

Subcommittee on Harmonization (SOH) Update

David Forster

July 12, 2012

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Meetings

- Convened meetings:
 - April 15-16, 2010
 - September 21-22, 2010
 - February 8-9, 2011
 - June 29-30, 2011
 - September 12-13, 2011 (joint meeting with SAS)
- Monthly teleconferences

Completed Activity – HHS Conflict of Interest Policies

- Recommendation regarding adoption of a single conflict of interest standard across DHHS entities.
- Adopted by SACHRP at July 21, 2010 meeting.

Completed Activity – Commentary on NPRM on HITECH

- Recommendation adopted by SACHRP at October 19, 2010 meeting.
- Five topics:
 - Compound Authorizations
 - Future/Secondary Research
 - Minimum Necessary
 - Business Associates
 - Restriction on Sale of PHI

Completed Activity – Definition of Non-Scientist

- Recommendation adopted by SACHRP at October 19, 2010 meeting.

Completed Activity – Addition of FDA Considerations to SAS FAQs on Biospecimens

- Recommendation adopted by SACHRP at July 20, 2011 meeting.

Completed Activity – Definition of a Minor Change in Research

- Recommendation adopted by SACHRP at July 20, 2011 meeting.

Completed Activity – Early Processes in Research

- Application of 45 CFR 46 and 21 CFR 56 to early processes in research, such as identifying potential subjects, contacting subjects, and recruiting subjects.
- Recommendation adopted by SACHRP at July 20, 2011 meeting.

Completed Activities from Last SACHRP Meeting

- Recommendation regarding applicability of FDA regulations.
- Recommendation regarding protocol deviations.
- Recommendation regarding individual patient treatment use protocols.
- Recommendation regarding OHRP, ORI, and FDA overlapping jurisdiction of research misconduct and research non-compliance.
- Recommendations adopted by SACHRP at February 28-29, 2011 meeting.



Today's Recommendation

OHRP and FDA Guidance on
Local Research Context

Current OHRP Guidance

- “IRB Knowledge of Local Research Context “
- August 27, 1998 [Updated July 21, 2000]
- Does not include a “should” versus “must” statement, as is now found in FDA and OHRP guidance.
- “OPRR considers the following standards when evaluating the adequacy of IRBs designated under an institutional Assurance, particularly when the IRBs are geographically removed from the local research context. These standards reflect minimum levels of adequacy. More stringent standards may be required, depending upon the nature of the proposed research or the relevant research context.”

Section (A) Addresses Administrative Processes

- Section (A)(1) addresses minimal risk research:
- “Where the research involves minimal risk to subjects, the IRB should demonstrate that it has obtained necessary information about the local research context through written materials or discussions with appropriate consultants.”

Section (A)(2)

- Where the research involves greater than minimal risk but (i) the local research context involves no intervention or interaction with subjects and,
- (ii) the principal risk associated with the local research context is limited to the potential harm resulting from a breach of confidentiality, the IRB should,
- (i) demonstrate that it has obtained necessary information¹ about the local research context through written materials or discussions with appropriate consultants; and
- (ii) determine and specifically document that provisions to protect the privacy of subjects and maintain the confidentiality of data are adequate.
- [Point ii is already covered in bullets 8 and 9 of the footnote, thus (A)(2) is basically equivalent to (A)(1)]

The requirements of (A)(2) are already addressed in footnote 1, and the regulations:

- 1 Necessary information under DHHS regulations includes all of the following:
 - the anticipated scope of the institution's research activities;
 - the types of subject populations likely to be involved;
 - the size and complexity of the institution;
 - institutional commitments and regulations;
 - applicable law;
 - standards of professional conduct and practice;
 - method for equitable selection of subjects;
 - **method for protection of privacy of subjects;**
 - **method for maintenance of confidentiality of data;**
 - language(s) understood by prospective subjects;
 - method for minimizing the possibility of coercion or undue influence in seeking consent; and
 - safeguards to protect the rights and welfare of vulnerable subjects.

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- “(A)(3) Where the research involves greater than minimal risk to subjects and item (A)(2) does not apply, the IRB should demonstrate that it has obtained necessary information¹ about the local research context through one or more of the following mechanisms, or through other mechanisms deemed appropriate by OPRR for the proposed research and the local research context.”
 - Four methods to do so:

(A)(3)(a)

- “Personal knowledge of the local research context on the part of one or more IRB members, such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community.”
- Rare for a non-local IRB to have this expertise, but happens once in a while.

(A)(3)(b)

- “(b) Participation (either physically or through audiovisual or telephone conference) by one or more appropriate consultants in convened meetings of the IRB. Such consultant(s) should have personal knowledge of the local research context, such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community.”

(A)(3)(b) continued

- (3)(b) is the most readily available alternative for single grant research sites.
- However, there is an unstated dilemma. OPRR was very clear in 1998 that the consultant could not be the investigator.
- Therefore, the person on the phone often does not know the details of the research.
- A happy medium was to have the coordinator on the phone, but it was uncertain if it met OPRR intentions in 1998, or now.

(A)(3)(c)

- “Prior written review of the proposed research by one or more appropriate consultants (see (b) above), in conjunction with participation (either physically or through audiovisual or telephone conference) by the consultant(s) in convened meetings of the IRB, when such participation is deemed warranted either by the consultant(s) or by any member of the IRB.”
(underlining in original).

Two interpretation problems with (A)(3)(c), and a practical concern

- What should the “prior written review” encompass? It isn’t about the research, it is about local context.
- When is the decision to be made as to whether, “participation (either physically or through audiovisual or telephone conference) by the consultant(s) in convened meetings of the IRB, when such participation is deemed warranted either by the consultant(s) or by any member of the IRB?” Prior to the IRB meeting? At the IRB meeting?
- As a practical matter, some sites asked, “isn’t this your job as the non-local IRB? Why do we have to find a consultant for you and have them write up this analysis?”
- Between these three concerns, (3)(c) wasn’t very useful.

(A)(3)(d)

- “Systematic, reciprocal, and documented interchange between the IRB and elements of the local research context. Such interchange should include (i) periodic visits to the research site, occurring several times per year, by one or more IRB members in order to obtain and maintain knowledge of the local research context, including the research institution, its subject populations, and its surrounding community; (ii) periodic discussion with appropriate consultants knowledgeable about the local research context; (iii) regular interaction with one or more designated institutional liaisons; and (iv) review of relevant written materials.”

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- For large research institutions that commonly use the same external IRB, this is a common approach.
 - Avoids a phone call for every individual protocol.

Section B

- Section B addresses outsourcing to another institution's IRB (as opposed to an independent IRB)
- (B)(1): “The review arrangement must be approved in writing by OPRR and by appropriate officials of the institutions involved.”
- This is no longer required.

Section (B)(2)

- “The institution relying upon another institution's IRB has a responsibility to ensure that the particular characteristics of its local research context are considered, either (i) through knowledge of its local research context by the reviewing IRB (see (A) above); or (ii) through subsequent review by appropriate designated institutional officials, such as the Chairperson and/or other members of its local IRB.”
- Why is (ii) not applicable to section A for independent IRBs?

Section (C)(4)

- “Where institutions holding an OPRR-approved Assurance engage a separate entity to perform human subject protection activities, OPRR must review and approve those portions of the contract and/or other clarifying documentation detailing responsibilities and implementation mechanisms relevant to such activities.”
- No longer accurate.

Final paragraph

- “Assurance Coordinators within the Division of Human Subject Protections (DHSP) retain the authority to evaluate the adequacy of IRBs consistent with the above standards. Assurance Coordinators may require more stringent standards where warranted based upon the nature of the proposed research or the relevant research context. Assurance Coordinators should approve less stringent standards only in extraordinary circumstances and with concurrence by the Chief of the Assurance Branch or the DHSP Director.”
- From the OHRP website, it appears that neither the job titles nor the division still exist.

FDA guidance

- Using a Centralized IRB Review Process in Multicenter Clinical Trials
- March 2006
- Footnote 1: “This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Good Clinical Practice Program in the Office of the Commissioner (OC), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration. ”
- CDRH not included. Therefore, not applicable to clinical investigations involving devices?

Section IV

- “ADDRESSING LOCAL ASPECTS OF IRB REVIEW”
- This section echoes the OHRP guidance:
- “The preamble to the final rule indicates that where a centralized IRB review process is used (21 CFR 56.114), the review should consider the ethical standards of the local community.[\[11\]](#) Therefore, a centralized IRB review process should include mechanisms to ensure meaningful consideration of these relevant local factors. Possible mechanisms include: ”

Section IV, continued:

- “Provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, institution, and/or clinical research
- Participation of consultants with relevant expertise, or IRB members from the institution's own IRB, in the deliberations of the central IRB
- Limited review of a central IRB-reviewed study by the institution's own IRB, with that limited review focusing on issues that are of concern to the local community”



BUT...

Section VI

- **VI. Using A Central IRB at unaffiliated sites**
- “At clinical sites that are not already affiliated with an IRB, investigators and sponsors typically rely on the review and oversight of a central IRB. In this situation, the central IRB should document in meeting minutes or other records how it considered relevant local factors for the various communities from which research subjects are to be drawn (see Section IV). The central IRB must also document its action in agreeing to conduct IRB review for the site (21 CFR 56.115) and must have written procedures in place that describe how it will perform its initial and continuing review responsibilities at remote sites (21 CFR 56.108, 56.115(a)(6)).”

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- In section IV, it suddenly isn't important to have “Provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, institution, and/or clinical research.”
 - The only differentiating factor between sections IV and VI appears to be whether there is an OHRP assurance in place, which is outside of FDA regulations and jurisdiction.

Summary

- Both OHRP and FDA should update these guidance documents or issue new guidance.
- The OHRP and FDA approach should be harmonized.



Feedback or Questions?