Subcommittee on Harmonization (SOH) Update

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Membership

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- **Susan Alpert, Ph.D, M.D.**
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- **Gary Chadwick, Pharm.D., CIP**
- **David Forster, J.D., MA, CIP – Co-Chair**
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- **Justin P. McCarthy, J.D.**
- **Marjorie A. Speers, Ph.D.**
- **Susan Stayn, J.D.**

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)
  - September 20-21, 2012
  - February 20-21, 2013 (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.
- Approved by SACHRP at July 21, 2010 meeting.

Completed Activity – Commentary on NPRM on HITECH

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

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

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

Completed Activity – Definition of a Minor Change in Research

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

Completed Activities

- 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.
- All four recommendations approved by SACHRP at February 28-29, 2011 meeting.

Completed Activities

- SOH recommendation on IRB knowledge of local context.
- Commentary on the OHRP and FDA draft guidance documents on transfer of research to new IRBs and institutions.
- Both approved by SACHRP at October 9, 2012 meeting.

Today's Topics

- Cluster Randomized Trials
- Certificates of Confidentiality
- Non-Compliance

Cluster Randomized Trials

- At the last SACHRP meeting, Andrew McRae presented on informed consent issues in cluster randomized trials (CRTs).
- There has been very little guidance or literature on the application of US regulations to CRTs.
- In your materials you have a draft outline of a recommendation from SOH to SACHRP on this issue.

Definition of a Cluster Randomized Trial

- Provide examples
- Should we also try to provide a comprehensive definition?

Scientific Validity

- When are CRTs either less powerful or more powerful than other study designs?
- Are CRTs ever used to avoid the need to obtain informed consent?

Overlap with Quality Improvement

- When does a CRT fall into the definition of a Quality Improvement project as described in the OHRP FAQs on QI activities?
- http://answers.hhs.gov/ohrp/categories/156

Who is a Subject in a Cluster Randomized Trial?

- HHS definition - (f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
- (1) Data through intervention or interaction with the individual, or
  (2) Identifiable private information.

Who is a Subject in a Cluster Randomized Trial?

- FDA definition, Part 56 - *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

Who Must Provide Consent?

- Which participants in cluster randomized trials must provide consent?
- Which participants are not subjects, and thus do not need to provide consent?
- When can a waiver of consent apply for participants who are subjects?
- When can deception be used in the consent process to help blinding?

When Must Subjects Provide Consent?

- Often in cluster randomized trials subjects are randomized before they can be consented. Is this acceptable? Is a partial waiver of consent necessary?

Identifying Risks and Benefits

- The risks and benefits in CRTs can be hard to identify:
  - What are the risks to medical providers when data is being collected about their decisions?
  - What are the risks to patients when their hospital or clinic is randomized to an arm of a study?

Engagement in Research

- Which institutions are engaged in research in CRTs?
- Should the assessment of engagement differ for CRTs when the randomization is by institution?
- Should the assessment of engagement differ for CRTs when the randomization is by community?

Subparts B, C, and D

- Are there any unique issues in applying subparts B, C, and D to CRTs?
- To what extent do these subparts apply when subjects are randomized by institution or community?

Questions for the Committee

- Does SACHRP agree that SOH should move forward on this project?
- If so, what is the most useful format for structuring a SACHRP recommendation on the application of US regulations to CRTs?

Certificates of Confidentiality

Basic Information

- Originally created in 1970 for protecting subjects in research on substance abuse.
- A Certificate of Confidentiality helps researchers protect the privacy of human research participants enrolled in sensitive research.
- Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant.

How Long does a Certificate's Protection Last?

- Individuals who participate as research subjects (i.e., about whom the investigator maintains identifying information) in the specified research project during any time the Certificate is in effect are protected permanently- even if the subject gave the researcher data before the Certificate is issued.

In What Situations may Information Protected by a Certificate be Disclosed?

- Voluntary disclosure of information by study participants themselves or any disclosure that the study participant has consented to in writing.
- Voluntary disclosure by the researcher of information on such things as child abuse, reportable communicable diseases, possible threat to self or others.

In What Situations may Information Protected by a Certificate be Disclosed?

- Voluntary compliance by the researcher with reporting requirements of state laws, such as knowledge of communicable disease, etc.
- Release of information by researchers to DHHS as required for program evaluation or audits of research records or to the FDA.

Who Provides COCs?

- NIH (FIC, NCCAM, NCI, NCATS, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, Magnuson Clinical Center.)
- CDC
- FDA (CDER, CBER, CDRH)
- HRSA
- HIS
- SAMHSA

Can NIH give a COC to Non-Federally Funded Research?

- Yes, but…
- Ineligible studies include projects that are
  - not research based,
  - not approved by an IRB operating under a relevant agency, or
  - not involving a subject matter that is within a mission area of the National Institutes of Health.

Difficulties

- Sometimes the agencies/institutes decide not to issue a COC.
- Limited history of legal cases to prove the effectiveness of COCs.

Difficulties

- Which agency do you go to, especially if not federally funded and not involving an IND or IDE?
- Hard to find the right people at some agencies/institutes.
- Most agencies require IRB approval of research and consent prior to issuance, so adds another two weeks or up to 2 months after IRB approval.

Difficulties

- Multi-site research can be challenging.
  - For NIH, a coordinating center or lead institution can apply for and receive a Certificate on behalf of all member institutions. In the application for a Certificate, multi-site applicants must list each participating unit, its address, and project director. New members can be added.

Difficulties

- For FDA, sponsor can hold a COC for all sites, but often the sponsors prefer that each site apply individually.

Difficulties

- Some agencies/institutes are very demanding as to the description of the COC in the consent form.
- For instance, some institutes require removal of statements such as "absolute confidentiality cannot be guaranteed."
- The agencies/institutes are not consistent on what is unacceptable.
- The back and forth between the IRB and agency on this issue can cause more delays.

Difficulties

- Some agencies have different processes, particularly DOJ and AHRQ.
- DOJ requires a Privacy Certificate under 42 U.S.C. § 3789g for all research, even if minimal risk and not sensitive.
- AHRQ has a statute protecting all identifiable information (42 U.S.C. § 299c-3(c)).

Difficulties – Final Slide

- COC's are voluntary, not mandatory.
- As a result, they are used inconsistently to research.
  - Often not used when they would be appropriate.
  - Sometimes applied to research of low risk, such as tissue banks.

Questions for the Committee

- Does SACHRP agree that SOH should move forward on a recommendation regarding COCs?
- If so, what is the most useful format for structuring a SACHRP recommendation?

Future Topics

- Always more to come.