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The Department of Health and Human Services
Meeting of the
Secretary's Advisory Committee on Human Research Protections (SACHRP)
Tuesday, March 8, 2011 – Wednesday, March 9, 2011
Hubert H. Humphrey Building, Room 800
AGENDA

Voting SACHRP Members Present

Barbara Bierer (Chair), Carl H. Coleman, David G. Forster, Gary H. Gibbons, Steven Joffe, Lisa Leiden, Lainie F. Ross, Stephen O. Sodeke, David H. Strauss

Tuesday, March 8, 2011

Welcome and Opening Remarks

Barbara Bierer, M.D., SACHRP Chair

The Chair welcomed everyone to the meeting and expressed appreciation for the many contributions of Patty Marshall, Lisa Leiden, and David Strauss, who are leaving the committee. Patty Marshall has been a voice for the community who has thought constantly of those not present to speak for themselves. Lisa Leiden's service has highlighted the importance of considering how regulations affect the individuals that manage and work with them. David Strauss led the Subcommittee for Inclusion of Individuals with Impaired Decision-making in Research (SIIDR), a masterly, longlasting contribution to the field. He has brought an ability to think through the most difficult ethical issues and frame them so people can think about them. Certificates will be available for these members when new replacement members are approved.

She noted that an RFI was published in the March 2 *Federal Register* by the Presidential Commission for the Study of Bioethical Issues. She suggested that members may wish to respond. Comments must be received by May 2, 2011 in order to be considered.

She thanked OHRP staff for their work in preparing the meeting.

Report of Issues/Remarks

Jerry Menikoff, M.D., J.D., Director, OHRP

Dr. Menikoff thanked all committee members, guests, and ex officios for their presence and contributions, then echoed the Chair's appreciation for the "exceptional service" of the three departing members.

He reported that OHRP has issued final guidance on Continuing Review and Approval with Conditions, areas in which SACHRP has pointed to a need. See: <http://www.hhs.gov/ohrp/policy/continuingreview2010.html> and <http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html>. OHRP is actively working on other guidance to harmonize rules between OHRP and FDA.

Federal Demonstration Partnership: Current Initiatives for Reducing Burden of Regulatory Compliance

Lois Brako, Ph.D., Assistant Vice President, University of Michigan; Jane McCutcheon, DDS, Ph.D., Associate Professor, New York University; Ann Hardy, Dr.P.H., NIH Extramural Human Research Protection Officer, National Institutes of Health; Elizabeth Bankert, M.A., Assistant Provost, Dartmouth College

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

Dr. Bierer explained that the Federal Demonstration Partnership (FDP) is a cooperative initiative among 10 Federal agencies and 120 institutions that receive Federal funds. See: <http://www.thefdp.org>. The Partnership seeks to reduce the administrative burdens associated with research grants and contracts. It has the following charge:

- *Reviews existing and new administrative requirements imposed by federal regulations and program officers related to but not limited to the human research participant protections, animal use and care, conflicts of interest (individual and institutional), objectivity in research, and export controls. The emphasis should be on harmonization of requirements across federal agencies, reduction of redundancies and identifying good practices.*

Dr. Brako said that the FDP is sponsored by the Government, University, and Industry Research Roundtable of the National Academies. A “faculty burden survey” by the FDP in 2007 showed that human subjects research was one of the activities that rose to the top as time-consuming. Responses are posted on the FDP website and highlight areas in which efficiencies could be introduced.

The FDP established the Human Subjects Protection Subcommittee to address this area of concern. It not only seeks to identify areas of unnecessary burden, but also to identify effective practices and examples that meet regulatory requirements and protect human subjects while also decreasing administrative burdens. There are a number of business processes that do not require guidance to be implemented – only a commitment to change.

Currently, the subcommittee is organizing projects in keeping with its mission. It benefits from consulting assistance from Julia Gorey and Ivor Pritchard, OHRP staff. Priority projects include:

- Producing a *Practical Guide for Reducing Regulatory Burden*, which will contain a set of tools useful in reducing administrative burdens. The subcommittee is seeking input from SACHRP and others on this project.
- Developing a nonproprietary “exemption wizard” that can be used online. A planned demonstration will consist of two stages, in which the wizard is first tested to discover how often it accurately “diagnoses” cases in which an exemption is appropriate, then studied to see how expedited research has fared and whether problems have developed that suggest a false reading from the wizard. The findings of the tool are reviewed by the IRB, and acting on them is not intended to be mandatory.
- Implementing a “Harmonization Project” that documents human subjects protection policies for each agency and seeks to identify areas that are “ripe for harmonization.”

Ms. Bankert saw the subcommittee's work as an opportunity for SACHRP recommendations to reach "the real world" and help colleagues identify and think through causes of administrative burden. She suggested that members contribute topics to the *Practical Guide*, review and critique project materials, clarify guidance, share ideas from SACHRP subcommittees, suggest demonstrations for FDP, and either volunteer themselves or suggest individuals who would be good members for working groups. She is working to ensure that FDP's work does not duplicate that of SACHRP, adding that the *Guide* is aimed more at grants and contracts staff than IRB staff and members.

Discussion

Coordination with SACHRP. The subcommittee is aware of SACHRP recommendations and actively reviewing them to identify areas in which procedural changes suggested by SACHRP are relevant to FDP's charge. SACHRP members were interested in supporting the work of the FDP subcommittee. Specifically:

- The Harmonization Project of the FDP subcommittee and SACHRP's Subcommittee on Harmonization (SOH) are interested in collaborating to avoid duplication of efforts.
- There was interest among FDP speakers in collaborating with SACHRP on demonstration projects, for example in the handling of minimal risk research.
- Lisa Leiden expressed interest in participating in the partnership.

Implementation strategy. Dr. Strauss wondered how the good ideas and tools developed by the subcommittee will be put into practice. Dr. Brako said that 120 institutions have pledged to look at the *Practical Guide* and identify areas in which they can change. The University of Michigan has a large technology group that can share tools with smaller institutions. Dr. McCutcheon added that some of the subcommittee's work is aimed at institutional legal counsel, pointing to the fact that some of their policies and practices add burden but do not protect the institution.

Potential for confusion. Dr. Bierer expressed concern about confusion that could result if OHRP guidance is restated or reframed in the FDP's products. Dr. Brako responded that OHRP has been working with the group to help ensure that what the subcommittee posts on its website will not conflict with OHRP guidance. Dr. Menikoff said OHRP is supportive of the subcommittee's work and looks forward to continued collaboration. An FDA spokesperson expressed interest in input from the subcommittee on ways that it can clarify its guidance to make it more applicable to academia.

Sustainability. The subcommittee is aware of the issue of sustainability and hopeful that synergy among FDP participants will help keep the initiative alive.

Exemption wizard. A SACHRP member was concerned that faculty members using the wizard might lie. A panel member pointed out that they could also lie on an application. In either case, the same documentation exists. The electronic format offers some protection against "skewing" the presentation of the relevant facts.

The wizard does begin by exploring whether or not the project constitutes research and, if so, whether or not it can be considered human subjects research. The subcommittee is trying to use definitions and examples to help faculty members arrive at the right answer for each component of the decision tree.

Dr. Bierer noted that risk assessment for studies in behavioral social sciences will differ from biomedical studies. She hoped the tool would be one that institutions could trust, facilitating collaboration.

The wizard does not address questions related to HIPAA.

Harmonization. Mr. Forster noted that the first meeting of SACHRP's newest subcommittee, the Subcommittee on Harmonization (SOH), produced a good list of inconsistencies among regulations that he would be happy to share.

Coordination. SACHRP members suggested that FDP coordinate with the Office of Science and Technology Policy (OSTP), which has a human subjects initiative related to the Common Rule. Panel members said they were already linked to recipients of NIH's Clinical and Translational Science Awards (CTSA). They are also sharing information with the Association for the Accreditation of Human Research Protection Programs (AAHRPP) but until recently were unsuccessful in finding someone to represent AAHRPP on the subcommittee.

Problem areas to address. A SACHRP member suggested that the subcommittee consider Quality Improvement projects as they relate to human subject protection issues. (See the SACHRP minutes for March 27-28, 2008, posted on the OHRP website, for a SACHRP panel on this subject.)

Dr. Bierer noted that the protocol review process is often hung up in areas in which a "handoff" occurs from one review process to another (for example, Conflict of Interest reviews). She added that such areas complicate multi-agency review projects. Communication issues in handing off protocols to grants and contracts following IRB review can also slow review and add administrative burden. She suggested that addressing such issues would have "universal impact."

Documenting burden on researchers. Dr. Strauss pointed to the need for data showing the burden placed on investigators as a result of unnecessary regulation. Dr. Brako said the subcommittee would welcome input on strategies they could use to reach out to investigators. She also said they had considered a survey to IRB administrators and would appreciate help.

Dr. Bierer suggested that the subcommittee address risk assessment issues. Dr. Hardy said she would be interested knowing how many studies in the U.S. are deemed minimal risk or expedited and how many human subjects are involved in relatively risky studies.

Report of Subpart A Subcommittee (SAS)

Dan Nelson, M.S., CIP, SAS Co-Chair; Elizabeth A. Bankert, M.A., SAS Co-Chair; David Borasky, M.P.H., CIP, SAS member

Co-Chairs reviewed the subcommittee's charge, membership, meetings to date, and recommendations forwarded to the Secretary. One area of concentration has been improving the form and process of informed consent. Previous work has led to SACHRP-approved recommendations on the waiver of informed consent (2007), the waiver of documentation of informed consent (2008), and FAQs addressing issues specific to informed consent for research use of biospecimens (2010). Current work focuses on broader sets of issues relating to informed consent, including:

- Areas where regulations may provide flexibility,
- Areas where interpretation or understanding may warrant clarification, and
- Development of FAQs that embody recommendations.

The committee's recommendations focused specifically on parental permission and assent. Recommendations were presented and actions were taken by SACHRP as follows.

FAQs on Parental Permission and Assent

1. Is assent of a child/adolescent required before participating in research?

Recommendation as presented:

1. Is assent of a child/adolescent required before participating in research?

Assent is required unless an IRB determines that one of the following conditions is met:

- (1) the children are not capable of providing assent, or
- (2) the research offers the prospect of direct benefit that is available only in the context of the research.

Note that condition (2) is not restricted to biomedical research, but may apply to behavioral interventions that hold the prospect for direct benefit.

If an IRB determines that one of these conditions is met, there is no requirement to waive assent.

Discussion

Dr. Bierer found the last sentence confusing in that assent is not required, so there is no requirement to waive assent (there is nothing *to* waive, as another SACHRP member put it). However, Mr. Forster stressed that it is still important to document why the waiver is not needed.

Dr. Strauss observed that it was silly to make this determination for neonates, for example, and suggested that institutions should be able to make policies that say when no determination is needed as to whether or not assent is required. Others agreed.

Dr. Menikoff was concerned that logical steps are used to determine that institutional policies apply. For example, if the institution's policies say that no child under five years of age is required to give assent, it is important to verify that every child in the study under consideration is really under the age of five.

Recommendation as approved:

1. Is assent of a child/adolescent required before participating in research?

Assent is required unless an IRB determines and **documents** that one of the following conditions is met:

- (1) the children are not capable of providing assent, or
- (2) the research offers the prospect of direct benefit that is available only in the context of the research.

Note that condition (2) is not restricted to biomedical research, but may apply to behavioral interventions that hold the prospect for direct benefit.

If an IRB determines and documents that one of these conditions is met, **assent is not required and therefore the issue of waiver of assent does not arise.**

2. If the two criteria listed above do not apply, is there a way to waive the requirement for assent?

Recommendation as presented:

2. If the two criteria listed above do not apply, is there a way to waive the requirement for assent?

Yes, the IRB may waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A. However, the waiver is limited to minimal risk research.

Discussion

Mr. Forster asked whether the first criterion was interpreted in different ways depending on the situation. He added that consent cannot be waived in FDA-regulated research. Dr. Bierer suggested that the differences in OHRP and FDA will be addressed through the work of the Subcommittee on Harmonization and suggested concentrating on OHRP's interpretation.

Dr. Joffe suggested that the last sentence is superfluous and should be dropped. Another member agreed, noting it "sends people in the wrong direction" and "sounds like an additional requirement."

Recommendation as approved:

- 2. If neither of the two criteria listed above is met, can the requirement for assent be waived?**

Yes, the IRB may waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A. ~~However, the waiver is limited to minimal risk research.~~

3. Does assent always need to be obtained in writing?

Recommendation as presented:

3. Does assent always need to be obtained in writing?

No.

The regulations do not require that assent be obtained in writing. IRBs have the option of determining if and how assent is obtained. Separate written assent forms are not required. However, an IRB has the option to require a separate form if it determines it is appropriate for the research. IRBs must document their decision in the meeting minutes.

If an IRB determines that written assent is not appropriate, it is not required to approve and document a waiver.

Discussion

Co-Chairs stressed that the focus of this recommendation is on waiving *documentation* of assent. A SACHRP member suggested always starting the answer with “yes” or “no” to improve clarity.

A SACHRP member questioned the need for the last sentence. Another noted, however, that many IRBs erroneously think they do need to approve and document a waiver.

Mr. Coleman found the word “always” unnecessary and confusing. Others agreed. Dr. Menikoff said there was no need for a signed document, but stressed the importance of specifying what the IRB is requiring. The IRB has full discretion in making its decision; the regulations specify no criteria.

Dr. Strauss said that more guidance was needed on what the IRB should be thinking about in requiring documentation. For example, a healthy 17-year-old would be treated similarly to an adult. He suggested noting that IRBs should carefully consider at what age a written consent form should be required.

Recommendation as approved:

3. Does assent always need to be **documented in writing**?

No.

The regulations do not require that assent be obtained in writing. **If an IRB determines that assent is to be obtained, IRBs have full discretion in determining whether and how assent will be documented.** Separate written assent forms are not required. However, an IRB has the option to require a separate form if it determines it is appropriate for the research. IRBs must document their decision **in IRB records as to how assent is to be obtained.**

As there is no regulatory requirement for written assent, the issue of waiver of written assent does not arise.

4. If an IRB determines that verbal assent is permissible, do you need to document that verbal assent was obtained?

Recommendation as presented:

4. If an IRB determines that verbal assent is permissible, do you need to document that verbal assent was obtained?

There is no regulatory requirement to document that verbal assent was obtained. IRBs have the flexibility to determine whether and how assent is documented. Institutions may have other institutional policies or other reasons for documenting verbal assent but it is not a regulatory requirement.

Discussion

Dr. Joffe raised the question of how an IRB could judge whether or not the requirement was met. He suggested it might be useful to have this documentation. Mr. Nelson countered that this would be an issue of best practices rather than regulatory requirements, the focus of this FAQ.

Minor wording choices were suggested and accepted.

Recommendation as approved:

No.

There is no regulatory requirement to document that verbal assent was obtained. IRBs have the flexibility to determine whether and how assent is documented. **While not a regulatory requirement**, institutions may have other policies or other reasons for documenting verbal assent.

5. Does assent need to contain all the elements required in a consent document?

Recommendation as presented:

5. Does assent need to contain all the elements required in a consent document?

There are no regulations that specify the elements of assent. Therefore, IRBs have the flexibility to determine what is appropriate to cover in an assent form or during the assent process.

Discussion

SACHRP members suggested it would be clearer to specify that the focus is on either the “process or form” associated with assent. As for other questions, the yes/no answer was added.

Recommendation as approved:

5. Does the assent process or form need to contain all the elements required in a consent document?

No. [The rest is unchanged.]

6. If the IRB determines assent is required, is there an age at which it becomes mandatory to obtain assent?

Recommendation as presented:

6. If the IRB determines assent is required, is there an age at which it becomes mandatory to obtain assent?

There is no regulatory requirement for the age of assent within the HHS or FDA regulations. IRBs may make this determination for their institution in general or on a protocol-by-protocol basis. In addition to age, IRBs should consider the maturity and psychological state of the children involved when making this determination.

Discussion

Dr. Strauss noted that regardless of the discretion IRBs have in this regard, they would be found lacking if they made certain determinations. He suggested a rewording that placed greater emphasis on what should be considered and changed the tone.

Mr. Coleman suggested the use of the term “presume.” He noted that there is no absolute black-and-white case besides neonates. Dr. Joffe agreed, noting that the complexity of the protocol is one of many factors to be taken into account. Mr. Borosky added that the child’s maturity and psychological state must be considered in relation to the specific protocol at issue. Risk is also a factor.

Dr. Strauss said the default position should be that children should participate in the assent process to the extent to which they are able to do so. The research team should engage them unless they determine the children are unable to participate in a meaningful way. He has been told that children like a process in which adults tell them what they are about to experience and they sign. Therefore, Dr. Strauss does not think it is an error to ask a child to sign a paper. Dr. Ross felt, however, that more guidance is needed on what it means for a child to be “engageable.”

Recommendation as approved:

6. If the IRB determines assent is required, is there an age at which it becomes mandatory to obtain assent?

No.

There is no regulatory requirement for the age of assent within the HHS or FDA regulations. **IRBs may set institutional policy that presumes that children of particular ages have or do not have the capacity to give assent, but should consider the maturity and psychological state of the children involved, as well as other factors,** on a protocol-by-protocol basis.

Children should be offered the opportunity to participate in decisions about research participation to the extent they are able.

7. *Is parental/guardian permission always required before a child/adolescent participates in research?*

Recommendation as presented:

7. Is parental/guardian permission always required before a child/adolescent participates in research?

In most situations, permission of parents or guardian is required for children/adolescents to participate in research. However, there are three ways in which it is possible to involve children in research without parental/guardian permission. They are as follows:

- (1) If a child or adolescent does not meet the definition of “child” for the purposes of research, their involvement in the research would not fall under the subpart D requirements.

(As an example, in some states adolescents may obtain contraception without the permission of their parents. If a research protocol involves the comparison of different contraceptive methods, it is possible for the IRB to determine that, for purposes of the research, these adolescents do not meet the definition of a child).

- (2) The regulatory criteria found in §46.116 of Subpart A may be used to waive parental/guardian permission if the IRB determines that these criteria are met.

- (3) In accordance with Subpart D, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, it may also waive the parental/guardian permission requirements (for example, abused or neglected children, or research aimed to understand the psychological well being of adolescents who have not informed their families of their sexual preferences). This provision does not apply to FDA regulated research.

Discussion

Dr. Ross pointed out that, in reference to the example, the use of a new contraceptive method might place the protocol in the “FDA world” and could increase risk. SAS Co-Chairs responded that this would be part of the IRB’s deliberations. Dr. Strauss suggested giving additional examples. Co-Chairs responded, however, that a number of examples, along with criteria to be considered by the IRB, were given in previous SACHRP work on Subpart D. SACHRP members suggested a reference to the appropriate Secretarial letter.

Dr. Strauss also reminded SACHRP that SIIDR had recommended that the decisionmaking capacity of subjects be attended to in all circumstances, not just when children are involved. He suggested included the term “as always” to underline this obligation.

A SACHRP member suggested the use of the term “sexual orientation” rather than “sexual preferences,” which could be controversial.

Recommendation as approved:

In most situations, permission of parents or guardian is required for children/adolescents to participate in research. However, there are three ways in which it is possible to involve children in research without parental/guardian permission. They are as follows:

(1) If a child or adolescent does not meet the definition of “child” for the purposes of research, their involvement in the research would not fall under the subpart D requirements. (As an example, in some states adolescents may obtain contraception without the permission of their parents. If a research protocol involves the comparison of different contraceptive methods, it is possible for the IRB to determine that, for purposes of the research, these adolescents do not meet the definition of a child). **If the IRB determines that the subjects may be treated as adults for the purposes of the research, investigators should carefully consider each participant’s capacity to consent to the research.**

(2) The regulatory criteria found in §46.116 of Subpart A may be used to waive parental/guardian permission if the IRB determines that these criteria are met. **This provision does not apply to FDA-regulated research.**

(3) In accordance with Subpart D, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, it may also waive the parental/guardian permission requirements. Examples include research involving abused or neglected children, or research aimed to understand the psychological well being of adolescents who have not informed their families of their sexual **orientation**. This provision does not apply to FDA-regulated research. (see also Secretarial letter dated Nov 9, 2006)

8. Is the permission of both parents required to enroll their children in research?

Recommendation as presented:

8. Is the permission of both parents required to enroll their children in research?

Parental permission of both parents is required only for research that is approved under categories §46.406 or 46.407, if both parents are reasonably available. For research in categories §45.404 or 45.405, the IRB may determine that the permission of one parent is sufficient. The IRB is required to make this determination and advise the investigator as part of the IRB approval process.

Discussion

No objections or considerations were identified.

Recommendation as approved:

Unchanged.

9. If a subject reaches the age of majority during the study do they need to provide consent in order to remain in the study?

Recommendation as presented:

9. If a subject reaches the age of majority during the study do they need to provide consent in order to remain in the study?

Minors who were initially enrolled with parental/guardian permission and then reach the age of majority must provide legally effective consent if the project continues to meet the definition of research involving human subjects. This includes interacting or intervening with the subject or having access to private identifiable information. However, the IRB has the ability to waive the requirements for consent if the criteria of §46.116 can be met. The IRB may consider whether consent will be required or waived when a subject reaches the age of majority, or as part of the initial review of a protocol that anticipates subjects reaching the age of majority during the course of the research.

Discussion

A SACHRP member suggested starting with “yes” or “no,” but others responded that there are grey zones, as in biobanking; the answer really begins with an implied “it depends.”

The FAQ was said to overlap with guidance OHRP has already given. Mr. Borosky responded that in this instance, SAS felt the point was an important one on which there is continuing confusion in the field. OHRP may choose to say it is already covered, but SAS wanted to emphasize it.

Recommendation as approved:

Unchanged.

Documentation of Informed Consent

1. Who is required to sign the informed consent document?

Recommendation as presented:

1. Who is required to sign the informed consent document?

HHS and FDA regulations require that informed consent documents must be signed by the subject or their legally authorized representative, except in those cases where the IRB has waived the requirements for documentation of consent. There is no regulatory requirement that a member of the study team, the principal investigator, or a witness sign the consent form, except in the event that the short form is used. When the short form document is used, then a witness must sign both the short form and the written summary, and the person obtaining informed consent must sign the summary. It is noted that some non-regulatory guidelines (e.g., ICH GCP, JCAHO) may have additional documentation requirements.

Discussion

Dr. Strauss asked, “what do we think should happened?” He was concerned about situations in which no one can be held responsible. Co-Chairs responded that the emphasis was on understanding what was required, not on disseminating best practices.

Dr. Joffe commented that it might not be appropriate for a member of the research team to sign. Dr. Strauss said most major institutions do require someone to sign, with the understanding that the

investigation team has an “affirmative role” in this instance. Most have moved away from the use of witnesses in favor of attestation by a representative of the investigation team.

Dr. Menikoff said that OHRP was not interested in issuing guidance that only says, “these are the minimum requirements.” It will consider all the issues raised; often, it does make recommendations on good practice.

Recommendation as approved:

·
Unchanged.

2. Do informed consent documents always have to be signed?

Recommendation as presented:

2. Do informed consent documents always have to be signed? No. IRBs may approve a waiver of documentation of consent in accordance with 45 CFR 46.117(c).

(Note: SACHRP has previously approved recommendations on waiver of documentation, which were included in the Secretarial letter dated September 2008.)

Discussion

No objections or considerations were identified.

Recommendation as approved:

·
Unchanged.

3. Must the informed consent process and documentation of consent take place at the same time?

Recommendation as presented:

3. Must the informed consent process and documentation of consent take place at the same time?

No, the regulations do not indicate when documentation must occur in relation to the rest of the consent process. In fact, there may be instances where it is in the best interest of potential participants that the process includes time to contemplate their participation instead of immediately providing consent and documentation.

Discussion

No objections or considerations were identified.

Recommendation as approved:

·
Unchanged.

4. Do individuals who sign consent forms need to write the date of their consent or initial each page of the form?

Recommendation as presented:

4. Do individuals who sign consent forms need to write the date of their consent or initial each page of the form?

HHS regulations do not require that participants or others include the date of their signature. Note, however, that FDA regulations do require the date of signature. There are no regulatory requirements that each individual page of the document be initialed and/or dated.

Discussion

No objections or considerations were identified.

Recommendation as approved:

Unchanged.

5. May participants return signed consent forms to the researcher by mail, fax or electronically?

Recommendation as presented:

5. May participants return signed consent forms to the researcher by mail, fax or electronically?

Yes, OHRP and FDA consider signed consent documents that are submitted to the investigator by mail or fax to be in compliance with the requirements for documentation. Scanned documents that are returned as attachments by email would also satisfy the requirements. A waiver of documentation is not necessary in this situation.

Discussion

A SACHRP member pointed out that an electronic signature is not acceptable to FDA. The term “email” could be used to avoid potential confusion; the requirement is adequately described in the body of the document. A member also suggested addressing HIPAA problems that may come as a result of emailing attachments, but others clarified that there is no conflict here with what HIPAA permits. It was decided that these issues could be clarified by OHRP in its guidance but did not need to be specified in the recommendation.

Recommendation as approved:

5. May participants return signed consent forms to the researcher by mail, fax or **e-mail**?

Otherwise unchanged.

6. Can waiver of documentation occur separately from waiver of informed consent?

Recommendation as presented:

6. Can waiver of documentation occur separately from waiver of informed consent?

Yes. Informed consent and documentation of consent are separate concepts and separate regulatory requirements. IRBs can waive written documentation without waiving informed consent. In either case, the IRB must make separate determinations and document their decisions.

Discussion

No objections or considerations were identified.

Recommendation as approved:

Unchanged.

7. Is it permissible to initiate a study (or selected study procedures) based on verbal consent prior to having obtained written documentation?

Recommendation as presented:

7. Is it permissible to initiate a study (or selected study procedures) based on verbal consent prior to having obtained written documentation?

This would be acceptable only if the IRB has made a prior determination that a waiver of documentation is appropriate in accordance with HHS regulations as specified in 45 CFR 46.117(c). Otherwise this is not permissible under the current OHRP interpretation of HHS regulations.

Note that FDA has not adopted the waiver of documentation found at 45 CFR 46.117(c)(1).

Discussion

No objections or considerations were identified.

Recommendation as approved:

Unchanged.

8. Must the order of information provided on informed consent documents follow the order in which they appear in HHS or FDA regulations?

Recommendation as presented:

8. Must the order of information provided on informed consent documents follow the order in which they appear in HHS or FDA regulations?

There is no requirement in the HHS or FDA regulations that the elements of consent be presented in a particular order or format. The IRB shall determine what the appropriate format is for presenting the information on the consent document.

Discussion

A “no” should be added.

Recommendation as approved:

Unchanged except for adding the word “No, there is no requirement...”

9. May IRBs approve a waiver of documentation for studies that qualify for expedited review?

Recommendation as presented:

9. May IRBs approve a waiver of documentation for studies that qualify for expedited review?

Yes. A waiver of written documentation is allowed in expedited research. Many of the procedures that qualify for expedited review do not require written documentation outside of the research context. Therefore, consent documentation could be waived for much of the research approved using the expedited review process.

IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review utilized by the IRB, whether expedited or convened meeting review.

Discussion

No objections or considerations were identified.

Recommendation as approved:

Unchanged.

10. Are electronic signatures considered valid documentation of informed consent?

This recommendation is placed on hold pending input from legal counsel. The question to be considered regards state jurisdiction in determining what type of documentation is considered valid.

A SACHRP member asked about jurisdiction in the case of mailed surveys that cross state lines. Mr. Nelson said SAS’s working understanding is that it is the place where the research is conducted that determines what law applies. Dr. Bierer pointed out the focus in this instance is solely on requirements for the legality of the signature.

11. Does a participant’s agreement to participate by internet (e.g. clicking an “I agree” link or a radio button on a web-based survey) constitute an electronic signature for the purposes of documenting informed consent?

This recommendation is placed on hold pending input from legal counsel.

12. Is the short form option for documentation of informed consent restricted to use with non-English speaking or illiterate subjects?

Recommendation as presented:

12. Is the short form option for documentation of informed consent restricted to use with non-English speaking or illiterate subjects?

HHS [45 CFR 46.117(b)(2)] and FDA [21 CFR 50.27(b)(2)] regulations do not limit the use of the short form to these participant populations. IRBs should consider when the use of the short form is appropriate and what information should be included in the written summary.

Discussion:

A SACHRP member observed that FDA has current guidance that suggests the use of a translated consent form for non-English speaking subjects as opposed to a shorter form. Mr. Nelson said SAS plans to dig more fully into the issue of short forms later.

Mr. Borasky said these recommendations were included to “start a conversation.”

Dr. Menikoff noted that SAS is interested in using the short form. OHRP is concerned that the use of the short form may be an inappropriate workaround to avoid compliance with regulatory requirements.

SACHRP agreed to continue discussion of the short form in the context of other closely related recommendations.

A SACHRP member wondered whether a future panel might address issues related to consent for non-English speaking subjects. Mr. Borasky agreed that this would be helpful.

13. Is it permissible to use the short form option for documentation of informed consent in studies that are determined to be greater than minimal risk by the IRB?

Recommendation as presented:

13. Is it permissible to use the short form option for documentation of informed consent in studies that are determined to be greater than minimal risk by the IRB?

HHS [45 CFR 46.117(b)(2)] and FDA [21 CFR 50.27(b)(2)] regulations do not limit the use of the short form to minimal risk research. IRBs should consider when the use of the short form is appropriate and what information should be included in the written summary.

Action on this recommendation was deferred for the same reasons relevant to 12 above.

ACTION

Initially, SACHRP approved a motion to forward the second set of recommendations to the Secretary, on Documentation of Informed Consent.

Following lunch, it returned to revisit the first recommendation on assent and confirm that SAS's presentation was correct. Minor changes in wording were made at this point (reflected in the final approved version above). SACHRP then voted to approve the first set as well.

SACHRP agreed to submit approved FAQs to the Secretary without waiting for the complete set.

Return of Individual Research Results

Hank Greely, J.D., Professor of Law, Stanford University; Robert C. Green, M.D., MPH, Professor of Neurology, Genetics and Epidemiology Boston University Schools of Medicine and Public Health; Greta Lee Splansky, M.A., Operations Director, Framingham Heart Study, Boston University; Penelope Meyers, M.A., Centers for Medicare & Medicaid Services CMCS/SCG/Division of Laboratory Services

Remarks by Hank Greely

The speaker observed that not returning results has become the most popular position (“if we don’t promise to return results, we can’t be sued for not keeping our promise”). He observed that the field has been held back by confusion about the kind of “result” that is at issue. Much of the focus had been on the value of uncertain results. Today, he said, we should address issues regarding the return of results that are not uncertain. What happens when review of subject data yields findings on a condition we *know* is dangerous, such as catastrophically elevated blood pressure? Another striking example was the discovery of the presence of a genetic condition that has a very high probability of causing cancer but for which prevention measures do exist, such as the Lynch Syndrome.

Reasons for returning results in such circumstances include:

- Participants expect it.
- A legal argument can be made that researchers, like physicians, have a “fiduciary duty” to their subjects.
- Another plausible legal argument, based on contract law, holds that having accepted a gift from the participant, the researcher owes something back.
- Ethically, by accepting the subject’s help, the researcher acquires an obligation, including the “duty to rescue.”

Mr. Greely argued that clients should be told about findings based on well-established data that have a strong connection to the disease profile. He suggested limiting disclosure to those that are personally or medically actionable. Ideally, results would be conveyed to a physician, but today it is commonly difficult to locate the subject’s physician.

He urged SACHRP to endorse the idea that research subjects have a right to get back results that are scientifically and medically established as strongly associated with a serious condition for which there is an effective intervention.

Remarks by Robert C. Green: Insights from Research in Translational Genomics

Dr. Green stressed that return of significant results is an extension of clinical obligations to patients. Difficulties include the possibility of errors, the fact that “we don’t know what to do with much of the information we collect,” and the fact that to some extent the “medically actionable” criterion is context-specific. Without context, it is difficult to interpret most genomic data.

A problematic example is finding a gene associated with an increased risk of Alzheimer’s. A study found that one-third to one-fourth of potential participants do want to know this information, even though there may be little they can do to prevent the disease. Research also suggests that, when there are things people can do to prevent a disease or mitigate a condition, people will change their behavior based on study findings. For example, those who learned of their susceptibility to heart disease were more likely to increase exercise and improve their diet.

Dr. Green stressed that starting from the idea that we should return all the information we find will “just land us deeper in the minefield.”

Remarks by Greta Lee Splansky: The Framingham Heart Study Experience

The Framingham Heart Study (FHS), a population-based observational study that began in 1948, has now dealt with issues related to return of results for three generations. The study has had over 15,000 participants, of whom 900 are still living. Most participants indicated they would like to know of any findings, but do not want private companies to profit from a freely donated sample. Most would like to be notified personally.

A number of recent changes have affected the public’s interest in return of research results. These include:

- “High-throughput” technology,
- Non-hypothesis driven analyses, especially in the area of genetics,
- The increasing use of repositories and data sharing (Framingham collaborates, but insists that any reporting back to the subject comes through Framingham),
- The availability of genetic as well as phenotypic results, and
- Increasing public awareness of genetics in medicine and interest in getting feedback.

The study reports some measures routinely, such as blood pressure and cholesterol levels. It also reports incidental findings that reach “alert values” on CT scans, low levels of Vitamin B12, vertebral fractures, and brain MRIs. Additional findings that are proposed for reporting but not yet approved include Vitamin D phenotypes, Hemochromatosis, and Familial Mediterranean Fever. Possible new reports are considered when the Principle Investigator (PI) identifies new results that may benefit some or all participants. The FHS Executive Committee then considers the proposal and submits to internal committees for review and comment, including the IRB. The new report is added only if approved.

The speaker saw several instances in which reporting individual research results might not be indicated. These included cases in which the analytic validity for the genetic result has not been established, the genetic variant poses no significant and replicable risk for an important health condition, or there are no proven therapeutic or preventive interventions for the condition. Ms Splansky felt that investigators and review boards could benefit from formalized access to expertise and education in the area of evaluating new research findings for reporting individual results in observational studies. She recommended that SACHRP and OHRP do what they can to make resources available to IRBs and others involved that will help them make the right decisions.

Remarks by Penelope Meyers: CLIA and Research Results

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) address the need for registration and inspection of labs in order to ensure that all patients that receive lab results receive results that meet quality standards. Facilities register and are inspected every two years. Mandated qualifications for personnel are tied to the complexity of testing the lab performs. Obligations for CLIA certification are triggered by the following:

- Patient-specific results are reported from the laboratory to another entity, and
- The results are available to be used for health care for individual patients.

In regard to the issue of how CLIA applies when research results are returned to individuals, Ms. Meyers counseled,

- The test results are available to individuals or their health care providers for use in “providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of” the individual, and
- Test results returned to individuals are always considered subject to CLIA.

She noted that when medical laboratory test results are returned to individuals, the laboratory conducting the testing is subject to CLIA regulations.

Discussion

Overriding subject direction. One thorny issue is whether there are instances in which an individual’s choice should be overridden. Dr. Joffe asked whether issues might arise in which a subject who declined to receive results should nevertheless be informed.

Ms. Splansky observed that deciding an issue like this is much easier in an individual case than it is when trying to make general policies. Mr. Greely felt that if the “no” is unfocused (does not address the return of a particular finding), and the finding is something most reasonable people would want to know, the dialogue should at least be opened.

Dr. Green cited one study in which all subjects had to agree that findings could be communicated to a physician identified by the subject.

Subjects’ right to know. Mr. Greely saw the ethical obligation in terms of a “duty to rescue,” stemming from the nature of the relationship between the subject and investigator, rather than an issue of the subject’s “right to know.” However, Dr. Green argued that subjects have a right to learn

as much as they can about themselves – though they may not have a right to ask for information that is impossible to explain.

Active decoding and related expense. SACHRP explored the extent to which the research team should be expected to make extra effort to decode information for subjects that would otherwise not be included in the scope of the research. Dr. Green argued that the investigator should “step into the river of clinical responsibility,” in which case he or she is “wet” and has to return significant findings. Dr. Menikoff, however, emphasized the difference between having a result and “sitting on it” and having to actively decode a finding and access expert advice to understand what it means.

Results that should not be returned. Participants gave examples of instances in which it would not be helpful to return results. These included cases in which findings would alarm subjects without offering an opportunity to take remedial steps to prevent disease or in which there is little knowledge to back a conclusion about significance. For example, Mr. Forster cited a genetic finding that is understood to be a very slight indication that birth defects could be passed on to offspring. He argued that such a result could be harmful to couples, sounding an alarm unnecessarily and with little foundation. On the other hand, Mr. Greely observed that “if there is actual knowledge, it is hard not to see some obligation to convey it.”

False positives. Dr. Joffe highlighted the risk of false positives. In this light, he wondered how an IRB might approach a risk-benefit analysis for study that proposes a whole genome analysis. Additional costs for testing may be anticipated, and subjects may be worried unnecessarily. Dr. Green saw this as a complex question for which the answer can only be “it depends.” Mr. Greely noted this is especially difficult in the case of minors, when the parents will be receiving the data. For example, minors might not want their parents to know information related to late onset diseases and reproductive issues.

Importance of CLIA. Ms. Meyers stressed that a lab that is reporting results to subjects should be CLIA certified. In the case of findings the investigator feels should be reported that come from a lab that is not CLIA certified, Dr. Joffe suggested the investigator confirm the results in a CLIA-certified lab. (Others called this an “elegant solution” to the certification issue.)

Conveying results to relatives. Dr. Lux raised the question of whether the “duty to rescue” extends to third parties. Examples include people who are carrying a disease that could be transmitted to a sexual partner and people with a genetic condition likely to be shared by close relatives. Mr. Greely observed that identical twins, who share a genotype, are a good example of this concern. He believes the duty to rescue would apply in the case of a life-threatening disorder such as Lynch Syndrome.

Dr. Green commented that a “duty to warn” has been applied in a variety of situations. For example, he was legally required to notify the Department of Motor Vehicles when a patient suffered a seizure.

SACHRP recommendation options. Dr. Bierer observed that many people believe that the time has come to provide direction on this important issue. The simple answer “no” is not where anyone wants to go; rather, what is needed is a process that includes guideposts.

Mr. Greely argued strongly that SACHRP should urge OHRP to make a statement that says it is neither appropriate nor ethical for researchers to tell subjects they will never return results. Any research may lead to a situation in which there is an ethical duty to respond. Another panelist

suggested identifying guideposts for returning results, such as having a high degree of validity and being actionable. Dr. Green pointed to a model at Brigham University, which has a molecular laboratory that flags pertinent data for inclusion in medical records. Other pertinent guidance comes from the FDA and the International Committee on Harmonization (ICH).

Dr. Joffe suggested that SACHRP recommend a process for deciding on the ethical course of action for specific findings, such as a standing advisory committee.

Public Comment

No comments were offered.

Wrap-up Discussion and Adjourn

Dr. Bledsoe commented that the National Cancer Institute (NCI) held a workshop on the return of research results. The report is posted on the NCI website:

<http://biospecimens.cancer.gov/resources/publications/workshop/rrra.asp>

A SACHRP member added that the University of Minnesota will hold a workshop on May 18 that will address biobanking and develop some recommendations.

Wednesday, March 9, 2011

Remarks

Barbara Bierer, M.D., SACHRP Chair

The Chair observed that the previous day's discussion was excellent. She relayed the observation of one participant in that discussion of the phrase "return of results" is misleading, since it gives the impression that results are being returned to the natural owner.

She introduced the discussion of the return of aggregate results, stressing that the issues involved differ significantly from those involved in returning results to individuals.

Return of Aggregate Research Results

Ann Partridge, M.D., M.P.H., Harvard Medical School, Dana-Farber Cancer Institute; Maurie Markman, M.D., Vice President for Patient Oncology Services, National Director for Medical Oncology, Cancer Treatment Centers of America; Elizabeth Frank, Ed.M., Lead Patient Advocate Dana Farber Cancer Institute; Deborah A. Zarin, M.D., Director, ClinicalTrials.gov, Lister Hill National Center for Biomedical Communications, National Library of Medicine

Remarks by Ann Partridge: Returning of Aggregate Research Results to Patients

Dr. Partridge began with the observation that, for most research enterprises, no routine mechanism is in place to share study results. In the field of epidemiologic research, however, models do exist, which arose from the fact that more underserved populations were asked to give routinely to research and then felt exploited. A growing literature provides information on how to share results and how

patients may react to information, particularly for treatment trials. Data is particularly strong in regard to the return of findings related to cancer. For example, in early 2002, the Patient Advisory Board developed Guidelines for Notifying Patients About Early Closure of Cancer Clinical Trials. See <http://www.cancertrialshelp.org/patientAdvocates/policies/closingGuidelines.jsp>

Return of results could potentially improve patient/physician communication, patient satisfaction, quality of care, future health, and the patient's perception of the value of research. However, certain information may increase patient's anxiety without conferring a benefit.

Physician concerns about offering results encompass the possibility of giving "unnecessary" bad news (information that has no impact on health or treatment), concern that patients would not understand the information, the need for resources (e.g., clinician and staff time), and potential conflict between the roles of clinician and researcher.

Potential solutions to come of the issues raised include:

- Offering results, but not providing them without consent;
- Including this option in consent documents, and manage expectations by explaining what results might show;
- Providing results in writing and/or on a web site; and
- Involving patient advocates, who can provide support and resources, such as help lines, and review materials targeted to subjects.

The speaker believes a plan to share results should be included in the design of phase III clinical trials (at a minimum) and tied to ClinicalTrials.gov. While further research is warranted, she argued against waiting for more research.

Remarks by Maurie Markman: Providing Research Participants Completed Study Findings: A (Slightly) Different Perspective

Dr. Markman stressed the following basic concepts:

- Patients have a right to be informed of completed study results.
- Researchers have an absolute obligation to inform patients of study results (during and following completion of a trial) that may impact their current and/or future health. He noted that this is a moving target, since results that have no apparent medical import may be found to be significant at a later time.
- Patients do not have an obligation to be provided study results that do not impact their current and/or future health.

Findings should be expressed in terms of a chance or probability that something will occur. The ideal time to have a conversation with the subject and explain their options is at the outset of the study, when the outcome is theoretical and the patient can consider theoretical possibilities. It is more difficult at the end, when findings are no longer theoretical. However, subjects should be able to change their minds.

Remarks by Elizabeth Frank: Returning Clinical Trial Results to Patients

Speaking as a 6-year cancer survivor and patient advocate, Ms. Frank said subjects want to know the results of trials in which they participated, how results are being used, whether their participation made a difference, and what results mean to them. Results should be conveyed in plain language, and subjects should be encouraged to talk them over with their physicians.

As examples of what can be done, she cited the Cancer and Leukemia Group, which has made a major effort to summarize results of Phase III trials. See <http://www.calgb.org/>. The International Breast Cancer Study Group (IBCSG) is creating summaries of research, though it is not yet clear whether results will be translated. The Australia /New Zealand Breast Cancer Trials Group uses a different model in which a national group called IMPACT – Improving Participation in Advocacy for Clinical Trials – invites patients to participate in research forums and receive results and summaries. The Eastern Cooperative Oncology Group is trying to do this to some extent but summaries are less than transparent and hard to find.

At the Dana Farber/Harvard Cancer Center, Ms. Frank is part of a group of 16 patient advocates who collaborate with researchers through a structure integrated into the center. They are developing a pilot study aimed at developing a protocol for returning results to participants. The study will evaluate the process and materials used and attempt to estimate the time and costs required. She stressed the importance of having a “clinical collaborator” such as Dr. Partridge to make an effort like this work.

Remarks by Deborah A. Zarin: Overview of ClinicalTrials.gov Reporting Requirements

The ClinicalTrials.gov site reports summary results at the end of trials, targeting information to those able to understand the medical literature. No discussion is provided. The service is designed to complement rather than replace journal articles.

In making results available, Dr. Zarin stressed the difficulty of getting accurate information. Even harder is arriving at a summary that conveys results fairly. A trial may have over 100 primary and secondary outcome measures. Determining what will be relevant to participants is no easy task. In addition, it can be very complicated to express a primary outcome measure in lay language. Adding to the difficulty is the fact that investigators are usually unable to craft dispassionate and objective summaries of their own research.

Discussion: Return of Aggregate Research Results

Role of the IRB. Participants differed on whether the IRB should have a role in reviewing plans to share research results. Dr. Joffe was concerned about “mission creep.” Dr. Partridge said that in her experience, if results are shared as a routine part of a study, the IRB should approve this as an intervention. Dr. Markman felt it was the IRB’s role to ensure that the communication with subjects actually occurred if it was proposed as part of the study.

Double blind studies. Dr. Strauss argued against “letting the perfect be the enemy of the good.” He held that IRBs should be integrated into the process appropriately and provide some level of oversight. In some studies, participants do not learn their treatment assignment until the data set is locked; this denies them access to information that might have a bearing on their medical care (for example, what drugs they have been exposed to). Pertinent information that should guide care should not be withheld. Results should be released, but with caution and some degree of IRB oversight. He

stressed that it is possible to release results using a “reverse double blind” in which members of the research team never know what arm of a study subjects were part of.

Return of results and level of risk. The Chair suggested it might be worthwhile to develop some optimal models for return of results that would apply in low, moderate, and high-risk situations.

Communicating results accurately. Dr. Leiden pointed out that different studies may reach different conclusions. Knowing what occurred to a particular group of subjects in research is distinct from understanding the state of research on the issue. Dr. Zarin agreed; she said the findings of any trial must be interpreted in the light of everything else that is known. A particular study is “one link in a big chain.”

As a “baby step,” Dr. Zarin suggested simply citing an available source such as a published journal article or information on ClinicalTrials.gov. She pointed out that potential harm can result when subjects receive contradictory information, or information that appears contradictory to them.

Relaying findings. Ms. Frank stressed that a go-to person who can explain the findings should be part of any responsible plan for releasing study results. Even so, Dr. Partridge observed that studies show that patients only hear about half of what a physician tells them.

Dr. Ross stressed that primary care physicians are unlikely to have the depth of knowledge in specialty areas to accurately relay research findings and place them in context. The problem is even more complex when dealing with patients who have limited education or literacy. Dr. Strauss suggested that a study team member, preferably one involved in the consent process, could be a resource for subjects in understanding results.

Dr. Leiden stressed the importance of peer review to ensure that summaries given to subjects are really accurate. Dr. Gibbons suggested that for FDA-approved studies, the FDA advisory structure might become a way of ensuring accurate communication.

Mr. Forster expressed concern about the cost involved in relaying results and speculated that this may be a reason it does not occur routinely. Another SACHRP member noted that the Children’s Oncology Group had a budget of \$250,000 to create an infrastructure to relay results to subjects (later unfunded). Dr. Gibbons suggested that the cost of communications with the subject must ultimately become part of the cost of doing business.

Dr. Lux, ex officio representing the Environmental Protection Agency, observed that return of results is relatively routine in regard to environmental issues. The following question is used to determine what results should be returned: “Would a reasonable person alter his or her behavior in any way based on this information?”

Therapeutic misconception. While Dr. Markham was concerned that communicating findings to patients might underline the “therapeutic misconception” in which subjects view clinical trials as a form of treatment, Dr. Joffe and Dr. Strauss saw this communication as a way of treating the subject as a partner in a study. It is also consistent with expressing gratitude to the subject for his or her help. Ideally, Dr. Joffe said, this type of communication would be only part of a broader plan of ongoing communication. He noted that journals that include lay summaries are providing an important public

service. Dr. Strauss added that communication helps keep subjects engaged in trials and is equally important in trials that are not treatment oriented.

Changing medical knowledge. Dr. Gibbons commented that the standard of care in his field, oncology, can easily change every 12 months, and such changes are often hotly debated. User-friendly contextual information is essential if study results are being reported, especially when extrapolating from study results to the implications for care. In order to help a subject answer the question, “what should I do next?” someone would have to synthesize not only the findings of the one trial in which the subject participated, but all the clinical trials that relate to the patient. Dr. Zarin agreed, explaining that this is the reason that ClinicalTrials.gov presents clinical data in table form and includes links to other information.

Dr. Ross pointed out that the real meaning of data may not be apparent for 10-20 years, if then. It is often unclear which is really the “best” study arm when the study concludes.

Asking participants to express preferences. SACHRP members differed on the issue of when subjects should be asked to express a preference on results. Some held this should be part of the consent process. However, Ms. Frank felt it was too early for subjects to make a meaningful commitment one way or the other; subjects are still in a learning process and their view could change. Instead, she suggested simply letting them know that at a future point they will be asked whether or not they wish to be informed of research findings.

Implications for protocol review. Dr. Pritchard expressed concern about the implications of the return of results for the IRB’s consideration of study risks and benefits. If a small number of subjects are adversely impacted, how would this affect the analysis of risks? An IRB member might argue that under 45 CFR 46.111(a)(1), risks should be minimized, and that therefore the plan to return results should be dropped. He wondered if IRBs would need guidance about how to balance the requirement to minimize risks with the determination that benefits outweigh risks, as well as the understanding of what constitutes sound research design.

Report of Subcommittee on Harmonization (SOH)

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

Co-Chairs reported on the work of the subcommittee to date and presented proposals in four areas (Attachments A-D). They requested SACHRP’s response but said the proposals were not yet ready for a vote. Mr. Forster asked for SACHRP’s take on whether or not SOH was headed in the right direction. These areas included recommendations relating to:

1. Minor changes in research that can be reviewed through an expedited procedure;
2. Deviations from the planned protocol (a far more complicated problem than SOH originally envisioned);
3. Early processes in research (e.g., subject identification and recruitment, and other activities that may occur in the phase prior to the consent process); and
4. The applicability of FDA regulations, especially in regard to studies that do not clearly involve drugs and devices.

Minor Changes in Approved Research that Can be Reviewed through Expedited Procedure

For a copy of draft recommendations and analysis presented at the meeting, see Attachment A to these minutes.

Co-Chairs presented alternative definitions of minor changes in approved research that can be approved through an expedited process. Mr. Forster noted that this was the subject of a SACHRP panel two years ago (March 3-4, 2009), but did not result in any recommendations. Sources for the definitions SOH sought to harmonize included OHRP training materials; an OHRP letter to the Cancer Therapy Evaluation Program (CTEP), an office of the National Cancer Institute; and FDA. The committee proposed the following definition:

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

They felt this definition was preferable to the three examples of possible definitions that were included in Attachment A, which was distributed at the meeting. Those were:

Example I

Minor changes in approved research that can be approved through expedited review procedures are minor changes that neither increase risk (FDA guidance) nor materially affect the assessment of the risk/benefit ratio (OHRP guidance).

Example II

Minor changes in approved research that can be approved through expedited review procedures are minor changes that do not materially affect the assessment of the risk/benefit ratio

Example III

Minor changes in approved research that can be approved through expedited review procedures are changes that do not materially affect the criteria for IRB review at 45 CFR 46.111 and 21 CFR 56.111.

Discussion

Although some SOH members were worried that the term “materially” introduced too much “wiggle room,” Dr. Bierer felt it was extremely important and must be included in the definition. Trivial changes, she said, should not be brought to the full IRB Board. Expedited research could still come to full board review. Dr. Strauss challenged the Co-Chairs to operationalize the term “materially” and explain how it differs from words such as “significantly.” Mr. Barnes said “materially” is a broader term than “significantly”; it refers to something that might influence the judgement of any reasonable person.

Dr. Joffe was initially drawn to the third example. If the definition were limited to risks and benefits, he suggested, equitable subject selection might not be fully addressed. Also, commentary would need to remind people that risks and benefits should include changes to the quality of science. However, informed consent, provisions for monitoring subject safety, and protections for privacy would be included.

Dr. Strauss asked what operational barriers would apply depending on what definition was adopted. Mr. Forster said there were no significant differences.

Dr. Bierer suggested that the use of the word “assessment” in Example I is valuable. Mr. Forster said this language comes from the OHRP Guidance. SAS previously submitted recommendations related to risk analysis that are highly relevant (see SACHRP minutes for March and July, 2007). A member observed that a change that increases risk cannot be considered minor.

Usefulness of cases or examples. Dr. Forster asked whether or not cases should be developed by SOH. He suggested that simply giving clearcut cases might be most helpful in analysis. He noted that FDA’s guidance on nonsignificant and significant risks for devices and envisioned a similar set of examples related to expeditable review. Dr. Bierer said that cases were significant for the guidance to have a palpable impact. However, she noted that there is little “black and white” in the real world.

Comments on examples. SOH gave several examples of minor changes that are not on the list of changes that can be expedited. These were discussed as follows.

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 procedure that is minimal risk to a research study, when that procedure is not on the expedited list. Two examples, low dose radiation procedures and drawing 3-5 blood draws from an in-dwelling catheter.*

SOH understood these two examples to reflect current OHRP policy. Dr. Bierer asked why the two examples should be repeated if they are already included in OHRP guidance. Mr. Forster explained, and an OHRP spokesperson confirmed, that these statements reflect OHRP’s position but this position has not been formalized in guidance.

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:*
 - a) *Change in the individual who will do statistical analysis.*
 - b) *Consent form wording changes – e.g., “nausea” changed to “nausea and stomach upset,” or fixing a run-on sentence or a comma.*
 - c) *Change of the sponsor name on the protocol when the sponsor is purchased by another sponsor.*
 - d) *Old case report forms are replaced with new ones, and the change is noted in a revised protocol.*
 - e) *Adding the word “approximately” to the table of the lab test schedule.*

SACHRP members did not agree that all these examples necessarily represent minor changes. Dr. Strauss observed, in reference to (a) that if the researcher plans to replace a world-renowned statistician with a high school student, there may be cause for concern. The default position should be that an individual will review this type of change, however. Dr. Bierer stressed that guidance should emphasize the fact that there is a difference between assigning the level of review and approving the change. Dr. Menikoff agreed with Dr. Strauss that the examples cannot stand alone as guidance because they are not sufficiently specific and contextualized. The example regarding the statistician might read instead “replacing a biostatistician with a similarly qualified biostatistician.”

Mr. Barnes suggested an introduction that clarifies that the examples are not necessarily expeditable. He thought this would be easier than developing exhaustive examples that are not very useful as guidance. Dr. Strauss agreed this might work.

SACHRP members agreed that example (b), which comprises minor wording changes, was noncontroversial. In regard to (c), the change might not be minor if a conflict of interest developed as a result of the change in sponsor. Mr. Barnes suggested the example might refer to a change in a sponsor that “poses no material change to the potential for conflict of interest.” Example (d) was not discussed. Example (e), the addition of the word “approximately,” was noncontroversial.

4. *New media advertisements that are submitted after the research is approved, such as newspaper or radio advertisements.*

This might be qualified by wording such as “consistent with previously approved advertisements.” So qualified, the change was noncontroversial.

5. *A change to the number of subjects one investigator in a multicenter study will enroll, e.g., from 20 subjects to 30 subjects in a study involving 1,000 subjects.*

An FDA spokesperson said this could be a problem if the distribution of sites changed as a result of the addition of subjects. Co-Chairs explained that a single site would be assumed for the purpose of this example.

6. *Changes/serial additions to total subject “n”. Presumably a small increase in the number of subjects is acceptable for review and approval through the expedited process, such as a 1% increase or a 10% increase. However, is there a difference between a 10% increase in a multicenter study that is projected to enroll 30 subjects versus a 10% increase in a study projected to enroll 3,000 subjects? Is a 100% increase a minor change?*

Mr. Forster noted that every new subject increases the risk or that each new subject is simply exposed to the same risk, so the total risk does not change.

A SACHRP member said the reason for the change would be important, and FDA would need to review it. Dr. Bierer suggested deleting the change or using a decrease instead. Dr. Joffe noted that a decrease might affect the quality of the science.

Mr. Barnes suggested instead specifying that the example refers to research that is not regulated by FDA. Another consideration would be whether or not the research is minimal risk.

7. *Change in study personnel (study coordinator / nurse / technician / recruiter), e.g., person leaves the institution and is replaced.*

Dr. Bierer suggested qualifying this as an “equivalently trained” replacement. With this change, it was not controversial.

8. *Change in PI, e.g., PI leaves the institution and a new PI takes over.*

SACHRP members agreed that, assuming the new PI is similarly qualified, this is expeditable. Dr. Menikoff was not convinced; he stressed the importance of the PI. He was concerned about giving a single person the power to determine that the new PI really is similarly qualified. He argued that the examples should be clear enough that the restraints on IRB discretion are clear; without sufficient clarity, they could mislead the IRB. Dr. Strauss said the fact pattern will determine whether or not the full board needs to review this change.

9. *Adding a new investigator at a new site for a multi-site study (central/independent IRB issue).*

Dr. Bierer was concerned about a distant IRB assessing the credentials for a site with which it is not familiar.

10. *A study with no prospect of direct benefit to the subjects involves three endoscopies. The investigator decides that she needs only two endoscopies to reach her conclusions, and submits an amendment to drop the third endoscopy. Is this a minor change in previously approved research?*

Dr. Bierer observed that this apparently decreases risk. Dr. Strauss commented, however, that the procedure might in some cases decrease the quality of the science. Dr. Ross agreed that the implications of the change might be critical, given that the investigator must have built a case that three endoscopies were required.

11. *In a coronary stent study, an amendment is submitted to extend follow up only from 12 to 60 months.*

This was considered a minor change.

Adding aims. Dr. Strauss noted that some amendment requests include an additional aim. For example, an investigator is doing research on Alzheimer’s and realizes that the study might be able to predict something else. The added procedure is minimal risk, but the aim was not considered by the Board. He wondered whether this would be expeditable. If the criteria to use is limited to an assessment of risks and benefits, Mr. Forster suggested it was expeditable.

Dr. Ross argued that a change to the aim would seem to require at least a new amendment. Dr. Strauss agreed, explaining that his question was intended to question whether risks and benefits provided an adequate framework. Mr. Forster agreed that most IRBs would consider this a “material” change.

Dr. Joffe argued that a change in a tertiary aim that involves no change in the experience of the subjects should be expeditable. Mr. Forster responded that this is a relatively rare change. Others said they saw this type of change frequently.

Social behavioral examples. Dr. Bierer stressed the need for examples from social and behavioral science.

Changes that add up. An ex officio noted that a series of small changes can add up to a significant change. Mr. Forster agreed this was an issue, but said SOH found it complicated to convey. Mr. Barnes said this might be a reason to frame the examples with a reference to the need to consider the protocol's history.

Deviations from the Planned Protocol

For a copy of draft recommendations and analysis presented at the meeting, see Attachment B to these minutes.

Mr. Forster said the intended focus is a protocol with inclusion/exclusion criteria and in which small deviations are proposed. He noted that examples in this area proved unexpectedly controversial when discussed by SOH members. There is inconsistency in how IRBs determine what level of deviation is permissible (for example, including a subject who is 61 rather than the stated upper limit of 60) and at what point deviations are beyond the permissible limit. SOH argued over what constitutes a planned protocol deviation and whether such deviations should be prohibited on a blanket basis. SOH determined that a planned protocol change is one that the investigator has control over and can choose not to make.

Regulations on the topic are inconsistent. De facto guidance from OHRP indicates that all such changes are changes in research and require IRB review. FDA's device regulations indicate that changes that do not affect the integrity of the research or the rights, safety, or welfare of the subject are permissible and do not require permission from the IRB or FDA; a "safe harbor" is available for such changes. The ICH says that the IRB must have procedures that specify no changes can be made except for minor changes and deviations required for subject safety.

One approach to the issue would be to define a "safe harbor" for the types and level of deviations that can be approved by the Chair. Another approach is to identify this type of change as always constituting a change in research (unless the study is not being conducted under an FWA). Dr. Joffe noted that amending a protocol for a multi-site study can be incredibly time consuming, so exceptions for individual sites might be needed.

One way to operationalize this type of change is that the investigator would have discretion to make a one-time deviation, but would have to report all such deviations during continuing review. Dr. Strauss expressed concern that risk could be affected by some investigator decisions that the investigator considers immaterial. Mr. Barnes said SOH was concerned that a number of deviations may add up and change the risk calculus. On the other hand, small deviations come up "every day" and many investigators see the paperwork involved as seriously impairing their work.

Dr. Strauss added that "infantilizing" the investigator is problematic. At the same time, from a philosophical standpoint, it is not clear where and how to draw the line. Mr. Barnes rejoined,

however, that investigators are routinely trusted about matters far more important than a subject's birthday.

Mr. Barnes stressed that whether in a clinical or social-behavioral study, a person who is almost qualified for a study in which subjects are hard to find may be standing in front of the investigator and will be lost if the investigator has to file an amendment. Mr. Forster said there is no clear guidance to IRBs on this situation.

Dr. Gibbons thought it would be possible to identify the type of changes that could be made at the discretion of the investigator and document them in the IRB's manual of procedures. Endless "one-off" amendments, he said, are in no one's interest. Dr. Bierer said SOH had discussed the option of identifying an acceptable range. However, when investigators get to the edges of whatever is allowable they may still want to push. Another consideration is that the same incident might be treated differently depending on conditions.

Early Processes in Research

For a copy of draft recommendations and analysis presented at the meeting, see Attachment C to these minutes.

Mr. Forster observed that FDA has provided guidance related to recruiting subjects and administering screening tests prior to enrollment that IRBs use frequently (see Appendix 1 and 2 of Attachment C). In 2004, OHRP, FDA, and OCR issued joint guidance that says that due to the definition of "human subjects," the IRB should approve a waiver of consent to cover the research period up to consent. Mr. Forster observed that most IRBs are not doing this. SOH believes it would be helpful for OHRP to adopt guidance similar to FDA's that relates to recruitment, review of medical records, and other areas and perhaps seeks harmony with HIPAA.

Mr. Barnes said one approach would be including a description of recruitment in the protocol that satisfies the IRB. Dr. Bierer stressed that these procedures are reviewed by the IRB. Protocols must fully describe whatever is done during the recruitment phase of the research. Dr. Strauss saw the review of medical records as in a different category from advertising, screening and dialogue by subjects. He suggested that some type of consent should be required prior to a one-hour screening process. Dr. Bierer noted that the IRB would have the discretion to make this determination.

Dr. Joffe raised the issue of a subject who ultimately does not consent to research. An FDA representative said that FDA's position is that if you are doing nothing beyond routine clinical practice, the consent process is not needed. Consent occurs when additional procedures are performed that are not routine. However, the individual should still be counted as a subject, even if he or she withdraws.

Applicability of FDA Regulations

For a copy of draft recommendations and analysis presented at the meeting, see Attachment D to these minutes.

Discussion points included:

- Registries are an example of an activity that might or might not fall under FDA regulations.
- If surgeons are interviewed to determine how to calibrate a device, it is not clear whether that would make FDA regulations applicable.
- The intent of an activity becomes very important.
- Dr. Bierer commented that her IRB would not know how to apply the guidance as presented. Others agreed.
- The questions were not seen as helpful.

Discussion of Recommendation on Deception in Research

*For a copy of draft recommendations and analysis presented at the meeting, see **Attachment E** to these minutes.*

Dr. Strauss observed that the draft laid out the issues well and made it clear that the use of deception is something to take seriously. Dignitary harm and shame may occur when subjects find they have been deceived. He noted that the American Psychological Association (APA) has guidance on this subject. For convenience, **Attachment F** to these minutes excerpts relevant passages.

SACHRP members concluded that placebos should probably not be considered a form of research involving deception, since subjects do know they may receive a placebo. The issue of when to reveal to subjects in which study arm they participated is also important but separate. Informed consent for such studies does include an explanation of what blinded studies involve. There are ethical issues, however, especially in regard for ensuring standard of care; SACHRP may wish to address this subject in the future.

SACHRP members made the following additional points in discussion:

- It is not clear when waiver criteria apply.
- The default position should be to require debriefing in such studies; not providing a debriefing should require justification. The bar to not doing so should be “very high.”
- The aim of any SOH recommendations would be to “marry” the regulatory framework with ethical issues.
- There may be special sensitivities involved in deception research in multinational trials. While Mr. Forster said he was unaware of this type of research occurring outside academic settings, others thought it might be used, for example in regard to “homeland security.”
- It is important to ask social/behavioral researchers for comments on any recommendations in this area.

Dr. Menikoff stressed the importance of receiving input from social behavioral researchers as recommendations are finalized.

Public Comment

Public comment was invited, but none was offered.

Wrap-up Discussion and Adjourn

The meeting adjourned at 4:30 pm.

Attachment A. Definition of a Minor Change in Research

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.

SOH also recommends that the joint guidance include examples to illustrate their position.

Following are four possible recommendations for a definition of a minor change in approved research that can be reviewed through the expedited review that FDA and OHRP could jointly consider.

Example I

Recommendation as presented orally:

Minor changes in approved research that can be approved through expedited review procedures are minor changes that neither increase risk (FDA guidance) nor decrease benefit.

As revised (and as presented in written document used at the meeting):

Minor changes in approved research that can be approved through expedited review procedures are minor changes that neither increase risk (FDA guidance) nor materially affect the assessment of the risk/benefit ratio (OHRP guidance).

Commentary: This approach ties the definition to existing FDA and OHRP guidance. This approach has several advantages. It allows FDA and OHRP to avoid consideration of new policy. It is familiar to IRBs. Finally, if issued in a joint guidance document then IRBs would have the benefit of knowing the expectations of both agencies. This approach also has several disadvantages. It still leaves two different definitions in existence. It does not take into account the OHRP Memorandum to the National Cancer Institute Regarding IRB Review of Protocol and Informed Consent Changes, dated September 29, 2008.

Example II

Minor changes in approved research that can be approved through expedited review procedures are minor changes that do not materially affect the assessment of the risk/benefit ratio

Commentary: This approach adopts existing OHRP guidance. It has several advantages. It allows OHRP to avoid consideration of new policy. It is familiar to IRBs. It standardizes the definition. Finally, it limits the consideration solely to the issue of risk and benefit, which makes it simple to apply. This approach also has several disadvantages. It requires FDA to change its policy. It does not take into account the OHRP Memorandum to the National Cancer Institute Regarding IRB Review of Protocol and Informed Consent Changes, dated September 29, 2008.

Example III

Minor changes in approved research that can be approved through expedited review procedures are changes that do not materially affect the criteria for IRB review at 45 CFR 46.111 and 21 CFR 56.111.

Commentary: This approach the advantage of capturing all of the criteria for IRB approval beyond solely risk and benefit. Thus, any change that materially affected these criteria would be sent to full board. This approach also has several disadvantages. It is a fairly vague standard, in that the eight criteria for IRB approval are quite broad, so that any action could theoretically affect one of the criteria. Thus expedited reviewers would spend a lot of time deciding whether the change “materially” affected one of the criteria. Because of the breadth of this approach, there would be variability in application.

In addition to these examples, there are two other issues that SACHRP recommends.

Minor changes in approved research that can be approved through expedited review procedures are [any of I through III above]. Medical procedures that are added as a change in research must be on the current list of expeditable categories published in the Federal Register.

Commentary: This example could be ancillary to any of examples I through III above. The issue to consider is whether it helps to add the provision that changes that the addition of a procedure must be within the scope of the expedited list.

Finally, SACHRP recommends that the joint guidance provide examples of the kinds of changes that qualify as minor changes in approved research. Here are examples that we can consider:

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

Adding a new procedure that is minimal risk to a research study, when that procedure is not on the expedited list. Two examples, low dose radiation procedures and drawing 3-5 blood draws from an in-dwelling catheter.

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 individual who will do statistical analysis.
- Consent form wording changes – e.g., “nausea” changed to “nausea and stomach upset,” or fixing a run-on sentence or a comma
- Change of the sponsor name on the protocol when the sponsor is purchased by another sponsor.
- Old case report forms are replaced with new ones, and the change is noted in a revised protocol.
- Adding the word “approximately” to the table of the lab test schedule.

A new media advertisements that are submitted after the research is approved, such as newspaper or radio advertisements.

A change to the number of subjects one investigator in a multicenter study will enroll, e.g., from 20 subjects to 30 subjects in a study involving 1,000 subjects.

Changes/serial additions to total subject “n”. Presumably a small increase in the number of subjects is acceptable for review and approval through the expedited process, such as a 1% increase or a 10% increase. However, is there a difference between a 10% increase in a multicenter study that is projected to enroll 30 subjects versus a 10% increase in a study projected to enroll 3,000 subjects? Is a 100% increase a minor change?

Change in study personnel (study coordinator / nurse / technician / recruiter), e.g., person leaves the institution and is replaced.

Change in PI, e.g., PI leaves the institution and a new PI takes over.

Adding a new investigator at a new site for a multi-site study (central/independent IRB issue).

A study with no prospect of direct benefit to the subjects involves three endoscopies. The investigator decides that she needs only two endoscopies to reach her conclusions, and submits an amendment to drop the third endoscopy. Is this a minor change in previously approved research?

In a coronary stent study, an amendment is submitted to extend follow up only from 12 to 60 months.

Attachment B. Deviations from the Planned Protocol

In the area of human subject protections, there is wide divergence among institutions, sponsors, investigators and IRBs regarding the definition, the acceptability, and procedures for reviewing planned protocol deviations. The purpose of this recommendation is to identify various issues relating to planned protocol deviations and to provide HHS with a summary of the issues sufficient to provide consistent direction to the regulated community. SACHRP recommends that FDA and OHRP release a joint or a coordinated guidance document providing the regulated community with direction on addressing this issue.

Therefore, this recommendation will address:

Current Situation
Defintion/categorization
Existing regulations and guidance
Recommendations
Points to consider

Current Situation

Oftentimes in the conduct of research, investigators and other parties involved in the conduct of research wish to deviate from the written protocol. For the purpose of this recommendation, these deviations will be called “planned protocol deviations.” A planned protocol deviation is a situation in which an investigator or other party makes a conscious decision to not follow some aspect of the written protocol. Sponsors, institutions, IRBs and investigators have widely differing practices regarding the definition, the acceptability, and review of planned protocol deviations. For the purposes of this recommendation, we are considering a deviation performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR 46.103(b)(4) and 21 CFR 56.108(a)(4) to be a separate class of event. The focus of this recommendation is planned protocol deviations that are implemented for reasons other than elimination of an apparent immediate hazard. This is further discussed below.

Categorization

“Planned protocol deviation” refers to a situation in which an investigator or other party makes a conscious decision to not follow the written protocol. There can be many reasons. These deviations may or may not adversely affect the safety, rights and welfare of the research subject, and may or may not adversely affect the scientific validity of the research. Probably of the most common example of a planned protocol deviation is a deviation from the inclusion and exclusion criteria of a protocol in order to allow the enrollment of a subject who otherwise meets those criteria. However, there are other types of planned protocol deviations.

Examples:

- Lab criteria: One test is out of range for a benign reason (increased alkaline phosphatase, LDH or SGOT in a runner, or increased bilirubin in a person with Gilbert Syndrome).

- Age criteria: Age range is 20-60, but the subject “will be 20 in two months” or “turned 61 last week.”
- Timing of study visit: For example, a planned vacation interferes with the schedule of study visits. At the time of enrollment, the investigator realizes that due to the vacation the subject will miss one out of 12 regularly scheduled two-week study visits.
- Timing of washout: For example, a planned vacation interferes with a washout period. Shortening the wash-out period from 14 to 12 days will allow the subject to be enrolled.
- Pre-treatment exceeded: Entry criteria specify that only X amount pre-treatment of disease is acceptable, but potential subject has exceeded it.
- Drug allergy: Person is allergic to one of the study medications, but is “such a good candidate in all other respects” that the subject can be enrolled on a substitute drug or none at all.

In these situations, the investigator or another party plans to deviate from the protocol, and the proposed deviation is within their control. Furthermore, these deviations are not made to eliminate an apparent immediate hazard to subjects.,

Other Events Distinct from Planned Protocol Deviations

Planned protocol deviations need to be contrasted from four other types of events: 1) Deviations from the protocol performed to eliminate apparent immediate hazards to the subject, 2) unplanned deviations from the protocol that are identified before they occur but cannot be prevented, 3) unplanned deviations from the protocol that are discovered after they occur, 4) unanticipated problems, and 5) Serious or continuing non-compliance.

1. *Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR 46.103(b)(4) and 21 CFR 56.108(a)(4):* These differ from planned protocol deviations as described in the examples above in that these types of deviations are performed in reaction to a perceived hazard, such as the occurrence of an unexpected serious adverse event. As such, they are done to prevent harm to subjects in a time sensitive situation.
2. *Unplanned deviations from the protocol that are identified before they occur, but cannot be prevented:* An example is a research subject who is on a business trip and calls the investigator to announce that she is stuck in a snow storm and cannot be at the study visit scheduled for the next day. The investigator knows in advance that the deviation will occur, but it is not under the investigator’s control, and it is not the investigator’s intent to deviate from the protocol.
3. *Unplanned deviations from the protocol that are discovered after they occur:* An example is the coordinator’s failure to conduct a protocol-required blood test on two subjects. These deviations from the protocol are not planned or intended by the investigator. These events should be analyzed as to whether they constitute an unanticipated problem involving risks to subjects or others, or serious or continuing non-compliance.

4. *Unanticipated problems under 45 CFR 46.103(a)(5) and 21 CFR 56.108(b)*. Unanticipated problems include events such as unexpected side effects (physical harms) or inadvertent breaches of subjects' private medical information. A finding of "unanticipated problem" is a regulatory requirement applied to certain classes of events. A planned deviation from the protocol could theoretically qualify as an unanticipated problem. However, the majority of unanticipated problems do not involve a planned deviation from the protocol.
5. *Serious or continuing non-compliance under 45 CFR 46.103(a)(5) and 21 CFR 56.108(b)*. A finding of "serious or continuing non-compliance" is a regulatory requirement applied to certain classes of events. A planned deviation from the protocol could qualify as serious or continuing non-compliance. However, not all planned deviations qualify as serious or continuing non-compliance, and serious or continuing non-compliance includes many other events besides planned deviations from the protocol.

Recommendation for Guidance

SOH believes that OHRP and FDA should issue consistent guidance on this issue, or at the very least issue guidance describing the difference between the regulations and the interpretation of those regulations. SOH recommends that all planned protocol deviations be treated as changes in research (i.e., amendments to the protocol) requiring all of the administrative steps as a change to the written protocol, including prior IRB review and approval.

OHRP has stated verbally that it considers all deviations to be changes in research that need prior IRB review under 45 CFR 46.103(b)(4). The FDA IRB and drug regulations both use language similar to the Common Rule regarding changes in research. The FDA ICH guidance can be interpreted to say that all changes in research and deviations need prior IRB review. However, the outlier is the FDA device regulations, which specifically state that "prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required." However, FDA could issue guidance stating that it considers as best practice that all planned protocol deviations are changes in research that require prior IRB review, even for devices. (Alternatively, as discussed below as Approach C, the guidance could note that the device regulations are different, and that for device studies that are not funded by HHS or otherwise under the jurisdiction of HHS, a different standard for reporting planned protocol deviations is acceptable.)

There are several advantages to this approach. First, it involves a minimal amount of regulatory interpretation, and is easy to understand. Second, it provides a single standard across Health and Human Services (HHS) and FDA regulated research. This is valuable, because often research involving FDA regulated products is funded by or otherwise under the jurisdiction of HHS, and having a single standard to apply reduces confusion. Third, it is protective of subjects, in that it requires prior IRB review and approval of any planned protocol deviation.

There are also several disadvantages. First, it is likely to increase the administrative burden on IRBs, investigators and other parties, as each proposed planned protocol deviation will require IRB review. This runs counter to the current OHRP and FDA efforts to reduce the administrative burden on IRBs, including the OHRP and FDA guidance documents on unanticipated problems [citation], the OHRP

and FDA draft guidance documents on continuing IRB review [citation], and the OHRP draft guidance on IRB approval with conditions [citation]. In all of these draft and final guidance documents, OHRP and FDA have taken steps to ease the administrative burden on IRBs. A third disadvantage to this approach is that it creates a lack of symmetry between events that are reported *before* being done as opposed to those that must be reported *after* being done. Many planned protocol deviations would not qualify as an unanticipated problem or as continuing or serious non-compliance if they were not reported before being done. Therefore, the same event would be held to different reporting standards depending on whether the analysis of reportability is performed before versus after the event occurs.

Alternative Approaches to Guidance

SOH would also like to note that we also considered two distinct approaches in addition to the recommendation above. In the end, we believe the recommendation above is preferable, but in order to preserve the consideration of issues for the Secretary's benefit, we have kept the analysis of these other approaches.

Approach B: Create a class of deviations that are not changes in research and are not deviations made to protect the life or physical well being of the subjects:

This approach is based on the FDA device regulations, which specifically state that “prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required.”

In order to apply this approach to the Common Rule and to the FDA IRB and drug regulations, OHRP and FDA would have to issue guidance which distinguishes deviations that meet the FDA device regulatory standard from changes in research and from deviations enacted to eliminate apparent immediate hazards to the subject. However, 45 CFR 46.109(a) states that “an IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.” A guidance document could state that planned protocol deviations that do not affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects are not “research activities covered by this policy.” This approach provides a regulatory basis to avoid the interpretation that all planned protocol deviations are changes in research that require prior IRB review and approval because there is no other regulatory classification available.

FDA could issue joint or concurrent guidance which relies on this same regulatory basis for interpretation of the FDA IRB and drug regulations. However, FDA guidance must also provide an analysis of FDA ICH guidance referencing deviations in order to avoid inconsistency. ICH section 3.3.7, regarding IRBs, states that IRBs must have procedures,

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

ICH section 4.5.2 has nearly identical language regarding investigators duties. In order to harmonize approach B with this existing FDA ICH guidance, FDA could clarify that planned protocol deviations that do not affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects are comparable to the minor changes described in ICH that do not need prior IRB review, i.e., “logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).” ICH currently only addresses changes in research that do not require prior IRB review, but is silent regarding any comparable class of deviations that do not require prior IRB review.

Approach B has several advantages. First, as with approach A, it provides a single standard across Health and Human Services (HHS) and FDA regulated research. This is valuable, because often research involving FDA regulated products is funded by or otherwise under the jurisdiction of HHS, and having a single standard to apply reduces confusion. Second, approach B reflects a common, but not universal, approach to planned protocol deviations, and thus reflects status quo at those research sites. Third, approach B will result in less regulatory burden for IRBs, so that they can concentrate on important issues such as review of protocols and analysis of unanticipated problems. This is in line with the recent OHRP and FDA guidance on unanticipated problems, which was intended to reduce unnecessary regulatory burdens on IRBs. Fourth, this approach provides more symmetry in the level of review necessary between events that are reported *before* being done as opposed to those that must be reported *after* being done. While the standards would not be identical, an event that did not need to be reported as a minor planned protocol deviation would most likely also not qualify as an unanticipated problem or serious or continuing noncompliance.

Approach B also has several disadvantages. First, approach B provides a lower level of subject protection, in that prior IRB review is not required for every planned protocol deviation. However, if investigators and other parties can be trusted to submit unanticipated problems appropriately, then they can also be trusted to submit planned protocol deviations that do affect the scientific soundness of the plan or have the potential to adversely affect the rights, safety, or welfare of human subjects. Second, approach B it is not as simple as the bright line approach of stating that all planned protocol deviations are changes in research that need prior IRB review.

Approach C: Inconsistent guidance

Finally, it is worth noting that OHRP and FDA could take a third approach, and issue guidance that explains that for research under the Common Rule, and for research conducted under the FDA drug regulations, all planned protocol deviations must have prior IRB approval, while for research that is not under the Common Rule but is under the FDA device regulations planned protocol deviations that do not affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects do not need prior IRB review. This has the advantage of relying on currently existing regulations, but has the disadvantage for failing to achieve a harmonized and consistent approach to this issue. However, even this approach is preferable to the current situation where there is not written guidance for the regulated community and substantial inconsistency regarding the acceptability, definition, and administration of planned protocol deviations.

Additional points to consider

Any guidance on this topic from OHRP should include analysis and examples for social/behavioral research.

Consideration should be given to whether there are any HIPAA issues. It is not apparent that there are any. But, is a new authorization necessary if the deviation affects privacy rights? What if authorization is separate from consent? (As a broader issue, is re-authorization ever necessary, and if so when?)

It may be appropriate and useful for the guidance to discuss the drafting of protocols, with emphasis on the appropriate level of specificity in inclusion/exclusion criteria and other sections to ensure scientific validity but at the same time as allowing sufficient flexibility.

It might be useful to include in the guidance a definition of what constitutes a change in research. For example, it may be useful to define “changes in research” as changes to written materials, while deviations do not involve a change to the written research documents.

Attachment C. Early Processes in Research

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. Both FDA and OHRP have addressed this issue through guidance. HIPAA/HITECH extensively addresses activities that are conducted prior to the subject's providing consent to participate in research through regulation rather than guidance.

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 OCR regarding HIPAA. In that guidance, OHRP recommended that IRBs conduct a waiver of consent under 45 CFR 46.116(d) for all activities 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. There are several difficulties with this approach.

- It does not serve any practical purpose in protecting the rights and welfare of human subjects. It is often necessary to identify potential subjects to recruit for research through either records review or contact through 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 16.116(d) does not address these ethical issues. Rather, it is a pro forma finding 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. Much research is not minimal risk. Therefore, in order to apply this finding to all research that involves identification of human subjects 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.
- Much research is regulated by both OHRP and FDA. The FDA regulations do not include the 45 CFR 46.16(d) waiver of consent provisions. Thus, it is not theoretically not compliant with FDA regulations, or at least awkward, to apply 45 CFR 46.16(d) to FDA regulated research.

Because of these difficult interpretation issues, SACHRP recommends that OHRP abandon this approach to recruitment activities. There are several ways that OHRP could find regulatory justification for this change in guidance. SACHRP has discussed several possible ways that OHRP might find this regulatory justification, as outlined below.

- 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 project 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 any risks are minimized, and focus on the proposed consent process and 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 FDA and OCR 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 documentation. [An advantage to this approach is that it avoids suggestion that OHRP doesn't have jurisdiction over these pre-research activities. Rather, it says that these activities are an inherent part of the whole and shouldn't be bifurcated.]
- Alter the interpretation of “obtain” in the definition of a human subject. The OHRP guidance entitled “Guidance on Research Involving Coded Private Information or Biological Specimens” discusses the definition of “obtain.” It states, “In analyzing a particular activity under the second question, it is important to focus on what is being **obtained** by the investigators. If the investigators are not obtaining either data through intervention or interaction with living individuals, or identifiable private information, then the research activity does not involve human subjects.” [We discussed re-interpreting this at the convened SOH meeting, but I don't see how we could do so to make recruitment activities not involving obtaining data.]
- Alter the interpretation of “research.” 45 CFR 46.102(d) defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.” OHRP could establish in guidance that recruitment activities are not part of the definition of research. [This doesn't make much sense to me, because FDA uses the argument that recruitment activities are the beginning of the consent process. It won't be very useful to have OHRP arguing these activities are not part of research so we don't have to bother with a waiver of consent while FDA says they are part of the consent process in order to have jurisdiction.]
- 45 CFRE 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.

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, and take steps necessary to interpret the Common Rule so that this is possible. To the extent possible, OCR should also consider what activities must be performed due to HIPAA/HITECH

Attachment D. Applicability of FDA Regulations

For most, it is clear that the use of an investigational drug or device in a clinical trial is subject to the FDA regulations, 21 CFR 812 or 312, respectively, and 21 CFR 50, and 56. However, there are other types of research projects that meet the definition of a clinical investigation and involve human subjects and, therefore, are subject to the FDA regulations.

There are four definitions of clinical investigation found in 21 CFR 50 and 56, 312, and 812. Each definition differs slightly from the others.

21 CFR 50: Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

21 CFR 56: Clinical investigation means any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

21 CFR 312: Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

21 CFR 812: Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

Analysis: The term clinical investigation means an experiment in the broadest sense of the word. When looking only at the methods employed, any project that involves data collection and a test article is potentially a clinical investigation. There is nothing unique about the term clinical investigation. Terms such as research, clinical study, or study cannot be used to differentiate an activity that is regulated by FDA.

Two restrictions that are placed on clinical investigations that are regulated are those that are 1) subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act and 2) those that are not subject to requirements for prior submission to the

Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. Simply put, if the investigator or sponsor must submit the data to FDA or intends to submit the data to FDA or FDA might inspect the data, the clinical investigation (research, study, etc) is regulated by FDA.

The definition of a test article is broad and includes any product the FDA wishes to regulate. Common regulated products are drugs, biologics, devices, food, and electronic products. (See definitions below)

Determining whether a test article is “involved” in a clinical investigation depends on the use of the data and whether the test article is a drug or device. In all cases, if test article is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act and 2) is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit, then the clinical investigation is regulated. 21 CFR 312 provides further clarification that the use of a marketed drug outside of medical practice is regulated and 21 CFR 812 clarifies that medical devices are regulated when the purpose of the clinical investigation is to study the safety or effectiveness of the device.

Clinical investigations are regulated when they involve at least one human subject. The definitions of human subject are similar and include healthy individual as well as individuals with diseases. The definitions are written in the present tense and imply that they refer to living humans.

Test article

21 CFR 50: Test article means any drug (including a biological product for human use) medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 56: Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 312: Investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.

21 CCFR 812: Investigational device means a device, including a transitional device, that is the object of an investigation.

Human subject

21 CFR 50 and 56: Human subject means an individual who is or becomes a participant in research, either as a recipient of the test articles or as a control. A subject may be either a healthy human or a patient.

21 CFR 312: Human subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

21 CFR 812: 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.

Applicability of FDA Regulations

For the vast majority of clinical investigations regulated by FDA, the determination of whether the study is regulated is easy to make and clear. Phase 1, 2, and 3 clinical trials are clinical investigations. But not all clinical investigations are clinical trials. There are several areas of research or investigation involving humans where the determination of whether the FDA regulations apply is not clear. It is with these examples that investigators and IRBs seek assistance from FDA.

Areas of Activities that might be Subject to FDA Regulations and Guidance from FDA is Requested

Below are listed a total of seven areas where an investigation might meet the definition of a clinical investigation subject to FDA regulation. The first four areas relate to the use of specific methods; the last three relate to specific activities involving a test article. Under each area, a series of questions are proposed for use in making a determination of whether the activity is a clinical investigation.

Records review studies that sometimes are clinical investigations and others times are not clinical investigations.

Will data be collected and analyzed?

Does the data collection activity include collecting information about a test article?

Does the data collection activity involve the review or recording of identifiable data?

What is the intent of the records review – to support a new application, to change the label?

Does the investigator (or other party) intend to submit the data to FDA?

Does the investigator (or other party) intend to hold the data for inspection by the FDA?

If the data are published, is the intent of the data collection and analysis to make a claim about the safety or efficacy of the test article?

Is a retrospective records review classified differently from a prospective records review as to whether it is a clinical investigation?

Medical practice that sometimes is a clinical investigation and most of the time is not a clinical investigation.

Will data be collected and analyzed as part of providing care to patients?

Does the data collection activity include collecting information about a test article?

Does the data collection activity involve the recording of identifiable data?

What is the intent of the data collection – to support a new application, to change the label?

Does the investigator (or other party) intend to submit the data to FDA?

Does the investigator (or other party) intend to hold the data for inspection by the FDA?

If the data are published, is the intent of the data collection and analysis to make a claim about the safety or efficacy of the test article?

Is the physician changing medical practice to accommodate the collection of the data?

Use of randomization

Analyzing a couple of cases

Analyzing a case series

Undertakes analysis with no intention to publish the results and then subsequently publishes them

Reads an article and decides to conduct own analysis using own patients and publishes reports.

Off label use of two approved devices to treat patients

Does randomization of the approved devices influence whether it is a clinical investigation?

Registries that are sometimes clinical investigations but most of the time are not clinical investigations.

Does the registry collect information about a test article?

Does the registry involve the recording of identifiable data?

What is the intent of the registry?

What is the intent of the specific data analysis?

Does the investigator (or other party) intend to submit the data from the registry to FDA?

Does the investigator (or other party) intend to hold the data from the registry for inspection by the FDA?

If the data are published, is the intent of the data analysis from the registry to make a claim about the safety or efficacy of the test article?

Does the determination of whether it is a clinical investigation depend on whether it is a voluntary registry set up by sponsor or required by FDA?

Under FDA requires the sponsor to conduct postmarket surveillance for a Class 2 or 3 device, is the use of the registry for this purpose a clinical investigation?

Is the use of a registry to make claims about approved drugs, a clinical investigation?

Are Phase 4 trials or studies use in preparing a risk evaluation and mitigation strategy (aka medication guide) clinical investigations?

Is a registry mandated by a regulatory authority outside US under the jurisdiction of FDA?

Data and tissue banks are never clinical investigations but sometimes the analyses that are conducted from specimens are clinical investigations.

Does the data bank store information about a test article?

Are identifiable data stored in the data bank?

What is the intent of the data bank?

What is the intent of the specific data analysis using data from the bank?

Does the investigator (or other party) intend to submit the data from the data bank to FDA?

Does the investigator (or other party) intend to hold the data from the data bank for inspection by the FDA?

If the data are published, is the intent of the data analysis from the data bank to make a claim about the safety or efficacy of the test article?

Types of research that don't focus on the study of the safety or effectiveness of a device and, therefore, are not clinical investigations.

a. Training

Is studying the efficacy of training on the use of the device a clinical investigation?

Does the approval status (pre or post-approval) of the device influence the determination?

If the training is mandated by FDA does FDA consider the training to be a clinical investigation?

If the intent of the training is to change the label or affect the efficacy of the device, is it a clinical investigation?

b. Calibration tests

Are calibration tests involving human samples clinical investigations?

c. Surveys or interviews

Does the topic or outcome of the survey determine whether it is a clinical investigation (e.g., satisfaction, quality of life, consumer preference, or efficacy)?

Does the determination depend upon the medical condition, such as a psychiatric condition?

Does the determination depend on whether the survey is part of the overall clinical trial to determine safety or effectiveness or is it a separate study?

If a device or multiple devices are used in a survey of consumer preference testing, is the testing a clinical investigation and exempt if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk?

Does the type of subject being surveyed or interviewed determine whether it is a clinical investigation (medical providers, patients, caregivers)?

d. Use of medical devices, e.g., MRIs and cognition studies, in behavioral and social science research where the purpose of the study is to study cognition and not the safety or effectiveness of the device.

Training activities involving drugs that are not clinical investigations.

Is efficacy of the training on the use of the drug a clinical investigation?

Does the approval status (pre or post-approval) of the drug influence the determination?

If the training is mandated is it a clinical investigation?

If the intent of the training is to change the label or affect the efficacy of the drug, is it a clinical investigation?

Research involving dietary supplements that are not clinical investigations.

If a dietary supplement is studied but not for the purposes of making a claim about health, is the study a clinical investigation?

If the same dietary supplement meets the requirements for an IND, would that change the determination of whether it is a clinical investigation?

Attachment E. The Use of Deception in Research

Introduction

SACHRP recommends that OHRP issue guidance regarding the acceptability of the use of deception in research regulated by HHS. The guidance should inform institutions, investigators and IRBs of OHRP's expectations regarding the application of the IRB and informed consent regulations to the use of deception in research.

Current Situation

Deception is frequently used in psychology, neuroscience, behavioral, and economic research, and is occasionally used in clinical research. There are several reasons that the use of deception in research may be justifiable, including:

- For validity: to achieve random assignment and stimulus control.
- To study low-frequency responses.
- To obtain valid data without serious risk to participants.
- To obtain information that people cannot validly self-report.

The guidance should provide a definition and or examples of deception in research. Deception in research can be defined as “deliberately misleading communication about the purpose of research and/or the procedures employed in the research.”

Examples of the use of deception in research include:

- Misleading disclosure
 - Lack of accurate disclosure by withholding specific information about research
 - Misinforming subjects about the research
- Fake or rigged instruments or procedures
- Misleading play-acting in experimental design: researcher, confederates
- Covert procedures: e.g. observation behind one-way mirror
- Covert research
 - Undercover observation
 - Staged experiment in public place

Analysis of Procedural Applicability of Regulations

The guidance should address the following regulations and their applicability to research involving deception:

Some activities involving deception will not qualify as research, or will be research that does not involve human subjects.

Some research involving deception will fall under one of the exempt categories at 45 CFR 46.101(b).

Some research involving deception may qualify for expedited review if it is minimal risk, does not involve any interventional procedures other than those included in the guidance entitled “Categories of

Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure”, and where identification of the subjects and/or their responses would not reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

When research involving deception is reviewed either through expedited review or at a convened meeting, there are several regulatory issues that the IRB should consider.

The guidance should address the applicability of certain of the criteria for IRB review at 45 CFR 46.116:

- 45 CFR 46.116 (a)(1) requires that risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- 45 CFR 46.116 (a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
- 45 CFR 46.116 (a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
- 45 CFR 46.116 (a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
- 45 CFR 46.116 (a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- 45 CFR 46.116 (a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- 45 CFR 46.116(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Analysis of Substantive Applicability of Regulations

The OHRP guidance should address the following ethical issues and explain how the regulations cited above apply to these issues:

The OHRP guidance should clarify that deception should not be used when nondeceptive alternatives are available and should not be used unless the research has sufficient potential social value to justify the risks associated with deception.

The OHRP guidance should clarify that risks of the use of deception include psychological distress or harm, and mistrust in the enterprise of research. [Are there other risks?]

The OHRP guidance should clarify that informed consent for research involving deception should disclose the deception to the extent possible without invalidating the integrity of the research.

The OHRP guidance should specifically address whether or not an IRB must always apply 45 CFR 46.116(d) to research involving deception:

45 CFR 46.116(d) “An IRB may approve a consent procedure which does not include, or which alters some of the elements of informed consent . . . provided the IRB finds and documents that:

- (1) the research involves no more than minimal risk to the subjects;
- (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) the research could not practicably be carried out without the waiver or alteration; and
- (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The guidance should also address whether the research as a whole must involve minimal risk under 45 CFR 46.116(d)(1), or whether the deception itself must involve minimal risk under 45 CFR 46.116(d)(1).

The OHRP guidance should specifically address the role of debriefing, and the regulatory justification form and status of debriefing activities. For example, debriefing sessions can be used to mitigate the harm and wrong of deception by explaining the rationale for the deception. Debriefing is strongly preferred, but is not always required. Reasons it may not be required include:

- Research for which debriefing is impossible
- Concern that debriefing might be harmful
- Contamination of the subject pool

Additional points to consider

The OHRP guidance should discuss the whether or not the guidance applies to the use of placebo in clinical research. If it does not apply, then the guidance should outline the factual and regulatory distinctions that make clinical research involving placebos distinct from research involving deception. As background, the language that is used in a consent form for a placebo-controlled trial does address that the subject will not know if they have received the placebo. The consent form in some cases can disclose that deception will be used without affecting the validity of the data.

Attachment F. APA's Ethical Principles Related to Deception in Research

The following ethical principles of the American Psychological Association are excerpted from Ethical Principles of Psychologists and Code of Conduct, 2010 Amendments, Standard 8.

<http://www.apa.org/ethics/code/index.aspx>

8.07 Deception in Research

(a) Psychologists do not conduct a study involving deception unless they have determined that the use of deceptive techniques is justified by the study's significant prospective scientific, educational, or applied value and that effective nondeceptive alternative procedures are not feasible.

(b) Psychologists do not deceive prospective participants about research that is reasonably expected to cause physical pain or severe emotional distress.

(c) Psychologists explain any deception that is an integral feature of the design and conduct of an experiment to participants as early as is feasible, preferably at the conclusion of their participation, but no later than at the conclusion of the data collection, and permit participants to withdraw their data. (See also Standard [8.08, Debriefing](#).)

8.08 Debriefing

(a) Psychologists provide a prompt opportunity for participants to obtain appropriate information about the nature, results, and conclusions of the research, and they take reasonable steps to correct any misconceptions that participants may have of which the psychologists are aware.

(b) If scientific or humane values justify delaying or withholding this information, psychologists take reasonable measures to reduce the risk of harm.

(c) When psychologists become aware that research procedures have harmed a participant, they take reasonable steps to minimize the harm.

**Secretary's Advisory Committee on Human Research Protections
March 8 and 9, 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