**Scenario:** A U.S. federally-funded research study partners with an international Site (with its own FWA) for pedigree analysis of a genetic disorder.

The international site receives a subcontract to enroll participants and their affected family member control into a study that involves a medical exam, blood sample collection, and a questionnaire. The U.S. Investigator at the grantee institution receives coded DNA samples for SNP polymorphism analysis along with phenotypic coded data. At initial review, the U.S. IRB reviews the research activities limited to its institution, along with the grant and the translated consent form. The international site has a Federal-wide Assurance (FWA) and conducts initial review of the activities in their subcontract.

At the time of continuing review, the U.S. PI informs the U.S. IRB that the international IRB only conducts initial review. No changes have been made to the protocol and the research is progressing as planned, without adverse events of complaints. What should the U.S. site do?

**Ethical and Cultural Issues:**
1. International site may be unaware, unwilling, or unable to acknowledge its responsibilities under its FWA. Is the international site in compliance with its federal-wide Assurance?
2. The norm may be to conduct only an initial review of research projects. Are any corrective actions required?

**Regulatory Issues:**
1. Federal-wide Assurance Responsibilities and Continuing Review

International site may be unaware, unwilling, or unable to acknowledge its responsibilities under its FWA. The federal-wide assurance (FWA) mandates continuing review of human research at least annually. The grantee institution (domestic or foreign) is responsible for safeguarding the rights and welfare of human subjects in HHS-supported activities. The grantee institution must ensure that all sites engaged in human research have IRB approval consistent with 45 CFR 46 of the FWA. If an international institution selects a standard for IRB review other than 45 CFR 46, any requirements of 45 CFR part 46 still must be satisfied for non-exempt human subject research that is conducted or supported by HHS.

71 FR 38645) and the grantee institution is responsible for verifying all requirements are met. The international site should have reviewed the research annually to meet the FWA requirements.

**2. Corrective Actions**

Depending on the culture and regulations of the international site, the norm may be to conduct only an initial review of research projects. The U.S. IRB must inform the PI to request annual review from the local IRB and require that research activities cease until the international site provides annual review of the protocol. Additional grant and contract issues may need to be addressed by the sponsored programs administration. Many international Institutions are eager to learn best practices for research ethics reviews, so there may also be opportunities to provide helpful information to the international site on FWA review best practices such as:

1. The U.S. IRB may wish to form a collaborative relationship if the research will be ongoing, or if future research will be conducted at that site.
2. Discuss the U.S. regulatory system, and obligations under an FWA, and to learn about regulatory obligations in that country and Institution.
3. Request a copy of the IRB policies and procedures so the US IRB is better informed of the local requirements.
4. Request that the IRB conduct annual continuing review, including review of the consent form, as well as any modifications to the research, and unanticipated problems during the course of the study.
5. Offer its policies and forms for modification and use locally as appropriate, including the US PIs IRB continuing review submission for the study.

**References:**
Terms of the Federalwide Assurance, U. S. DHHS, OHRP.
http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html
International Compilation of Human Research Standards, U. S. DHHS, OHRP
http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html
FAQs, U. S. DHHS, OHRP, “Do international institutions seeking a Federalwide Assurance (FWA) have to comply with 45 CFR part 46?”
http://answers.hhs.gov/ohrp/questions/7147
**SCENARIO:** A subcontract for educational leadership assessment in Middle Eastern grade schools.

Dr. Smith has received funds from the Robert Wood Johnson Foundation to explore how and when new school leaders are trained, and whether they receive sufficient training before taking on a leadership role. Dr. Smith will also explore the significance of mandatory leadership qualifications in enhancing the leaders’ knowledge, skills, and abilities to lead schools. The researcher will interview teachers in leadership roles and high school students at 50 public schools in the Dar es Salaam, Tanzania area. The teacher interviews include questions about experience, perceptions, and suggestions for professional development. The student interviews include questions about their experiences, perceptions, and personal opinions around what makes a teacher engaging and knowledgeable.

Dr. Smith holds his primary appointment at a U.S. university, but will be working closely with the Superintendent of Schools in Dar es Salaam to ensure that the study is appropriate to implement in the schools.

**REGULATORY, CULTURAL & ETHICAL ISSUES:**

The U.S. university has requested that Dr. Smith obtain local EC review and approval. How can he satisfy this requirement?

1. Are local collaborators affiliated with an institution/organization that has an established IRB or ethics committee?
2. Is there an institution or organization that has an established ethical review committee (ERC) within Dar es Salaam that would be willing to conduct the review?

**RESOLUTION & DISCUSSION:**

The PI finds that there is no local ethics committee or IRB in the Dar es Salaam area to satisfy the requirement for local EC review and approval. This research is privately funded; therefore, the PI can form a community advisory board:

**Suggestions for the Composition and Role of a Community Advisory Board**

1. The community advisory board (CAB) should be comprised of a minimum of three members (not collaborators, co-PIs or research study staff to avoid actual or perceived conflict of interest(s)), and must include:
   a) One lay/non-scientist member;
   b) One member with appropriate experience and expertise to review research based on personal or professional qualifications, e.g., Tanzanian citizen, investigator well-versed in proposed methodologies, ie could be local teachers, local university education experts, or parents of school children.

2. The responsibilities of the CAB are to review:
   a) The recruitment and consent process and materials
   b) Research procedures
   c) Dissemination of research results

**REFERENCES:**

SCENARIO: Conducting an International for-cause audit.

A U.S. investigator is conducting a study abroad to examine the safety and efficacy of taking a daily iron supplement during pregnancy for women who live in areas with high rates of malaria, and determine whether it leads to better health outcomes for them and their infants. The study procedures include a self-administered health-history questionnaire, 5 ml blood draw (excluding participants with anemia), and HIV test (to exclude individuals with HIV). Eligible participants are randomized to receive either once daily iron supplements or placebo during their pregnancy. In response to an anonymous allegation of noncompliance, the QA/QI program at the U.S. university conducted a for-cause audit.

REGULATORY, ETHICAL & CULTURAL ISSUES:
The audit reveals the following:
1. Regulatory documentation is incomplete: Continuing review submissions to the National IRB were not on file; and periodic (six-month) progress reports were not submitted to the local medical hospital, national ethics committee, or the local Tanzanian FDA;
2. An ineligible participant was enrolled in the study: A participant reported as HIV-positive was also reported as “eligible” on the study “Eligibility Confirmation Form” as noted here:

   ![Eligibility Confirmation Form Image]

RESOLUTION & DISCUSSIONS:
1. Corrective Actions for incomplete regulatory documentation:
   The PI was instructed to file complete, signed, and dated hard copies of all IRB/ethics review committee correspondences in the regulatory binder. In instances where hard copy documentation is not maintained (e.g., electronic documentation) include a “note-to-file” that indicates where documentation is physically stored, who is responsible for maintaining the documentation, and how long these data are retained. The PI should check with the local medical hospital, national ethics committee, and the local regulatory agency to verify whether 6 month progress reports are required. (If applicable, document any changes in policy in a note-to-file.) If still required, the PI should promptly submit progress reports.

2. Corrective Actions for Enrolling Ineligible Participants:
The PI or U.S. based QA/QI program should review the complete participant file for ID #1234. This review will include the original lab reports documenting HIV status and all study data related to the participant.

   If the participant’s lab report indicates an HIV negative status, the PI should write a note-to-file correcting the HIV-positive result indicated in the Eligibility Confirmation form. In the absence of supporting lab documentation, or if the lab report indicates an HIV-positive result, the PI should report this event as a protocol violation to the U.S. and local IRB with sufficient justification for including this participant.

REFERENCES:
US Code of Federal Regulations, 45 CFR 46.103(b)(5)
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
**Scenario:** A U.S. researcher has funding from a private clinical research institute in the Middle East (ME) to identify salivary biomarkers as risk factors for metabolic diseases.

The study will be conducted entirely in the ME in elementary schools grades 4 and 5. Written parental consent and child assent will be obtained by a Middle East research team in the local language (Arabic). All data will be captured within the school setting using specialized computer tablet based electronic forms (eCRFs). eCRF data will be electronically transmitted in password protected files via wireless to a server in the U.S. The ME institution has its own ethics committee.

**Regulatory, Ethical & Cultural Issues:**
Salivary samples will be shipped frozen to the U.S. for analysis. The U.S. team will be responsible for data analysis and laboratory assays. What are the issues regarding the shipping of the biological samples?

1. What are the privacy issues involved in this study?
2. How will data and biological specimens be handled?

**Resolutions/Discussions**

1. Privacy Issues:
   a) Privacy standards - The research should uphold the highest applicable standard of privacy of U.S. and international guidelines (see CIOMS, Guideline 18).
   b) Data confidentiality – a unique subject identifier links clinical data and samples. The PI maintains the master code on a secured dedicated server. All personnel involved in the receipt and storage of this data are trained. The tablets are password-protected and kept in a secured locked location in at the ME site when not in use. One person has been identified as responsible for transmitting the data from the tablets to the U.S. and to monitor the transfer on a password-protected website.

2. Data & Biological Samples:
   a) Samples – a shipping agent is needed to handle international saliva shipment to the U.S. (Import of the samples customs).
   b) Use of computer tablets-export controls may require a license to export, re-import or transfer some technology to certain countries (and would not allow export to countries of customs holding up receipt of the goods when shipping hardware to site).
   Confer with the export controls expert at your institution.
   c) Check the local airline for transport of tablets on commercial flights due to lithium battery regulations.

**References:**

- International Compilation of Human Research Standards, U.S. DHHS, OHRP
  [http://www.hhs.gov/ohrp/international/index.html](http://www.hhs.gov/ohrp/international/index.html)

**SCENARIO:** A U.S. researcher receives funding from a private clinical research institute in the Middle East to assess salivary biomarkers to identify risk for metabolic diseases.

The study will be conducted entirely in the Middle East in elementary schools grades 4 and 5. Written parental consent and child assent will be obtained by the in-county Middle Eastern research team in the local language (Arabic). All data will be captured within the school setting using specialized computer tablet based electronic forms (eCRFs). eCRF data will be electronically transmitted in password protected files via wireless to a server in the U.S. Salivary samples that will be shipped frozen to the U.S. for analysis. The U.S. team will be responsible for data analysis and laboratory assays. The Middle Eastern institution has its own ethics committee.

**REGULATORY, ETHICAL & CULTURAL ISSUES:**
The Middle Eastern university wants to enter into a IRB Authorization Agreement to rely on the U.S. site. Can this be done? If so, can it be done if the international site does not have an FWA?
1. Does the foreign site need a Federalwide Assurance (FWA) from PHS?
2. What are the options for IRB review reliance agreements?

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**RESOLUTIONS/DISCUSSIONS**

1. **FWA:**
An institution (U.S. or abroad) must obtain an FWA if they are engaged in research that is not exempt from the regulations, and is conducted or supported by any HHS agency. In this fact pattern, the funding is from an HHS agency and instead comes from the foreign institute, so no FWA was needed (although the institutions may have a FWA if it performs other PHS funded research).

2. **Options for IRB Review:**
   - **Single IRB Reliance:**
     U.S. IRB relies on ME EC, or ME relies on U.S. IRB (this is unlikely because funding, procedures, and subjects are in the ME and the ME EC will have more knowledge of the culture and research norms) signs an IAA designating the IRB of record.
   - **Collaborative IRB Review** – joint IRB review:
     ME IRB reviews and U.S. IRB member videoconferences in as a voting member or consultant of international IRB. This allows U.S. IRB to verify that procedures and protections are equivalent to those provided in their policies.

**REFERENCES:**

International Compilation of Human Research Standards, U.S. DHHS, OHRP
http://www.hhs.gov/ohrp/international/index.html

International Ethical Guidelines for Biomedical Research Involving Human Subjects http://www.cioms.ch/frame_guidelines_nov_2002.htm (1 de 64)
08/03/2007 9:10:05

Federalwide Assurance (FWA) for the protection of human subjects http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html
**SCENARIO:** Research study seeks to provide anti-retroviral therapy and assess how it will affect overall health and fertility.

including fertility issues in indigenous cultures that do not have access to modern hospital-based medicine and have high levels of HIV. This study takes place in remote tribal communities across Rwanda.

**REGULATORY, CULTURAL & ETHICAL ISSUES**

1. Recruitment:
   - Access: Because there are several remote tribes, the languages and dialects are different from tribe to tribe.
   - Hierarchies: Tribal elders must give permission before anyone may access the community. In addition, there is a strong male hierarchy; women in this culture must seek permission from their husbands or fathers before they participate in research activities.

2. Written Informed Consent:
   - Because the data will be used for a FDA NDA application, full written informed consent must be sought. As an added challenge these tribes have very few people who can read written language and the tribal dialects are very distinct from tribe to tribe.
   - Cultural taboos: In this population, losing a pregnancy is a shameful event. For this reason, collecting data on fertility might be a sensitive issue. It would also be inappropriate in this culture for women to speak to men about reproductive issues.

**Resolution/Discussions:**

1. Recruitment:
   - The investigator consults an anthropologist and linguists from a university who have worked in these communities. These cultural consultants have contacts in the country who will help implement the research in this remote site.
   - The cultural consultants will help the researcher make connections with tribal contacts who will coordinate the research activities (site coordinators) and serve as a liaison and translator for the

2. Informed consent tool:
   - A technology enhanced “speaking” picture book recorded in the local dialects is used. This picture book explains research and all the elements of consent without having to read any documents.
   - Documentation of informed consent: The midwife records verbal consent on a tablet/laptop (asks the participant’s name, whether they have questions, and if they agree to participate, and that they understand that participation is voluntary and how to safely stop participation). A witness will verify consent and each participant will make an X on the picture book to indicate consent.
   - Consent data will be sent via a satellite-enabled tablet to the researcher in the U.S. The tablet is backed-up remotely every night, and there is a solar cell that charges the battery daily.

**REFERENCES:**


**ACKNOWLEDGEMENTS**

**INTERNATIONAL SITE COMPLIANCE WITH THEIR FWA, INCLUDING CORRECTIVE ACTION OPTIONS FOR CONTINUING REVIEW**
The materials are the work of Fariba Houman and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst | The Harvard Clinical and Translational Science Center.

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The materials are the work of Leslie Howes and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst.

**INTERNATIONAL MONITORING FOR-CAUSE AUDIT**
The materials are the work of Leslie Howes and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst.

**INTERNATIONAL BIOLOGICAL SAMPLES IN INTERNATIONAL STUDIES**
The materials are the work of MaryAnn Cugini, Sabune Winkler, and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst.

**INTERNATIONAL FWAS AND RELIANCE AGREEMENTS**
The materials are the work of MaryAnn Cugini, Sabune Winkler, and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst.

**INTERNATIONAL RECRUITMENT AND INFORMED CONSENT TO RURAL INTERNATIONAL SITES**
The materials are the work of Christina Booth MS HPM, CIPP and the Regulatory Knowledge & Support International Subcommittee affiliated with Harvard Catalyst.

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