Guidance and Procedures for Investigators

Topic: International Research

Introduction

It is important that all international research with human subjects adequately protect the rights and welfare of the subjects. All human subject research in which UNTHSC or John Peter Smith Health Network (JPS) personnel (including faculty, staff, students, residents or employees) are involved, and which would be subject to the federal regulations if it were conducted wholly within the United States, must comply with the federal regulations for the protection of human subjects in all material respects.

Background and Considerations

The regulations recognize that "the procedures normally followed in the foreign countries [in which the research will take place] may differ from those set forth in this policy" [Federal Policy 45 CFR 46.101(h)]. Research may be approved, therefore, if "the procedures prescribed by the [foreign] institution afford protections that are at least *equivalent* to those provided in this policy." The foreign country's procedures may then be substituted for the procedures required by the federal regulations. Approval of the substitution is to be given by the relevant federal department or agency head after review of the foreign procedures; notice of actions taken on such reviews are to be published in the *Federal Register* (or elsewhere, as provided for in department or agency procedures). [Note that the FDA has not adopted this provision for research that it regulates. All FDA-*funded* research, however, must comply with both DHHS and FDA regulations.]

The procedure for approving research with a foreign component begins with the domestic institution with which the U.S. investigator(s) are affiliated. If the U.S. institution has an approved FWA and IRB on file with DHHS, the proposed research must be reviewed and approved by the institution's IRB before any research involving human subjects.

The Concept of Equivalency

One difficult issue is determining what constitutes "protections that are at least equivalent" to US federal regulations. The broad policy outlines of international standards, such as the Declaration of Helsinki or the Nuremberg Code, are a starting place, but are not alone sufficient. Written descriptions of the specific procedural implementation of such policies that have been adopted by the foreign institution and/or host country are required.

In many, if not most, cases the foreign institution or host country has an IRB of record, duly constituted, and in many cases, registered with OHRP, a branch of the US governmental agency, DHHS.

Procedures normally followed outside the United States for research involving human subjects may differ from those set forth in federal and University policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make U.S. forms and procedures inappropriate. Additional laws, regulations, and international directive may apply to research conducted in foreign countries, and may require further protections for research subjects.

If protections are deemed "equivalent", requests to review or waive some standard elements of U.S. approvals may be considered. However, protections afforded subjects must approximate those provided to subjects in the United States. The investigator is encouraged to contact the North Texas Regional Institutional Review Board (IRB) to discuss these issues. Investigators will be required to obtain a Research Ethics Review Board (IRB equivalent) approval from the host country for research done internationally for studies that are more than minimal risk.

Many universities, research institutes and medical centers outside of the United States have Ethics Committees that can review and approve the research. In many cases, these Ethics Committees are registered with the US federal Office for Human Research Protection (OHRP) and have an FWA and/or IRB of record listed on the OHRP website at: http://ohrp.cit.nih.gov/search/search.aspx

Researchers should verify the availability of an IRB or relevant ethics committee in the country hosting the research study/site as earlier as possible before initiating the IRB review process.

Note that international research studies must adhere to a recognized Ethics Codes such as: 45 CFR 46, Declaration of Helsinki, and Council for International Organizations of Medical Sciences (CIOMS). Consent and recruitment documents must be in the language that is readable and understandable by the subjects or an approved translation method may be used.

Issues to Consider during Development of Research Project, Protocol, and Consent Documents

Because of the variable nature of research projects conducted in other countries with possible differences, in language, laws, customs, and traditions, investigators are encouraged to keep in mind the following issues. Among the many points to be discussed in the IRB application or that might be addressed in the IRB discussion:

- Benefits to subjects;
- Community leader and/or main project contact person at the research site;
- Culturally-sensitive to local area;
- Paternalism;
- Potential coercion;
- Genetics/homogeneity/validity to other populations;
- Language sensitivity;
- "Helicopter" Research (data/sample collection & leaving site with no follow-up);
- Infrastructure;
- Justify use of this population;
- Ethics body equivalent (Research Ethics Review Board/IRB) approval.

Sources and Information: Published and local

See the "International Compilation of Human Subject Research Protections" for information on research in specific countries such as Costa Rica, Venezuela, Uganda, and many more. And the International Guidelines Complied by OHRP: http://www.hhs.gov/ohrp/international/HSPCompilation.pdf

Also, some IRB members are familiar with specific international settings. When there is not an IRB member that knows of the culture being studied, a consultant in that culture may be utilized. In both cases, investigators are encouraged to seek such input and guidance well in advance of their application submission.

Research in Populations With No Written Language

When appropriate, the use of an English consent form can be a template for translation into the oral language and include a statement about the process of informed consent. Although the subject will not be able to read, an orally-read consent document can be signed by the interpreter, the study Principal Investigator, and the subject, who will be requested to make a mark or thumb print, as appropriate. In all such cases, the IRB will work with investigators and determine, on a case-by-case basis , the proper course of action and set of procedures to ensure subject consent and protection, while at the same time not adding undue or unnecessary burdens to the investigative team.

Minor Subjects

The standard IRB requirements for assent for minors in research studies are applicable. Written, parental permission is also required.

However, if local customs and regulations are such that active parental permission would be culturally inappropriate, the researcher must supply the IRB with proof that such permission is not culturally appropriate. Examples of such proof would be specific regulations (in English and certified to be accurate) that indicate that such permission is not required, an official letter from a ranking official in the country of interest indicating that such permission is not culturally appropriate, or the appearance at an IRB meeting by someone of official standing in the research or academic community who can attest to the cultural inappropriateness of the requirement for active parental permission.

In those cases where seeking active parental permission for minors to participate in research is culturally inappropriate, a waiver of such permission may be granted at the discretion of the IRB, as long as the research does not place the subject(s) at untoward risk. Regardless of the type of risk, all subject(s) in research projects, including minors, retain the right to discontinue participation, without penalty, at any time.

If a waiver of active parental permission is granted, and if a letter informing the parents of the research is deemed appropriate, it must be written at a literacy level that would be understood by the parents, and should be sent to them by the most expeditious method possible.

IRB Operational Procedures

<u>Submitting Protocols for IRB Review</u>

Using standard IRB Application forms and procedures, the principal investigator should submit application and supporting materials well in advance of project start date, especially if research staff or students are scheduled to visit the host country. Typically at least *3 months* lead time is encouraged, to allow for delays in receiving documentation from various participants and authorities involved.

In addition, the Principal Investigator should consider the following checklist to prepare or arrange for appropriate documentation as needed:

- Letter of approval from host country/foreign site Ethics Review Committee (IRB or equivalent) approving the specific research project.

  Note that many international research centers, institutions and universities have IRBs registered with the US government. See OHRP website link for information and search capability to identify

these IRBs. Also note that many international research institutions and universities have specific requirements and laws regarding the conduct of human subject research within their country.

It is the responsibility of the Principal Investigator to obtain all required and appropriate documentation from the host country well in advance of the onset of the study. It is also the responsibility of the Principal Investigator to provide this documentation to the North Texas Regional IRB in a timely manner to allow for adequate and effective review of the protocol.

- Letter and/or evidence of other IRB approvals (collaborating investigators at other institutions within the United States)
- CITI training completed and documented for all UNTHSC-JPS and other U.S.A key personnel (for other institutions, we will accept that institutions' training CITI certificate).

- CITI training (or host country equivalent) completed and documented for foreign (key personnel).

  Note: If host country does not require human subject research training, the Principal Investigator must obtain and provide documentation from an appropriate official of the host country/foreign research site stipulating to this assertion.

- Conflict of Interest Disclosures from all key personnel and collaborating investigators within the United States.

  Conflict of Interest disclosures from non-US personnel are not required at this time.

Letters of support from non-IRB government officials (legislators, mayors, cabinet officers, etc.) or other sponsors or supporters are helpful but not required. Also note that such letters of support do not substitute for official host-country ethics board review and approval.

In general, given the added document demands, as well as the compounding effects of numerous collaborating institutions (who may have their own IRB and regulatory requirements) investigators are encouraged to contact the North Texas Regional IRB (817-735-0409) and prepare their applications well in advance of their travel and research initiation schedule.

<u>For UNTHSC Student Projects:</u>

Because UNTHSC is the degree-granting agency associated with a given student project (in which the degree advisor/mentor is on the UNTHSC faculty) protocol review and approval must be obtained from the North Texas Regional IRB first. If other collaborating organizations are involved, their IRB review and approval will follow after IRB approval. For proper coordination of these activities, contact the IRB staff well in advance of the planned project start date.

Recall that students cannot serve as Principal Investigators (PI) on human subject research protocols, and must designate a faculty member as PI of record. That faculty member, not the student, becomes the Principal Investigator and is responsible for providing all documentation and arranging contacts and interactions with the IRB. While the student may participate as part of the overall learning experience, it is the faculty member who is primary responsible for everything related to that project.

For studies that are *minimal risk and Exempt category*, the IRB equivalent to an approval letter or permission letter from the research site may be acceptable; however, it will be reviewed on a case-by-case basis by the IRB staff for accuracy and completeness prior to review and approval by the IRB Chair.

Under no circumstances will the investigator be solely responsible for determining level of risk or whether a protocol requires formal IRB review. In all cases, North Texas Regional IRB review and approval must be obtained for any research involving human subjects, including those conducted outside the borders of the United States.