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13.1 Definitions

**Local context**: state and local laws, policies and conventions, community and/or cultural differences, institutional requirements, consent form template language.

**Local Adverse Event**: an event that occurs at the University of Louisville or one of the local affiliated sites where UofL faculty conduct research. The local adverse event would include: any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of any study procedure or treatment, regardless of whether it is considered related to the study procedure or treatment.

**Local Serious Adverse Event (SAE)**: an adverse event that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) results in a congenital anomaly/birth defect, or (6) is an important medical event that jeopardizes the subject or requires medical intervention to prevent one of outcomes listed above.

**Transnational Research**: research extending or going beyond national boundaries.

**Unanticipated Problem Involving Risks to Subjects or Others (UIRITSOs)**: any incident, experience, or outcome that meets all of the following criteria:

1. Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB approved research protocol and informed consent, Instructions of Use/Device Manual and/or Investigator’s Brochure; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research or test article (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involving in the research);

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known.
13.2 Transnational Research

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<td>I.3</td>
<td>The University of Louisville’s transnational research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted at the University of Louisville while complying with local laws and taking into account cultural context.</td>
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All transnational research conducted by UofL researchers will follow federal guidelines, be reviewed by the UofL IRBs, and follow requirements of the location where the research is conducted. All UofL policies and procedures which are applied to research conducted domestically will be applied to research conducted in other countries, as appropriate.

The UofL IRBs will consider developing an IRB Authorization Agreement (IAA) with a transnational site if that site is an AAHRPP accredited organization or if the IRB/EC of record has adopted the International Conference on Harmonization Good Clinical Practices guidelines for human subjects’ research.

Transnational research applications submitted for UofL IRB review should identify whether there is a local IRB, Ethics Committee (EC), or government entity that will perform review in the host country. If local review has been conducted, a copy of the approval letter/notice should be included in the application. If local review has not been initiated or is still in process, this should be made clear in the application.

There are countries in which a local review board or government review mechanism is not available. In such cases, the UofL IRB must obtain a consult from an individual who is familiar with the cultural background, local context and community attitudes of the country in which the research will be conducted. This individual may not be associated with conduct of the proposed research.

Written consent is presumed required for transnational research. Requests for waiver of written consent, or for use of an oral consent process, will be considered if the protocol has received local approval. If a consultant is required, the consultant will be asked to comment on the consent process.

The UofL IRB reserves the right to make the final decision whether to allow a consent process other than written. The UofL IRB requires consent forms (or oral consent scripts) to be written at a level that will be understandable to the subject population. Submission of copies of consent documents in the local language(s) is required in most situations. A sample informed consent template should be used to submit the English version of the consent document for UofL IRB review. In addition, the investigator may be required to submit a translation in the local language of the consent along with a Certification of Accuracy. This requirement may be modified depending on the nature of the research and the risks associated with the research.

The UofL IRB will not take action to approve an application without either written documentation that local review and approval has been granted in the host country, or the consult requested by the IRB has been received and accepted. The protocol will be submitted following the same procedures utilized to submit any other protocol.

The investigator should include the following information to assist the UofL IRB in the review process:

a. Proposed payments (if any) to participants: The remuneration should be described in terms of both US and local currency. Include a description of payment in relative terms (i.e. payment equates to a day’s work, hourly salary, or another local reference).
b. Local contact information: Include a local phone contact number for co-investigators or the local IRB/EC who could answer research related questions. If the project is a clinical trial, include local emergency contact phone numbers for participants.

c. Treatment options: For clinical trials, explain if any treatment(s) will be available to participants after study completion. If a placebo arm is included in the trial, explain whether participants will be able to receive the study drug/intervention after study completion.

d. Recruitment materials to be used locally in both the language of the host country and in English.

e. If study team members are U.S. citizens and plan to travel to the site of the research, include the U. S. Department of State International Travel Safety and Security assessment of the conditions in the research site.

HIPAA Considerations in Transnational Research

UofL transnational researchers are strongly encouraged to only transmit or receive de-identified research data from areas outside the United States. This eliminates the need to meet HIPAA requirements for the data transmitted. HIPAA does not apply to transnational research as long as no protected health information (PHI) is transmitted back to a covered entity or employee of a covered entity in the United States. However, once identifiable health information is received by a covered entity, that information becomes PHI (with a narrow exception for overseas foreign nationals receiving health care from US agencies). As UofL is a hybrid covered entity, this means that when a researcher employed in a part of UofL considered inside the covered entity sends identified health information collected transnationally across a UofL network or stores such information on a UofL computer or server, the information becomes PHI.

If it is necessary to collect and transmit PHI to the United States in transnational studies, researchers have several options. The first is to ask the IRB to approve an altered or simpler form of the required Authorization language, and/or to approve the obtaining of Authorization in oral form. Another option, where cultural barriers are significant, is for the IRB to waive the requirement of HIPAA Authorization entirely. To grant any of these requests, the IRB must determine that the request meets all of the waiver criteria in the HIPAA Privacy Rule.

13.3 Communication among IRBs in Multi-Site Research

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<td>I.2</td>
<td>University of Louisville ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that University of Louisville conducts or oversees</td>
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The IRB is responsible for the review of all University of Louisville research that involves human research participants, whether the research is conducted at University of Louisville, a University of Louisville affiliate institution or another site outside of the University.

When University of Louisville is conducting research at an external site and is not the coordinating site or lead investigator, and that site is engaged in research, the IRB requires contact information for the coordinating/lead site, whether the site has an IRB, and if so, confirmation of the IRB’s permission to conduct the research.

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University of Louisville IRBs rely on the IRBs of other sites and also agree to have other sites rely on University of Louisville IRBs on occasion. Presently, the University of Louisville IRB relies on the National Cancer Institute’s Central IRB (CIRB). University of Louisville FWA includes the Adult and Pediatric CIRBs as the IRB of Record for eligible Oncology cooperative group protocols.

If University of Louisville agrees to serve as the IRB of Record for an external site, that site obtains an FWA through OHRP. An IRB Authorization Agreement or a Reliance Agreement is signed by the institutional officials of University of Louisville and the external site, authorizing University of Louisville to serve as IRB of Record for that site.

**University of Louisville Serving as Participating Institution**

When the University of Louisville is a participating institution (sending data or tissue samples out of University of Louisville) the PI must submit data in a timely manner to the coordinating institution, report unanticipated problems (UPIRTSOS) and other reportable events in a timely manner to the coordinating institution and the University of Louisville IRBs, and ensure that the PI’s study team has the current approved version of the protocol and consent form.

The NCI CIRB is an AAHRPP accredited human research protection program and is sponsored by the National Cancer Institute in consultation with the Department of Health and Human Services Office for Human Research Protections (OHRP). The University of Louisville IRB works in collaboration with the NCI CIRB and the investigators, and as a resource to investigators when needed. The HSPPO has a Project Liaison who works with all NCI CIRB studies.

University of Louisville is participating in the independent CIRB model. The HSPPO completes the Annual Institutional Worksheet which indicates to the NCI CIRB local context issues, includes required informed consent template language, applicable local and state regulations, and University of Louisville policies.

Investigators submit an Annual Investigator Worksheet for each investigator, and a Study-specific Worksheet for each study in which they wish to enroll participants directly to the CIRB. The CIRB is responsible for continuing review, review of subsequent modifications, non-compliance, and unanticipated problems. Investigators copy the University of Louisville IRB on reports of local non-compliance, and unanticipated problems, and report these directly to CIRB on forms designed for this purpose. NCI CIRB does not serve as a Privacy Board. The University of Louisville IRBs serve as the Privacy Board for UofL. The University of Louisville IRB chair/vice chair or designee review and approve the HIPAA partial waiver for recruitment for these trials.

The University of Louisville also works with other external academic IRBs utilizing one off IRB Authorization Agreements to work cooperatively, and with central IRBs such as Quorum Institutional Review Board. For projects where the University of Louisville cedes review/approval authority to the NCI CIRB, a guidance document has been developed to assist investigators in fulfilling their institutional responsibilities. See Guide-031 – **Utilizing the NCI CIRB – Guidance for Investigators**
13.4 Information Management in Multi-Site Research

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<td>II.2.H</td>
<td>The IRB has and follows policies and procedures for managing multisite research by defining the responsibilities of participating sites that are relevant to the protection of research participants, such as reporting of unanticipated problems or interim results.</td>
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When the University of Louisville is serving as the coordinating institution, the PI must describe the plans for communicating information relevant to the protection of participants among the participating sites and institutions as part of the protocol application, including communications of adverse outcomes, UPIRTSOs, protocol modifications, and interim results.

When completing the Protocol Application, PIs must indicate if the University of Louisville is serving as the coordinating institution. The PI must list all other sites involved with the proposed research, the contact person at each site and contact information, such as phone number and email address. The PI must indicate if each participating site has an IRB and if that IRB has reviewed and approved the research or if the site will rely on the University of Louisville for IRB review.

When the University of Louisville is the coordinating institution receiving data or tissue samples from other sites, the PI must submit the following documentation for each of the other participating sites along with the Protocol Application to the IRB before receiving any data or tissue samples from a site:

- IRB approval letter from each participating site that includes the type of review, the other institution’s FWA information, and
- When appropriate, the consent forms from all participating sites.

The University of Louisville IRB will keep this information on file for all internal and external reviews.

By submitting the protocol application form, the PI documents his/her acceptance of the responsibility of ensuring that all participating sites have obtained IRB approval prior to initiation of the research at that site. The participating sites must have written procedures that define the scope of studies subject to review by their IRB. The University of Louisville IRB staff will review and confirm that each protocol application for a University of Louisville coordinating site project includes the appropriate documentation from all participating institutions.

When conducting multi-site research, a formal agreement between institutions may be required to specify the roles and responsibilities of each party. If the research is subject to Department of Defense regulations, a formal agreement between institutions specifying roles and responsibilities is required.

If a participating site does not have an IRB, that site may request that the University of Louisville University IRB serve as the IRB of Record. A written agreement must be reached between the participating site and the
University of Louisville IRB which clearly outlines the review and approval procedures. This written agreement must be reviewed, approved and signed by the Institutional Official or designee.

For a prospective clinical trial, the consent forms used at all sites must indicate that data or samples are being sent to the University of Louisville. Data or tissue samples, even though they are anonymous, may not be received from an outside institution whose consent form prohibits data or tissue from going outside the institution.

There must be documentation of regular communication (e.g., teleconferences) with the participating sites to update and inform all participating sites about progress of the study.

**Reporting to the IRBs in Multi-Site Research**
As the lead investigator at the coordinating institution, the PI is responsible for receiving data and reports from the outside sites in a timely manner and distributing them to the University of Louisville IRB as required. University of Louisville IRBs give the same considerations to such reports in multi-site research as they do to internal reports.

**Reportable Events**
Internal and External Reporting is discussed in Chapter 3, Compliance Monitoring (3.6) and in Chapter 15, Investigator Compliance, Chapter 15.3, Events Reportable to the IRB.

**Identifying Material Changes in Multi-Site Protocols**
The PI must report any material changes in the protocol that take place at any of the participating research sites. The IRB may require independent verification to ensure that no material changes have occurred in multi-site research or cooperative study protocols since the previous IRB review.

**ADDITIONAL GUIDANCE**
OHRP [International Compilation of Human Research Protections](#)
[International Conference on Harmonization Guidelines Good Clinical Practices](#)