr. Menikoff invited SACHRP to suggest where the line should be drawn to provide adequate protection while easing the administrative burden appropriately. He noted that the current rules do not provide a means of preventing studies declared to be exempt from taking place. The proposed system would replace the current “vague” exemption categories with a more straightforward yes/no form for use by investigators that leads to the conclusion that the study is or is not exempt.

A SACHRP member said his IRB currently requires investigators only to upload a copy of the protocol and grant and provide answers to questions about the sponsor and potential conflict of interest. If the investigator declares the study to be exempt, the online form then branches away from the review category.

Categories of subjects. Dr. Joffe suggested adding wording to the effect that SACHRP does not believe that the intended revisions focus on Subpart A and will therefore apply only to adults. Dr. Ross added that any list of excusable categories of research would look very different for children as opposed to adults.

Dr. Allen said he was sensitive to the historical tendency to overprotect children in ways that prevent them from benefitting from research. He agreed that some research conducted with children would be eligible for the excused category. He agreed with other SACHRP members that guidance, rather than regulation, could be used to clarify this. SACHRP members also agreed that the term “competent adults” should be removed on the grounds that it might lead to the conclusion that the proposed approach is not appropriate for children.

Question 25. The ANPRM includes the following question: “Are there certain fields of study whose usual methods of inquiry were not intended to or should not be covered by the Common Rule...?” Dr. Joffe suggested that the “creep” of oversight into the fields of literature and history suggests where the appropriate boundaries of the Common Rule should fall. However, another SACHRP member gave the example of interviews of people associated with the Irish Republican Army (IRA) conducted for historical research, noting that those involved are now being subpoenaed by the British government.

Dr. Allen stressed that the methods used, not the field of study, define whether or not something should be considered human subjects research. Often, research crosses boundaries or discipline. One SACHRP member, on the other hand, saw the term “generalizable” as applicable only to scientific research.

SACHRP voted specifically on whether or not to include the following paragraph:

With regard to question 25, SACHRP does not believe there are disciplines or fields of study that should not be covered by the Common Rule. The determination that an activity constitutes research involving living human subjects or identifiable information about living subjects is not dependent on the scholarly discipline or occupation of the researcher(s). That said, it would be of great value if OHRP would consider providing guidance about how to assess whether a proposed data collection/generation activity meets the generalizability standard.

The majority voted to include the paragraph.

Mandatory Auditing

Dr. Menikoff said the premise of OHRP's proposal is to eliminate the need for IRB's to review every proposal to see whether or not it qualifies for exemption by developing clear rules leading to this determination. He said OHRP was contemplating a process similar to FDA's; clear questions would lead to a specific conclusion.

Dr. Allen proposed adding language to this section of SACHRP's letter to ensure that audit processes meet basic standards and that investigators receive the training they need: "To the extent that the Federal Government (and sponsors) need to ensure a common level of accountability by institutions and investigators for the protection of human subjects participating in low risk research, guidance could describe basic operations, expectations, and potential consequences to inform institutions as they establish quality assurance and control mechanisms and to educate investigators." Other SACHRP members suggested specifying the need for guidance for institutions and for basic performance standards. The Chair stressed that preparing investigators to assume this level of responsibility would be critical.

Dr. Rivera asked what would happen if the audit found that some studies should not have gone forward. Would the investigator be found in noncompliance? Currently, prior IRB review helps prevent findings of noncompliance. Mr. Nelson said this was a concern of the subcommittees as well. For the new system to work, investigators will need education to accept new responsibilities. Dr. Allen wondered whether investigators would have to destroy data under these circumstances or if, instead, there would be a corrective process (for example, removing social security numbers or reconsenting participants). Mr. Nelson noted that some error rate can be expected. A SACHRP member suggested specifying that guidance should address "corrective action plans" for institutions; others agreed, but preferred the term "corrective actions." Dr. Joffe held that misclassifications of research made in good faith should not be viewed as serious and continuing noncompliance. Others stressed that misclassification intended to avoid protecting human subjects should be taken seriously and handled differently.

Dr. Bierer observed that none of the major cases that have raised concerns about human subject protection were the result of deliberate misdirection. She feared that "as soon as you are confident that the category is really safe, it will be too narrow." Dr. Ross noted that the Havasupai case did not necessarily violate Federal regulations. She was concerned that retrospective review will result in errors and apologies to the public. She held that "the best ethics is preventive ethics." Dr. Bierer added that the best education occurs when people need it; IRB staff do need an opportunity to educate investigators. Dr. Sodeke noted that even the use of a short form like the one proposed will require education. An ex officio, however, pointed out that educational interventions are not always effective.

Dr. Ross saw a need to clarify what the monitoring of excused studies would look for and how. Another SACHRP member said that while the ANPRM appears to envision a review of the form, real auditing may be needed. Members agreed that review of paperwork would require little effort, but a full study would be time intensive. Dr. Menikoff said the proposed approach asks IRBs to do what is currently done for all studies for a reasonable percentage of them. In regard to the need for auditing, Mr. Barnes noted that “we let investigators alone to do more potentially damaging things.” He felt that the level of concern was misplaced.

Dr. Allen suggested that it should be easy for investigators to fill out the required form, as they will already have an outline of the proposed research that was submitted for the grant. Mr. Nelson commented that this will not always exist (for example, for research by students).

Subcommittee Co-Chairs proposed a new paragraph related to monitoring, which was approved by SACHRP:

Post hoc monitoring should be implemented as an educational operational activity by institutions to assess experience with investigator classifications and to make adjustments when necessary. Furthermore, this should not be approached as a compliance activity that results in sanctions or penalties for investigators who acted reasonably and in good faith and proceeded with registered studies or reporting by their institutions.

SACHRP also approved a final paragraph to address the concern that changes in Subpart A might have unintended implications for studies of vulnerable populations, such as children:

The ANPRM indicates that survey research of “competent adults” should be classified as “excused.” SACHRP notes that under existing categories of “exempt” research, some survey research not of “competent adults” (e.g., observation of children’s public behavior without involvement of researchers) is exempt. Any changes to the “exempt” category should be carefully tailored so that they do not inadvertently make “non-excused” all research that is currently “exempt.”

Expedited Review

Dr. Joffe suggested that any minimal risk study should qualify for Expedited Review (ER), though there could be a list of exceptions. This would go further than the ANPRM contemplates. There would still be a category of exempt or excused risk, then all other minimal risk would be assumed to be eligible for ER. Dr. Chadwick thought this approach was consistent with the recommendations already contained in the letter. The letter suggests that the list of studies eligible for ER would be construed as example. Dr. Joffe felt the proposed change was subtle, but it would mean that the list would define things that are eligible for minimal risk, not for ER. Dr. Bierer encouraged him to draft language for committee review.

The following language was proposed and approved insertion following the first paragraph:

SACHRP believes that most research involving no greater than minimal risk should qualify for review under expedited procedures. This would involve a change from the current presumption, as well as that proposed in the ANPRM, which envisions that minimal risk

research requires full-board review unless it involves only those procedures included in the published list. The Committee recommends that regulations be changed to allow expedited review of research that is judged by the IRB Chair or designee to be minimal risk. To facilitate consistency in decision making, HHS should publish a list, to be updated periodically, of examples of protocols and procedures that presumptively entail no greater than minimal risk. The preamble to this list should make clear that the list is intended only to provide examples, and not to constitute a comprehensive set.

If the regulatory framework is changed such that minimal risk research is presumptively eligible for expedited review, HHS may nevertheless believe that specific categories of protocol or research procedures should undergo full-board review. If so, HHS should publish a list, to be updated periodically, of categories of protocols or procedures that would not qualify for expedited review.

Criteria for IRB Approval

No changes were proposed to this portion of the letter.

Continuing Review

SACHRP members agreed to delete a sentence that referred to annual review as a “rote exercise” involving a form that receives only “ cursory review” on the grounds that this assertion was not required in a public document. Members also agreed to delete a specific reference to SACHRP’s previous recommendation that the continuing review cycle be extended “to a two-year cycle” because it implied that the review cycle would not be “flexible.”

Dr. Joffe wondered how a Federal funder who wanted to ensure that a protocol had been given adequate review would receive this assurance. Dr. Bierer suggested that the institution should be responsible for providing such assurances if they are required, not the IRB.

Reducing Administrative Burden

No changes were proposed to this portion of the letter.

Appeals Mechanism

Mr. Barnes observed that the Common Rule provides that when an IRB does not approve a study, it can be asked to reconsider. This allows an opportunity for dialogue, although the provision is not applied in a uniform way across IRBs. An appeals process would mean that if an IRB says the study cannot go forward, the investigator could appeal over the IRB’s head and the study could go forward. This would have the potential for legal cases. SAS Co-Chairs felt strongly that a mandatory appeals process should not be implemented.

Language was revised within the letter to avoid the use of the term “appeals” where no formal appeals process was intended.

Additional Reporting

No changes were proposed to this portion of the letter.

Public comment and ex officios were invited to comment, but no comments were offered.

ACTION

SACHRP approved Section I unanimously as revised.

Discussion of Section 2. Mandatory Review of Multi-Site Studies by Single IRBs

Mr. Barnes said there was a general feeling among subcommittee members that the approach described in the ANPRM would not be workable, though they agreed that it was a good idea to encourage greater use of central IRBs. He held that agreements between IRBs did not need to be mandated. Dr. Bierer observed that sponsors want to see greater use of single or central IRBs. She saw a need to do something that encourages sites to be more accepting and less worried about loss of control.

Dr. Joffe said that if regulations were revised as described, he would like to see an exception for “discrete and isolated” sites. He argued for a middle ground in which a central IRB is identified as the lead site and conducts a full Board review, but other sites are still able to review the protocol and make changes. This would be similar to the facilitated review process in use today at the National Institutes of Health (NIH). Dr. Bierer commented that there are models in which one IRB elicits comments from others but makes the final determination. Dr. Joffe, however, wanted more local control. He felt the local IRB should be able to say no or tell the central IRB it missed something. Dr. Bierer pointed out that local oversight is still an issue, and the approach chosen should segregate the function of protocol review from study oversight at the local level. She said the local response envisioned in the ANPRM would be simply “thumbs up/thumbs down.”

Dr. Allen said that from the standpoint of sponsors, whatever approach is chosen should not take longer than the current process. The process seems to slow to the lowest common denominator, and a balance of concerns is needed. Ms. Krivacic said more sponsors and funding agencies are asking for a different approach. She added that a consortium in Cleveland is successfully using the facilitated review process. She felt the language of the letter “struck the right chord.” Dr. Bierer said the key task is to clarify who is held responsible for what.

Dr. Ross was not certain that communities are as different from each other as they used to be. Mr. Barnes, however, noted that a study of addiction to crack cocaine would look very different in Malibu, California from one carried out in New York City. However, this would not lead to the conclusion that a central IRB would not be a viable approach.

SACHRP agreed to follow the language of the ANPRM and change all references to central IRBs to “single IRBs,” noting that the central IRB is not the only model for eliminating multiple reviews on multi-site studies.

Dr. Ross said the example of childhood sexual abuse should be removed since the ANPRM addresses changes only in Subpart A. She suggested leaving the footnote, however.

SACHRP members raised questions about the assertion that the adoption of central IRBs would likely be “more complex” (paragraph 3, Attachment A). Mr. Forster asked whether it would be “more complex” or simply complex. A member suggested further clarifying the rationale for this assertion.

Ms. Krivacic asked whether the mandated approach would extend to studies in which there are only two collaborating sites, or very few. She noted that the issues would look very different from those that arise in a multisite trial in which consistency across a large number of sites is critical. Dr. Menikoff clarified that the mandate would mean that one IRB represents all participating sites; OHRP would interact only with that site, and only that site would receive letters from OHRP.

A SACHRP member asked what would happen when a local IRB disagrees with the single IRB’s conclusions. Another explained that, as in the current system, that site might end up not participating in the study.

Consequences of ANPRM approach. Members considered the possible consequences of the proposed mandatory approach. Mr. Barnes said that a pattern would be established in which some IRBs would crowd out others, which would recede. Smaller IRBs, Dr. Bierer commented, could “sunset.” Dr. Bierer also expressed concern that the single IRB would enter an alliance with the sponsor that would interfere with its decisionmaking process. She suggested adding a sentence about the need to ensure the IRB’s independence from the sponsor. Dr. Allen agreed that this was a risk, adding that large companies do look for recognized IRBs. He noted, however, that if there is a more limited number of IRBs, there is more opportunity to ensure they are functioning well and monitor quality. Members agreed, however, that the reference in the draft letter to a “monopoly effect” went too far and should be removed.

Cost recovery. Dr. Bierer stressed the importance of indirect cost recovery (p. 10, paragraph 2, attachment A). She said having a plan would be important, and SACHRP members agreed that the letter should say that “a plan for cost allocation and recovery would have to be developed.”

Legal issues. David Forster asserted that legal issues related to human subject protection differ among States and would have a bearing on strategies for multi-site review. SACHRP agreed to add language recommending that this be taken into consideration. An ex officio suggested that any data base created by the Federal government should be made public. Members agreed on the following:

- *SACHRP recommends that the federal agencies develop a database of state and country laws relevant to reviewing human research protocols that would be publicly accessible.*

Points to consider for single IRBs. A SACHRP member proposed a list of points to consider for “IRBs serving in a centralized capacity,” noting that these might reduce concerns about poor quality work by such IRBs. A member was concerned that overly professionalized standards would discourage medical centers. Another worried that a common set of expectations might predetermine acceptable models, which should be left open. Dr. Allen noted that the proposed standards might be overkill for social behavioral research. For other studies, these are the types of considerations that would be important to sponsors. Dr. Menikoff said he had heard from social-behavioral researchers that such considerations are also important in their work and help to minimize the costs of low-risk studies. Dr. Bierer suggested that the standards be offered simply as points to consider by OHRP.

Members also discussed whether the single IRB should have “capacity for site visits” as proposed in the original draft. Mr. Forster said he would lean toward ensuring the single IRB has the ability to “put someone on the ground if needed.” Clarifying language referred to the “capacity to provide for-cause site visits, as necessary.”

Mr. Forster also proposed “standard inspection by OHRP and/or FDA at one-year intervals” as a means of increasing public confidence. He noted that the Western IRB is audited frequently by sponsors. However, members voted on this specific suggestion and determined it should not be included.

Standards were finalized in integrated in the letter (see Attachment B, p. 11).

Mandated use of single IRB. SACHRP members differed on the issue of whether it was necessary to mandate the use of a single IRB in order to get the field to move forward. Mr. Nelson reluctantly expressed the opinion that the field would not make the needed changes unless they are mandated. Ms. Krivacic held that the change should be strongly encouraged but did not agree that a mandated change was warranted. She noted that she had been involved in some global trials involving orphan diseases where the use of a central IRB was difficult and was concerned that studies and patients could both be harmed by a mandate.

Dr. Bierer said she was in favor of single IRBs but felt that momentum in this direction has been dissipated. She noted that OHRP did not issue clear guidance indicating that external IRBs would be held responsible for their decisions, and the lack of such guidance continues to be a barrier for institutions. More could be done to encourage the use of single IRBs where appropriate, but institutions still need the flexibility to choose a different approach. Ms. Krivacic suggested that demonstration projects and incentives could be used instead of a mandate.

Dr. Joffe suggested a mandate for studies involving more than five sites. Another SACHRP member said it was not possible to agree on a specific number of sites because the type of study involved was also an important consideration.

SACHRP agreed to recommend that OHRP “encourage” the use of a single IRB. Members agreed on this and on several “helpful actions” OHRP could take to help IRBs move in this direction (see Attachment B, p. 12). These include delineating expectations for both the reviewing and relying institutions.

System compatibility. Dr. Bierer noted that based on her recent experience serving as a coordinating center for the National Institute for Neural Disorders and Stroke (NINDS), the cost of ensuring interoperability among the systems of cooperating IRBs cannot be overestimated. She suggested that if Government wants to mandate IRBs working together more effectively, it could facilitate that by providing an interoperable system everyone could use. SACHRP agreed and added a recommendation to this effect (see Attachment B, p. 12).

Public comment and ex officios were invited to comment, but no comments were offered.

ACTION

SACHRP unanimously approved this section of the letter.

Discussion of Section 3. Informed Consent

Mr. Forster commented that the explanation of research procedures is often a lengthy part of the consent form and could be presented as an addendum instead. Ms. Krivacic commented, however, that a brief description of study design or procedures is very helpful to prospective patients and should be included. A longer version could be appended.

A SACHRP member suggested that references to potential benefits to public knowledge and to subjects (Attachment A paragraph 9, p. 13) be combined in a single reference, “potential benefits of the research to subjects and society.” The change was accepted.

A SACHRP member did not agree that financial conflicts of interest should be presented as part of the consent form. Another member disagreed. Dr. Allen commented that some conflicts of interest do not rise to a level of concern. He added that subjects may find such disclosures to be positive or negative influences on their decision.

Ms. Krivacic said the proposed template should not be required, but rather provided as example. She also objected to the assertion they would be “slavishly followed”; in response, the word “slavish” was removed.

In regard to assessment of how well subjects understand the information presented, a SACHRP member noted that SACHRP’s Subcommittee for the Inclusion of Individuals with Impaired Decision-making in Research (SIIDR) developed recommendations for assessing the understanding of populations with impaired capacity to make decisions. SACHRP members agreed to reference this prior work as relevant to the ANPRM questions regarding assessment. They also agreed that it is appropriate to assess comprehension even for individuals who are not impaired in decision making.

Ms. Krivacic noted that IRBs struggle with the issue of what rights of subjects are at risk when waivers of consent are considered. What rights should be considered other than the right to consent? SACHRP addressed the concern by adding a reference to its previous recommendations on rights that IRBs should consider when granting waivers (January 31, 2008).

ACTION

The section was approved unanimously as revised.

Discussion of Section 4. Strengthening Data Protections to Minimize Information Risk

Ms. Heide of the Office for Civil Rights (OCR) explained that the intent of the changes proposed in the ANPRM was not to extend HIPAA rules to all research. Rather, the thought was that some data protections were needed to balance proposed changes in other areas. One key question is whether HIPAA’s definitions of “identifiable” and “nonidentifiable” as they apply in the context of research today, would be appropriate in regard to scaling research protections. Dr. Bierer said she was impressed by Ms. Heide’s openness and noted that the research community may be interpreting the proposed changes differently from the way they were intended.

Mr. Nelson noted that “covered entities” under HIPAA provide a logical point of contact and control for data protections. If HIPAA rules were extended, they would presumably apply to any existing data, not just data controlled by “covered entities.” Ms. Heide said that extending HIPAA Rules was not the question on the table. Rather, the issue is the protections on data to which researchers should be subject. Mr. Nelson highlighted the “paradox” that the ANPRM anticipates broadening the number of projects that could be self-excused, but at the same time envisions imposing consent and data protection responsibilities that were not there before.

Dr. Bierer asked whether OCR or OHRP would address breaches in data protection that occurred in research. Dr. Menikoff said both would. He further explained that the ANPRM sought to come up with reasonable protections for data security and that the key issue was how to define “identifiability.” He suggested that many researchers would welcome a clear rule on the subject. The problem with the Common Rule’s definition is that it is now too vague to enable researchers to confidently make calls about whether or not research is identifiable. Mr. Forster and Mr. Nelson both pointed out that the definition of identifiable data is interwoven with the concept of who is considered a human subject.

Dr. Joffe called attention to the following paragraph in the draft SACHRP letter (Attachment A, p. 16):

SACHRP recommends that it would be preferable to maintain the status quo under the Common Rule as it allows sufficient flexibility to protect subjects from informational risks. To the extent the perceived problems are created by inconsistencies between the Common Rule and the HIPAA Privacy Rule, we reiterate our standing recommendation that research be exempted from HIPAA.

He said the problem is that the Common Rule does not provide a “bright line” for defining identifiability. Mr. Nelson observed that currently, investigators at his institution are required to address all 18 elements that define identifiable under HIPAA when they file their online applications. Their responses determine how the IRB follows up. While current application of the 18 elements was said to be “ham handed” at times in the field, some SACHRP members felt these elements would provide a good starting point for a clearer definition of identifiability. SACHRP agreed to delete the current paragraph and further clarify its position.

Dr. Allen commented that the portion of the letter that addresses cloud computing was useful and points to challenges on the horizon. As more research is done across national and continental boundaries, new issues related to identifiability will require attention.

Public Comment

Ellen Fox commented that in her perception the discussion combined two different things without distinguishing between them. In regard to HIPAA requirements, she said, the subject is health information, which is therefore presumed to be sensitive if the individual can be identified. However, much of research in general pertains to data that may be identifiable, but “no one cares.” Some research, she reminded SACHRP, does not include any sensitive information.

Ms. Heide agreed that the nature of the data is among the considerations related to appropriate data protections. She invited SACHRP to identify whether there are cases in which little or no data protection is warranted based on the nature of the data.

Discussion of Section 4. Strengthening Data Protections to Minimize Information Risk (Continued)

Mr. Nelson noted that data protections required are larger than the issue of identifiability. Dr. Bierer said the differences in data security and other risks are already clear in the draft letter.

Mr. Nelson said that if the subcommittees could have envisioned a clear black and white line, they could have improved the coherence of their response.

MMs. Heide asked about a prohibition on reidentification of data.. Dr. Bierer commented that SACHRP's letter does not yet address the issue of whether the 18 identifiers cited in HIPAA regulations are clear enough to serve as a guide for the research community on whether or not data can be considered deidentified. Given more time, SACHRP might append a mechanism for assessing whether the 18 are definitive and for considering how to assess the risks associated with the data set. The next issues to consider would be whether or not the investigator has sufficient guidance to make a determination and how to devise appropriate data security standards for the level of risk.

Ms. Heide highlighted the fact that any reidentification of data would have to go back to the IRB for approval. Dr. Bierer observed that the lack of consequences for such reidentification is a problem with the current regulations.

Dr. Joffe said he did not agree with the current letter's stance on basing standards of identification on HIPAA, which is that it is a bad idea. He propped the following new language:

Despite the value of flexibility, SACHRP recognizes the need for clear definition of what constitutes identifiable data. SACHRP believes that the current HIPAA definition of a limited dataset (allowing for certain dates, geographic subdivisions, etc.) might be used as a starting point for developing a new definition of identifiability if the proposed excused framework is implemented.

SACHRP agreed, inserting the paragraph just before "Standards for Data Security and Information Protection" (Attachment B, p. 18). The new paragraph contradicted two existing paragraphs, which were accordingly deleted.

Dr. Bierer suggested that one could choose to change the breach notification if the breach is in no way sensitive. Dr. Chadwick held that breach notification is onerous and that extending it would cause major issues.

Dr. Joffe pointed to a need for a conclusion to section 4 that more clearly states SAHCRP's position. Members agreed and approved the following concluding paragraph (Attachment B, p. 20):

Finally, we wish to make the general statement that one reading of the ANPRM opens up the possibility of extending the HIPAA standards as they currently apply to covered entities to all research under the Common Rule. We believe that this approach would be exceedingly difficult to implement, burdensome to the research community and generally excessive in relation to the benefits realized. We believe it is essential to ensure proportionality between the information risks and the data protection requirements of any revised regulations.

ACTION

The section was approved unanimously as revised.

Discussion of Section 5. Adverse Event (AE) Reporting

Co-Chairs explained that all material included in Attachment A starting at the bottom of p. 23, beginning with “SACHRP supports harmonization,” was not intended to be part of the document presented for discussion and should be struck.

Dr. Joffe was concerned that the letter implied that Clinicaltrials.gov might serve as a systemwide source of information on safety and risks. Dr. Allen noted that Phase I trials are often constructed differently from other trials, and generalizations might be misleading. Qualifying language was added:

SACHRP believes that adverse event data in ClinicalTrials.gov merit consideration as a source of systematic data on research risk, including potential expansion of the scope to include Phase I trials.

ACTION

This section of the letter was approved unanimously.

Discussion of Section 6. Extension of Federal Regulations

A SACHRP member felt that most institutions that receive Federal funding do apply the principles in practice, and there is currently no way to reach the other institutions. Another observed that institutions that do not check the box indicating that they will apply the Common Rule to research that is not Federally funded do so to reduce the burden of having to report unintended consequences on these studies.

No changes were made to the draft as reviewed.

ACTION

The section was approved unanimously.

Discussion of Section 7. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Dr. Bierer suggested the first sentence be revised to clarify that the need for harmonization applies to all *Federal* agencies, as opposed to entities within HHS. The word “Federal” was added.

Dr. Allen suggested adding a sentence that makes it clear that some agencies will need Congressional action in order to harmonize their guidance. Others agreed.

A SACHRP member proposed that the task force proposed in the final paragraph as a means of harmonizing guidance on an ongoing basis should be interagency as well as multidisciplinary. Members agreed.

Ms. Krivacic asked whether the letter meant to imply that guidance should be reviewed every five years, or whether it was implying that the Common Rule itself required periodic review by the proposed task force. Mr. Nelson said the letter referred only to guidance.

ACTION

Approved unanimously

Discussion of Section 8. Future Use of Biospecimens

Mr. Barnes introduced the discussion by reviewing the ANPRM proposal that a general consent be obtained as prerequisite for future unspecified research use. Subcommittee members found this to be problematic on several grounds:

- *Inadequate protection of human subjects.* In the current system, the investigator applies for a waiver in order to use existing biospecimens, and the IRB classifies the research in real time based on an actual proposed protocol. Subcommittee members felt this was a superior approach.
- *Practicalities.* Given the way that researchers collaborate, members felt it was not practicable to gain this general consent and then track it over time. Massive systems would be needed to show that consent really was obtained.
- *Social justice.* Members felt that “we are in research as a community.” While agreeing with the need to educate individuals that their specimens may be used for other studies, opting in and out does not serve the spirit of justice. Subjects are relying on the beneficence of others.

Of the 20 persons who met to prepare the draft letter, all but one supported this section of the letter as written. That person felt that there should be a general consent that suffices for *every* future use without the need to return to the IRB.

Dr. Bierer further explained that issues around future research hinge on identified vs. deidentified specimens. This is a critical distinguishing element. She felt that a robust education of the population was required, whatever approach was chosen.

Principles. Dr. Ross objected to the “social justice” argument as presented. She saw “respect for persons” as the key principle, “trumping” both beneficence and justice. Another SACHRP member commented that the Belmont report presented them as coequal principles.

Grandfathering. (Attachment A, p. 36, paragraph beginning: “If current proposals...”). Dr. Joffe suggested deleting the paragraph that addresses the topic of grandfathering. Mr. Barnes, however, stressed the importance of affirming that SACHRP believes grandfathering is a good idea. Dr. Bierer noted that OHRP has clearly thought about the issue of how current biospecimens will be used. Ms.

Heide urged SACHRP to make its position explicit. The committee agreed to add the words, “SACHRP endorses this aspect of the proposal.”

Definition of human subjects. Dr. Sodeke stressed that decisions about the best approach on predicated on the definition of human subjects, and suggested that SACHRP has not fully examined that issue. He noted that in the case of the Havasupai, the human subject involved was not simply a living person. This could also be the case in international research.

Consequences of future use. Dr. Rivera observed that the change contemplated in the ANPRM constitutes a “huge paradigm shift.” Given that reidentification of deidentified specimens is an unusual occurrence, she was concerned that the changes amounted to “swatting a fly with a hammer” and would have unintended consequences.

Dr. Joffe stressed that even if there is no harm that can occur to the subject as a result of future use of biospecimens, the issue is the veracity of the original consent. When investigators foresee the possibility of using the samples in other ways than the one that is the subject’s reason for contributing the sample, this should be addressed “up front” in the consent process. Dr. Ross noted that based on Nuremberg Code (<http://ohsr.od.nih.gov/guidelines/nuremberg.html>), harm is done to the subject when the subject’s right to withdraw is not honored. Subpart A, she said, originated because of cases in which the principle of respect for persons was violated.

Mr. Lux stressed that harms that occur to individuals when they are lied to are real harms and should be taken seriously. The perception they have been lied to undermines public trust in research, and it is worth closing the loophole that allows this to happen. Ms. Krivacic agreed. She said the issue of future use is not clear to many patients, and some have significant levels of mistrust around what “the government or other entities” will do with their samples.

Dr. Menikoff said the issue was not limited to possible harms, but rather whether it is or is not acceptable to have research involving biospecimens occurring without subjects having any opportunity to say “yes” or “no.” Should they have that right or not?

Registration. Dr. Joffe raised the issue of whether or not it is appropriate to register studies that involve the use of biospecimens. He noted that some studies do need more than that level of minimal governance, and having them recorded may be helpful. Even if the materials are deidentified, someone could want to know how they are being used. Ms. Heide said the ANPRM does not propose a requirement that studies using deidentified data be registered but requests comment on this option. However, Dr. Menikoff clarified that the ANPRM does propose that all studies involving secondary use of biospecimens be registered. Dr. Ross argued that registration was insufficient; instead, the focus should be placed on preventing inappropriate use, regardless of whether the biospecimens were said to be identifiable.

Dr. Bierer, however, gave the example of using blood samples that are about to be thrown out to sample electrolytes for quality control. She did not think such use of biospecimens should require registration. Even “bench research” could be subjected to burdensome requirements, and this would be inappropriate. Dr. Less stated that FDA’s assumption was that IRBs would look into the ethics of the use of leftover specimens without consent.

Data vs. biospecimens. A SACHRP member asked why a distinction was made between biospecimens and data. Dr. Menikoff suggested that once data is analyzed, the process of analysis is complete; however, it is possible to continue to learn from biospecimens. Dr. Allen, however, said that findings from biospecimens may become data, and it is not possible to distinguish clearly between the two. He felt that data issues should be considered similarly, in general, but that the term “data” was too broad. With respect to language in the draft letter being discussed, Ms. Heide cautioned that data protection requirements are not privacy requirements.

Three SACHRP members, Dr. Ross, Dr. Sodeke, and Ms. Krivacic, were prepared to file a minority opinion regarding SACHRP’s recommendations in this section of the letter. The Chair noted that the minority specifically questioned the distinction between data and biospecimens.

SACHRP voted on a series of key questions in order to clarify where members stood:

- SACHRP does not endorse the presumption that all biospecimens are inherently identifiable. (The vote was 7-4 in agreement.)
- SACHRP believes that all research involving biospecimens should be registered with the IRB regardless of the biospecimens’ identifiability. (The vote was a tie, and remained the same when “with the IRB” was changed to “with the institution.”)
- SACHRP believes that all research involving prospective collection of biospecimens for research should be registered. (Unanimously supported.)
- SACHRP believes that all secondary research use of existing biospecimen without identifiers should be registered with the institution. (The majority did not believe this; six members disagreed with the statement and four agreed).

SACHRP members also agreed that there were circumstances in which a waiver should be required. They agreed to recommend the following (Attachment B, p. 36):

- *Adoption of Common Rule standards that promote a more rigorous IRB analysis of potential individual and group harms from the waiver of informed consent for research, including protections for discrete and insular communities whose individual members may be directly affected by use of apparently de-identified or anonymized data and/or biospecimens,*

Free use. Mr. Barnes said a situation in which the subject is told that the donated specimen will be used for diabetes and later it is used for cancer differs from one in which the consent form explicitly assures the subject that the specimen will not be used for anything else. He noted that to date, researchers have lived with a fundamental social decision made that in healthcare delivery, healthcare provider can shed identifiers and without consent of the individual publish, sell, or basically do whatever they want with deidentified data. The ANPRM proposal is inconsistent with the HIPAA principle of free use. He stressed that, from a legal perspective, it is not true that you own your biospecimen once it is separated from your body: “You’ve basically abandoned that part of yourself. You have some lingering rights, but the law does not say that you ‘own’ the biospecimen.”

Another SACHRP member strongly agreed: “Once my data is stripped of identifiers, it is not mine.”

Applicability of waiver criteria. Dr. Joffe suggested that the criteria for a waiver contained in Subpart A are quite good and generally applicable in this circumstance. He suggested that procedures for a waiver involving use of biospecimens could be spelled out and modeled on current waiver criteria.

Record keeping. Mr. Forster liked the ANPRM's basic approach and "elegant" solutions, but was concerned about the administrative burden of tracking and maintaining consent documents to determine who did and did not consent to which possible future use.

Mr. Coleman raised the issue of how compliance would be monitored. How would you know if deidentified material is being used?

General consent. Dr. Joffe questioned the summary statement regarding SACHRP's position on general consent, maintaining that it "seems to take a stand against general consent in general" and was "too strong" (Attachment A, p. 37, paragraph beginning: "In summary, SACHRP strongly disfavors..."). SACHRP agreed to strike the assertion that "non-specific consent cannot be thought to constitute consent."

Mr. Coleman asked for clarification of the ANPRM proposal, which he understood was that general consent should be construed as a necessary but insufficient condition for use of biospecimens. He asked whether a waiver would not also be required. Dr. Menikoff said OHRP envisioned that the broad consent would cover future use in most types of studies. If the biospecimens were later to be used in a study that would create and then destroy a human embryo, a separate consent would be required. Dr. Bierer asked whether it would suffice to explain to a subject entering a hospital that "this is how we work." Dr. Menikoff said it would.

Mr. Coleman was concerned about asking subjects to consent "at an abstract level before specifics exist" and felt the IRB would be better positioned to protect their interests. Dr. Rivera was also concerned that the general consent process could not give subjects enough information to make an informed decision; she was more comfortable with IRB members having a discussion about whether a proposed use is appropriate. Dr. Ross stressed that subjects have the right to know how their sample is used.

Dr. Menikoff suggested that privacy and data confidentiality rules should be sufficient to avoid new IRB reviews in most instances. Currently, nothing in Subpart A says that IRB review is required when deidentified samples are used.

Dr. Bierer said that trying to maintain a working knowledge of where particular biospecimens are going and how they are being used is almost impossible, and the desire of any subject to know the specifics of their biospecimen(s) cannot be satisfied in practice. She noted that there are many examples of current use of biospecimens that everyone seems to be comfortable with – for example, the use of leftover blood products for biomarker development – that would have an additional level of administrative requirements if the ANPRM approach is adopted. In her opinion, this would increase cost without increasing subject protections. She added that a variety of institutions receive data originally collected from entities that do not receive Federal funding, and the ANPRM approach would prohibit them from working on these data.

Dr. Allen held that "no should be no," and he was happy to ask a subject to clarify their terms of consent. He saw a middle ground in which consent forms would allow for a wide variety of uses of a

biospecimen related to research on a specific disease. This type of consent would be more relevant and understandable to the subject. He stressed that patient education is critical.

Harmonization. A SACHRP member asked what the implications would be for FDA regulations if the approach suggested in the ANPRM were adopted. Dr. Less, ex officio representative for FDA, responded that there would be a harmonized approach insofar as possible. However, she said there were some areas where FDA could not take a similar approach without a statutory change.

Ms. Decot, ex officio representative for the Department of Defense, said the agency would have trouble with some criteria in the ANPRM, but the new Department of Defense policy would be expected to offer some latitude when collaborating. She also stated the assumption that if Subpart A were revised, other agencies would have input.

Dr. Allen asked whether it would be possible to have two IRBs for studies that involve both Department of Defense and non-DoD sites. Ms. Decot said that was how DoD typically collaborates with other entities at present.

Industry studies. Dr. Allen stated that the section dealing with industry-sponsored studies reflected an antiquated model of how such studies are done. For example, industry may join collaborative groups funded by other entities and may or may not have biospecimens at the industry site. He drafted a new section for SACHRP review dealing with this topic.

Dr. Allen stressed that sponsors have an interest in maintaining trust in the research enterprise, which includes applying protections uniformly (including to internal research) whenever possible. Dr. Bierer noted that internal research is not currently subject to any human subject protection regulations. In response to a question from a SACHRP member, Dr. Allen explained that sponsors typically have a separate consent form related to biospecimens for clinical trial participants.

Ms. Krivacic asked her colleagues whether, in their opinion, it should ever be permissible to require giving a specimen as criterion for being in clinical trial. A SACHRP member thought that if the trial offers benefits to the participant, it might be appropriate, but if the specimen is given for other reasons it would be more problematic to make it a requirement. Dr. Allen observed that much of the answer to this question depends on the science. In some circumstances researchers are collecting biospecimens they intend to bank, while in others collecting specimens may be integral to diagnostic processes. He said no one approach is appropriate. Dr. Joffe said in reference to cancer studies, limitations on the use of biospecimens could undermine the study. However, it is generally thought to be unreasonable to require subjects to agree to unspecified future uses. Dr. Menikoff said this was similar to OHRP's position, which is that any such requirement should be related to the trial.

Need for a summary of recommendations. Dr. Joffe suggested that a summary of recommendations was needed, which he was willing to draft for review. He also held that the conclusion should clarify that SACHRP favors an approach more like the current one, in which subsequent uses should be compatible with the original consent. SACHRP approved an added paragraph and conclusion (Attachment B, p. 36).

Minority Report

Dr. Ross read a first draft of a minority report pertaining to this section of SACHRP's letter, which held that standards for clinical information and biospecimens should be similar since "everything can be reidentified" (see Attachment C). She held that people have a right to know how their clinical information and biospecimens are used. Ms. Heide commented that her perception was that the ANPRM does treat both similarly; with differences in that it would not require consent for certain secondary uses of nonidentifiable data.

Some members question the validity of the example contained in the minority report, in which a person's clinical file and a DNA sample were left on a bus. They pointed out that while the clinical file could readily be used to ascertain personal information, decoding the more extensive information contained in the DNA sample and applying them to a specific individual could not be accomplished without a referent sample of DNA that was identified.

In response to queries about practicability, Dr. Ross held that informatics are excellent and very few people will say no to requests to use their biospecimens in the future. She envisioned that informatics would flag and block and unacceptable use. She argued that "it isn't that hard to keep our promises." She agreed with others that using information any way researchers want to use it, regardless of what the subject understood, undermines public trust. Dr. Bierer, however, said her institution has spent millions of dollars designing a system that would reliably exclude data collected for various purposes and has still not been able to accomplish this.

A SACHRP member commented that most people do not care if deidentified information is shared. This member felt adults would look at the risks of research in the context of all the other risks we encounter in daily lives, such as shopping on the internet.

Dr. Bierer said the idea that DNA can readily be identified is a misperception. In fact, this can only be done if a referent DNA sample is available. Without it, a hundred DNA sequences could still not be used to identify the specific person. With this in mind, language in the letter was revised to indicate that such reidentification was a "remote possibility."

A SACHRP member was concerned with the precedent of a minority report. Ms. Gorey explained that while a single letter affords greater transparency, there would be no legal obstacle to SACHRP providing a minority report. Dr. Allen suggested that divergent approaches might be helpful advice.

A revised version of the Minority Report was read later in the meeting (Attachment D). SACHRP agreed that it should be referenced in the body of the text of the letter as Appendix 1.

ACTION

The section was approved by majority vote.

Discussion of Section 9. Areas to Address that were not Included in the ANPRM as Proposed

Requirement to Address Investigator Regulatory Responsibilities in the Common Rule

A SACHRP member suggested that SACHRP recommend that the Department have individuals barred from research when their failure to comply with regulations is at a level that warrants this response. Dr. Bierer recommended not including this.

A SACHRP member noted that the current draft implies that investigators do not have to report conflicts of interest if they do not believe it will influence their research. New guidance from NIH, however, says that the institution, rather than the investigator, has this responsibility. SACHRP reviewed the original statement under §46.105 *Qualification Standards for Investigators (Attachment A, p. 39)*:

c) Investigators should be responsible for reporting to the institution any circumstances, including financial interests that could present, or could reasonably appear to present, a conflict of interest that might bias the design, conduct, or reporting of the research; such reports would in turn be addressed by the institution in accordance with requirements to eliminate or manage any conflict of interest.

SACHRP approved the following simplified statement:

*c) Investigators should be responsible for reporting to the all financial interests **relevant to their institutional commitments**; such reports would in turn be addressed by the institution in accordance with requirements to eliminate or manage any conflict of interest.*

ACTION

This section was approved unanimously.

Pediatrics

Dr. Joffe explained that a concern in the pediatric community is that if there is a regime involving biospecimens from children for which prospective consent is required, and the children involved age into adulthood over the life of the research, it would be impossible to continue the research without obtaining the adult's permission. It is important to have a waiver of requirement for child's consent. Dr. Ross agreed but noted that to the extent that the children involved are still being followed, consideration should be given to reconsenting them, and this should be the default.

SACHRP also agreed to add the following recommendation at the end of this section:

SACHRP recommends removing all references to “competent adults” throughout the ANPRM as inclusion of this qualifying language is more restrictive than the current regulations and would introduce numerous unintended consequences. Sufficient provisions already are in place for protecting the rights and welfare of other subject populations.

ACTION

This section was approved unanimously.

Vulnerable Subjects

A SACHRP member objected to the statement that some individuals “are unable to adequately protect themselves through the protections afforded by the informed consent process.” This was considered too strong; it could also appear paternalistic. The language was revised to assert that some individuals “*may be* unable to adequately protect themselves....”

Dr. Ross pointed out that groups may be vulnerable as well. However, Dr. Bierer noted that this is a huge area that SACHRP does not have time to think through. Therefore, a revision was made to explicitly say, “our comments here relate to the vulnerability of the individual and not community-level vulnerability.”

Mr. Coleman observed that the term “vulnerability” may also apply to unjust allocation of risks and benefits. A subcommittee member observed that the document seeks to distinguish vulnerability and susceptibility. In the regulations, vulnerability has to do with consent. The term susceptibility, as commonly used, refers to the likelihood of being harmed. SACHRP accepted this distinction.

ACTION

This section was approved unanimously.

International Research

A SACHRP member objected to the statement that “Some countries have laws that are more expansive than the U.S. regulations and exceed the U.S. requirements for protecting human subjects (e.g., Mexico and Ukraine).” The member doubted it was fair to imply that Mexico and Ukraine were more protected. Dr. Allen noted, however, that a number of European countries do have requirements at least as strong as those of the U.S. The statement was revised to read:

Some countries have laws that are more expansive than the U.S. regulations.

ACTION

This section was approved unanimously.

Incurred Cost and Resource Commitment

Dr. Menikoff objected to the implication that a discussion of this topic was an “omission.” He said OHRP intended to take this up at a later stage.

Dr. Allen said the cost of any revision to the Common Rule would be significant, both for HHS and for institutions. Revision would also entail educating the public.

A final paragraph was added to provide closure and to acknowledge that the letter is necessarily “incomplete,” given the time available.

ACTION

This section was approved unanimously.

Public Comment

Deborah Runkle of The American Association for the Advancement of Science (AAAS) said her organization was thinking of including a statement in informed consent documents to the effect that complete confidentiality can never be guaranteed. Court subpoenas are a possibility, for example.

Attachment A. Draft of SACHRP Letter on ANPRM as Presented at the October, 2011 Meeting

See separate document.

Attachment B. Final SACHRP Letter on ANPRM

See separate document.

Attachment C. First Draft of Minority Report on Biospecimens

The ANPRM distinguishes between biospecimens and clinical data regarding future use. It expresses greater concern about privacy rights towards biospecimens and wants to ensure prospective consent for future uses. But it does not address prospective consent for future uses of clinical information in the medical record. This disconnect may not be held by the public whose trust and support is so critical to the research enterprise.

Suppose a hypothetical: a researcher is on a bus carrying a tube of your blood in one hand and your clinical information in the other hand. If the researcher were to leave one on the bus, which would be a greater threat to your privacy? Clearly the clinical information can be viewed and understood by a larger percentage of the population. The clinical information may also have such information as your address, social security number, names and ages of biological relatives (family history). The clinical chart expresses phenotypic information—what health problems you actually have. The tube of blood, if properly prepared, can be used by a smaller group of persons trained in particular sciences. They could use it to examine your DNA which will tell someone a lot about your risks, but cannot be certain whether or not the gene is expressed and to what degree. In sum, it seems that your clinical information reveals a lot more about you today. This may not always be the case. But clearly whatever protections we want for biospecimens similar standards should be required for clinical information.

What type of protections should that be? It is clear that a blanket consent is not an informed consent. It is a start however, because it allows those who do not want to have their data used to say no. But clearly additional oversight is needed to ensure that future uses preserve patient privacy and are consistent with the consent that they gave. And yet, today, no such oversight is required. OHRP has made it clear that de-identified data and biospecimens do not represent living human subjects and do not need further oversight. This is mistaken. First, the public believes (rightly we might add) that if you have an individual's DNA, the individual could be re-identified, and even if you don't re-identify, you still have that individual's genetic code (and not someone else's). Similarly, if you have an individual's clinical information, it is about that particular individual. While we may not want to burden IRBs with the oversight, one could argue that all future use of research should be reviewed by a local some group of diverse individuals who could 1) determine the scientific validity of the question; 2) determine that the samples requested are appropriate to answer the question; 3) ensure that the researchers have proper training and understanding of human subjects protections; 4) ensure that the research plan protects the privacy and confidentiality of the participants whose data are being used; 5) obtain assurance that re-identification will not be attempted unless prior consent permitted it; and 6) ensure that additional risks to vulnerable populations (e.g. identifiable communities) are identified and minimized. The creation of future use oversight boards may be able to supplement the role of the IRBs, but unless there is some official mandate to require some degree of oversight, researchers will be happy with the OHRP assessment that the research requires no oversight. The public is relatively unaware that such research is occurring ubiquitously, but with education, may feel that their trust was misplaced. And to the extent that HIPAA rules are extended to research, the public will have the right to know about these future uses. The importance of trust in the research enterprise cannot be overstated.

The notion that de-identified data do not involve human subjects must also confront the fact of what should be done if a research finding identifies something of significant clinical importance. If a

researcher can envision an interest in returning research results from a de-identified sample, regardless of how rare this might be, then there is a human subject behind the data. Do not assume that all persons would want this information and will say thank you. First, your findings may be wrong. Second, it may be too late. Third, the interventions may be invasive, not 100% effective, etc. If one wants to say that results will never be returned in this situation (a solution with which I am comfortable), then this argument fails. But the literature is full of examples of such cases and the surveys show that researchers, particularly researcher-clinicians want to return these results!

Attachment D. Final Version of ANPRM Minority Report on Biospecimens

A minority of SACHRP members were in disagreement with the consensus position expressed by SACHRP about the regulations regarding future uses of human-derived research materials.

The ANPRM distinguishes between biospecimens and clinical data regarding future uses. This disconnect may not be held by the public whose trust and support is so critical to the research enterprise.

What type of protections should exist for materials derived from human beings? One should consider protections that can be obtained by seeking permission prospectively and by ensuring greater transparency retrospectively.

It is clear that blanket consent for future uses is not an informed consent. It is a start however, because it allows those who do not want to have their data used to say no. But clearly additional oversight is needed to ensure that future uses preserve patient privacy and are consistent with the consent that they gave. And yet, today, no such oversight is required. OHRP has made it clear that de-identified data and biospecimens do not represent living human subjects and do not need further oversight. This is mistaken. First, the public believes (rightly we might add) that if you have an individual's DNA, the individual could be re-identified, and even if you don't re-identify, you still have that individual's genetic code (and not someone else's). Similarly, if you have an individual's clinical information, even if de-identified, it is about (derived from) that particular individual.

We are not beholden to any particular form of oversight. There are at least 3 options: 1) to consider biobank governance models similar to those being used in Europe which may be instructive; 2) to expand IRB oversight to cover human-derived research materials (including both biospecimens and de-identified clinical data); or 3) to create an alternative biobank oversight structure, consisting of representatives from both the scientific community and the public. The purpose of this oversight is: 1) to determine the scientific validity of the question; 2) to determine that the samples requested are appropriate to answer the question; 3) to ensure that the researchers have proper training and understanding of human subjects protections; 4) to ensure that the research plan protects the privacy and confidentiality of the participants whose data are being used; 5) to obtain assurance that re-identification will not be attempted unless prior consent permitted it; and 6) to ensure that additional risks to vulnerable populations (e.g. identifiable communities) are recognized and minimized. OHRP need not specify how oversight is done, but must mandate the need for oversight (at minimum, registration) for all research involving human materials.

There is also the need for greater transparency. The public is relatively unaware that such research is occurring ubiquitously. Education should focus on why they should want to support research using de-identified human materials both for themselves, for their families, and for society-at-large. Without such education, media attention (both positive and negative) may leave the public feeling that their rights were disregarded and their trust was violated. The public should have the right to know about the uses to which their data (information or biospecimens) were used. The importance of trust in the research enterprise cannot be overstated. This includes transparency regarding all secondary research use of existing biospecimens, whether or not there are identifiers. Within the ANPRM, all such research should be registered with the institution.

In this vein, OHRP may need to reconsider who or what is meant by the concept of “human subjects research” and whether it should include materials derived from living human subjects.

This comment should not be understood to reject the use of de-identified research materials (both clinical data and biospecimens) for research, nor is it meant to create undue obstacles, but only to ensure appropriate protections are in place. We want to emphasize that: 1) clinical information and biospecimens should be treated similarly because they are similar; 2) the public has the right to know when their data are used (even when de-identified) and for what purposes; 3) all such research should be subject to some type of oversight to respect the human beings from whom these materials were obtained; and 4) to the extent that de-identified data are being used for research, there should be no attempts at re-identification unless consent was obtained prospectively.

**Secretary's Advisory Committee on Human Research Protections
October 4-5, 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.

Barbara Bierer, M.D., Chair

Date