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1.3 Organization of the HSPP
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1.5 Organizations Covered by the HSPP and their Components Assurance of Compliance
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<td>I.1.D</td>
<td>The University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, Research Participants, and the Institutional Review Boards, as appropriate.</td>
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**1.1 Description of the Organization, its purpose, and how the HSPP relates to the organization's mission**

The University of Louisville, established in 1798, is one of the oldest urban institutions of higher learning in the United States. The University, located in the Commonwealth's largest metropolitan area, serves as Kentucky's premier urban/metropolitan university providing educational, intellectual, cultural, service, and research needs of the greater Louisville region. It has a special obligation to serve the needs of a diverse population, including many ethnic minorities and place bound, part-time, nontraditional students.

The University of Louisville is a premier, nationally recognized metropolitan research university with a commitment to the liberal arts and sciences and to the intellectual, cultural, and economic development of diverse communities and citizens through the pursuit of excellence in five interrelated strategic areas:

1. Educational Experience
2. Research, Creative, and Scholarly Activity
3. Accessibility, Diversity, Equity, and Communication
4. Partnerships and Collaborations
5. Institutional Effectiveness of Programs and Services.

In conjunction with this mission, the University of Louisville Human Subjects Protection Program works to:

- ensure safety precautions for and obtain the full informed consent for research participants at the University of Louisville;
- enhance the educational training of all researchers and their staff who conduct research utilizing human subjects to ensure the highest standards of research conduct;
- promote accountability and responsibility among all those involved in clinical research including those serving on institutional review boards (IRBs), institutional officials, researchers, and sponsors;
- ensure support for an effective oversight process; and
- enhance the efficiency and cost-effectiveness of the clinical research oversight system.
1.2 University of Louisville Organizational Structure and the Institutional Official

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<td>I.1.B</td>
<td>The University of Louisville delegates responsibility for the Human Subjects Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program.</td>
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<td>I.1.D</td>
<td>The University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, Research Participants, and the Institutional Review Board, as appropriate.</td>
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The President of the University of Louisville, Dr. Neeli Bendapudi, reports to the University’s Board of Trustees. The President of the University delegates responsibility for the protection of human research participants to the Executive Vice President for Research and Innovation. The Board of Trustees of the University of Louisville, the governing body of the University, appoints the President and the Executive Vice President for Research and Innovation.

The Executive Vice President for Research and Innovation, is the Institutional Official (I/O) charged by the President of the University to develop and maintain the institutional infrastructure for the proper conduct of all research.

As the University of Louisville’s Institutional Official, the Executive Vice President for Research and Innovation signs the Federalwide Assurance of Compliance (FWA) on behalf of the institution and is ultimately responsible for:

- Creating, establishing and maintaining the policies and procedures for the HSPP and related research policies and procedures on behalf of the University of Louisville.
- Overseeing the protection of human participants, regulatory compliance, and the implementation of the HSPP for Louisville.
- Ensuring that open channels of communication are maintained between the components of the HSPP.
- Ensuring the independence of the IRB, including the authority to act without undue influence.
- Requiring periodic reviews of the HSPP.
- Ensuring that the HSPP is functional, adequately staffed and funded, involving:
  - Annual review of the resources allocated to the HSPP.
  - Participation in the annual budget preparation for the HSPP and incorporation of the HSPP budget into the budget of the University of Louisville.

Federal-Wide Assurance (FWA): An agreement between a federally funded institution and OHRP that stipulates method(s) by which the organization will protect research participants. (66 Fed. Reg. 19139, 19141 (April 13, 2001)).

Institutional Official: An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human participant in biomedical and behavioral research.
1.3 Organization of the HSPP

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<td>I.2</td>
<td>The University of Louisville ensures that the Human Subjects Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that the University of Louisville conducts or oversees.</td>
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The day-to-day operational and oversight responsibility for the HSPP is delegated to the HSPPO Director, a non-faculty, full-time professional/administrative position. The HSPPO Director reports to the Executive Vice President for Research and Innovation.

The HSPPO Associate Director has day-to-day operational responsibility for the IRBs.

A current list of HSPPO Staff can be found at: https://louisville.edu/research/humansubjects/about/staff

IRBs: There is one biomedical IRB and one social behavioral educational IRB. Their authority, membership requirements, and responsibilities are described in Chapter 6. IRBs are responsible for the initial and continuing review, review of modifications, approval of all research subject to the HSPP, determining serious or continuing noncompliance, requiring modifications (to secure approval), disapproving research, and applying applicable ethical standards.

**IRB Chairs/Vice Chairs, Biomedical IRB**
- Laura L. Clark, MD, CIP, Chair
- Julie L. Goldman, MD, CIP, Vice Chair
- Diller B. Groff, MD, Vice Chair
- Serge A. Martinez, MD, JD, Vice Chair
- Paula G. Radmacher, PhD, Vice Chair

**IRB Chair, SBE IRB**
- Pete M. Quesada, PhD, CIP, Chair
- Melissa Evans Andris, Ph.D., Vice Chair

The Biomedical IRB (IRB00000251) and the Social Behavioral Educational IRB (IRB00000252) are the two University of Louisville IRBs and perform many of the core functions of the HSPP. The Executive Vice President for Research and Innovation appoints the chairs and the members of the IRBs. The IRBs are functionally independent (e.g., of the individuals who are conducting the research) and have ready access to the highest officials of the covered organizations, if needed, to ensure protection for human research participants.

The University of Louisville also participates in the Adult and Pediatric Central Institutional Review Boards (CIRB) Initiative of the National Cancer Institute (NCI). The NCI CIRBs are the IRBs of record for certain adult and pediatric national multi-center cooperative oncology group cancer treatment trials.

1.4 Goals and Objectives of the HSPP

The goals of the HSPP are to protect human research participants by ensuring that in all research:

- The rights and welfare of human research participants are adequately protected.
- Such research is guided by the ethical principles of respect for persons, beneficence, and justice as set forth in the Belmont Report, and is conducted with the highest level of expertise and integrity.
- Such research complies with applicable laws.

The objectives of the HSPP include mechanisms to:

- Establish a formal process to monitor, evaluate, and continually improve the protection of human research participants and dedicate resources sufficient to do so;
- Exercise oversight of research protection;
• Educate investigators and research staff about their ethical responsibility to protect research participants;
• When appropriate, intervene in research and respond directly to concerns of research participants.

1.5 Organizations Covered by the HSPP and their Components
University of Louisville maintains a Federalwide Assurance (FWA00002211) under OHRP (45 CFR 46.103) available to investigators and others involved in human subject research. The University of Louisville has three major campuses: the Belknap Campus, located in the heart of Old Louisville; the Health Sciences Center campus, located in the downtown hospital corridor, houses the Schools of Medicine, Dentistry, Nursing and Public Health and Information Sciences; and the Shelby Campus, located in the northeastern section of Jefferson County, houses the University’s Center for Predictive Medicine, a biosafety level three (BSL3) facility for the development of vaccines and other countermeasures to fight bioterrorism and emerging infectious diseases. The majority of biomedical research involving human subjects is conducted on the Health Sciences Center campus. The majority of the social behavioral education research is conducted on the Belknap Campus and in the Jefferson County Public Schools.

The University of Louisville has three major research partners: UofL Health, Inc., which includes University of Louisville Physicians, Inc., University Medical Center, Inc. (including University Hospital, University Hospital-Jewish Hospital, James Graham Brown Cancer Center, Frazier Rehab Institute, Rudd Heart and Lung Center); and Norton Healthcare, Inc., (operating Norton Hospital and Norton Children’s Hospital).

1.6 Essential Functions of the Offices primarily involved in the HSPP
The essential functions of the University of Louisville Human Subjects Protection Program Office are to:

1. conduct pre-review and facilitate IRB review of all submissions to the IRB;
2. assist in preparing agenda for and monitoring IRB meetings;
3. maintain files on all human participant research that takes place at the University of Louisville;
4. prepare meeting minutes;
5. maintain files of minutes of full board and subcommittee meetings;
6. screen research applications for completeness prior to initiating the IRB review process;
7. act as a resource for investigators on general regulatory information, guidance with forms, and assistance in preparing an application for IRB review;
8. maintain the institution’s Federal-wide Assurance and the IRB membership rosters;
9. provide staff support to the IRBs;
10. send notices of approval, study closure, and termination;
11. generate and sends reminder notices to investigators related to continuing reviews;
12. maintain information on federal regulations relating to human subjects research;
13. provide education regarding the IRB process and regulations to the University community;
14. provide educational opportunities to IRB members;
15. maintain records of IRB membership including training;
16. conduct quality assurance and quality improvement for the HSPP;
17. assist in preparing and providing educational opportunities to participants, prospective participants, or their communities, to enhance their understanding of research involving human participants.

All HSPPO staff are required to complete a non-disclosure agreement at time of hiring and an Attestation and Disclosure Form (COI) on an annual basis.

Other essential functions of the Human Subjects Protection Program are overseen by the following EVPRI offices and programs: The Research Integrity Program provides education on the Responsible Conduct of Research. The Office of Sponsored Programs Administration (OPSA) provides information and support relating to the negotiation of grants,
contracts and sub-agreements with sponsors, including budget review and application approval for submission to outside sponsors, tracking of proposals and awards, and serves as the official authorized signature authority for sponsored programs grants and contracts from federally funded, industry funded, and non-profit organizations. OPSA’s Negotiation Core provides information and support to faculty, staff and others engaged in sponsored activities with industry/for-profit organizations and clinical trials (sponsored by any entity, including governmental/non-profit entities). The Commercialization EPI-Center, UofL’s technology transfer office, assists in preparing Material Transfer Agreements when blood, tissue or data (slides, x-rays, etc.) are being transferred in or out of the institution.

1.7 Laws Applicable to the University of Louisville

The basic legal principles governing human subject research covered by the HSPP and applicable to individual protocols are:

- Federal Policy for Protection of Human Subjects (Common Rule) in 45 CFR Part 46
- Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
- ICH-GCP as adopted by the Food and Drug Administration
- Applicable Kentucky law.
In this chapter:

2.1 Sufficient Human and Fiscal Resources
2.2 Matching IRBs to Volume and Types of Human Research
2.3 Human Research Protection, Care of Participants, and Safety

### 2.1 Sufficient Human and Fiscal Resources

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The provision of adequate human and fiscal resources facilitated through the budgeting process results in a well-functioning and effective HSPP.

**Human Resources:** University of Louisville demonstrates a high level of institutional commitment to its HSPP in terms of human resources. The HSPP is led by and reports to the Executive Vice President for Research and Innovation, pursuant to the authority delegated by the Office of the President.

**Fiscal Resources:** University of Louisville demonstrates a high level of institutional commitment to its HSPP in terms of fiscal resources, and is committed to providing the HSPPO with adequate means to carry out its mission while keeping the protocols-to-staff-ratio within acceptable boundaries.

**Resource Allocation in support of HSPP:** The HSPPO receives the majority of its annual budget through the Office of the Executive Vice President for Research and Innovation. A portion of the HSPPO budget is derived from IRB review fees billed to corporate sponsors and collected to offset the costs of providing appropriate staffing, providing educational opportunities to IRB members and IRB staff, including off-site conferences.

The annual budget is established by a three-phase process:

1. IRB Chairs provide input regarding priorities and resources needed for each fiscal year. The input is communicated to the Executive Vice President for Research and Innovation during a budget discussion meeting.
2. The HSPPO Director prepares income and expense forecasts for the upcoming fiscal year. Income forecast includes fees collected for the review of protocols on corporate-sponsored clinical research. Expenditure forecast takes into consideration:
   - Adequate number of IRBs
   - Adequate staffing
   - Adequate technology support
   - Adequate funds for educational opportunities for IRB members and IRB staff, including off-site conferences
   - Adequate funds to provide on-going office and logistical support
   - Adequate funds to carry out agreed-upon special projects.
3. These forecasts are converted into a budget ultimately reviewed and approved by Executive Vice President for Research and Innovation. This budget is then integrated by the University Planning and Budget Office into the University’s consolidated budget forecast presented to the Board of Trustees for approval. It takes effect on July 1 of each year.
When unanticipated needs arise, they are communicated by the HSPPO Director to the Executive Vice President for Research and Innovation. These needs are considered in light of their urgency and fiscal implications.

2.2 Matching IRBs to Volume and Types of Human Research

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The Biomedical IRB generally meets the first, third and fourth Thursday of each month.

The Social Behavioral Education (SBE) IRB meets on a monthly basis, if needed. The majority of the research reviewed by the SBE IRB is expedited or exempt based on federal regulations. When a greater than minimal risk study is submitted, a full Board meeting is scheduled the first Wednesday of the month. The SBE IRB reviews research conducted in the field of human behavior, social sciences, education, engineering, and other similar areas. This IRB generally will not review protocols with physical interventions, e.g., MRI, venipuncture, or actions that involve the collection or analysis of protected health information.

The HSPPO assesses the levels of activity for both boards at least annually in order to optimize the workflow and IRB load. It considers the ratio of protocols to staff, the number of transactions generated by each protocol, the type of protocols (regular, expedited or exempt), and any other appropriate elements. Input from the IRB Chairs regarding the level of activity and other IRB-related matters are gathered in the IRB annual report that is presented to the Executive Vice President for Research and Innovation. New IRBs or new staff positions are created to meet the demands of the workload. When adjustments are necessary, the financial implications are considered during the budget process outlined above in Chapter 2.1.

2.3 Human Research Protection, Care of Participants, and Safety

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<tr>
<td>II.3.A</td>
<td>The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.</td>
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</table>

To approve research, the IRB must determine that, where appropriate, there are adequate resources to ensure the care and safety of participants, from the screening and recruitment phases throughout the project. During review of the submitted protocol, the IRB assesses the information in the Study Application and, as necessary, asks for additional details. If the protocol does not provide adequate protection, it will not be approved. See Chapter 7 for information about the review process.

For each research protocol the availability of resources is affirmed by the Division Chief, Department Chair, School Dean or their designee as part of the review conducted prior to initial submission to the IRB.

Principal Investigators (PI) should continually monitor the resources allocated for their research and notify the IRB if any change in the availability of resources may adversely impact the rights and welfare of participants.
In this chapter:

3.1 Policies, Procedures, and Resources Available to Investigators and Research Staff
3.2 Investigators’ Conflicts of Interest (COI)
   - Individual Conflict of Interest Policies
   - Disclosure of Financial Interests
3.3 Role of the IRB
   - Review of Potential Conflicts of Interest with Initial Approval
   - Review of Conflicts of Interest disclosed after IRB approval of Research
   - Recordkeeping
3.4 Institutional Conflicts of Interest
3.5 Non-compliance and IRB Report of Findings
   - Definitions and Examples
   - Review of Allegations or Findings of Non-compliance
   - Investigation of Non-compliance
   - Serious or Continuing Non-compliance Referred to the IRB
   - Possible IRB Actions for Serious or Continuing Non-compliance
   - Non-compliance Finding for Lapse in IRB Approval
   - Suspension or Termination of Previously Approved Research
3.6 Internal and External Report of Findings
   - Event Reporting to the IRB
   - Reportable Determinations
3.7 Research Compliance Monitoring Program Activities
   - Compliance Monitoring
   - Observation of the Consent Process
   - Reporting of Compliance Monitoring Results
   - Other Review Activities
   - Research Community Feedback
   - IRB Performance Metrics
3.8 Investigators’ Input to the HSPP
3.9 Inspection by a Federal Agency
   - Inspection of IRB
   - Research Site Inspection

3.1 Policies, Procedures, and Resources Available to Investigators and Research Staff

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<td>The University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Subjects Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate.</td>
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The Human Subjects Protection Program Office (HSPPO) has primary responsibility for ensuring the HSPP Policy Manual and related materials are available to the entire University of Louisville research community.

The HSPPO maintains the Human Subjects Protection Program website which provides access to:
- IRB Review Lifecycle Information (Before you Begin, Initial Submission, Continuation Review, Event Reporting, and Study Closure);
The HRPP Policy Manual;
• About the IRB: A list of the current Chairs and Vice Chairs for the two University of Louisville IRBs; IRB Membership Rosters (and Past Rosters, as required by sponsors); current FWA for the University and its affiliated HRPP components;
• Information for Research participants;
• Links to pertinent governmental regulations and guidelines;
• Links to University of Louisville policies (including the University of Louisville Research Handbook);
• Guidance on various topics such as special protections for vulnerable populations;
• Access to the electronic IRB submission system along with instructions and information on how to apply;
• News and Announcement alerts highlighting the posting of new information or changes in existing policies and procedures;

The IRB staff is readily available by telephone, e-mail, and in-person meetings to assist investigators and research staff on human subject research matters, particularly IRB applications and review questions.

The IRB staff regularly gives presentations, often to large research groups, and accepts invitations to attend classes and departmental meetings to provide information and guidance to the University of Louisville research community on IRB policies and procedures governing human participant research.

Within the HSPPO, the IRB staff is responsible for identifying new information involving human research participant protection such as new organizational policies, or emerging ethical and scientific issues. Information about new or modified laws might also be identified by legal counsel. New information is posted on the Human Subjects Protection Program website and is disseminated to the IRB staff, IRB members, and the University of Louisville research community via other distribution sources as noted above.

3.2 Investigator Conflicts of Interest (COI)

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<td>I.6.B</td>
<td>The University of Louisville has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the Institutional Review Board in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate.</td>
</tr>
<tr>
<td>III.1.B</td>
<td>Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with University of Louisville, manage, minimize, or eliminate financial conflicts of interest.</td>
</tr>
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</table>

**Covered Individual** shall mean all University employees. It also includes other individuals with responsibility for the design, performance, or reporting of Institution research, regardless of pay or student enrollment status. It also includes individuals conducting research at the University of Louisville, or using University of Louisville researchers, or using University of Louisville facilities or resources.

**Individual Conflict of Interest Policies**
Covered individuals at the University of Louisville must comply with Board of Trustees Policy: Individual Conflict of Interest and all applicable federal and state laws and contractual terms related to conflict of interest. This policy covers academic, business, clinical and research and scholarly activities conducted under the auspices of and / or for the benefit of the University of Louisville.
The University of Louisville has the following policies regarding individual conflict of interest:

- Individual Conflict of Interest Policy – Board of Trustees
- Addressing Potential Individual Conflict of Interest Policy – COI Office
- Guidelines for External Activities – The Redbook Sec. 4.3.3 – Faculty Work Outside the University
- Guidelines for External Activities – HR Policy PER 1.12 – Staff Work Outside the University
- Guidelines for External Activities – The Redbook Sec. 5.6 – Staff Work Outside the University
- Commitment of Effort – The Redbook Sec. 4.3.1 - Annual Work Plan and Presence at the University

**Disclosure of Financial Interests**

Covered individuals must disclose on an annual basis all financial relationships that reasonably appear to be related to their institutional responsibilities. This is done through University of Louisville’s Attestation and Disclosure Form (ADF). In addition, as faculty enter into changed or new financial relationships related to their institutional responsibilities, they can access their ADF to update previously reported activities or financial relationships, or to enter new activities.

Disclosure must be made by each investigator for him or herself and his or her immediate family. “Immediate family” means the investigator’s spouse or domestic partner and dependent children (as defined by the IRS).

Before a study application can be submitted to the IRB, the PI, faculty listed on the protocol, and any others identified as study personnel must complete and submit an Attestation and Disclosure Form.

Potential conflict disclosure in the informed consent process may be an important part of the management strategy, but will not necessarily be the only strategy used. It is the responsibility of the Conflict of Interest Office, in conjunction with the Conflict Review Board (CRB) to determine what strategy or strategies are appropriate to eliminate, mitigate, or manage conflict that has the potential to harm subjects or compromise the objectivity of the research, or are likely to be perceived as having that potential.

### 3.3 Role of the IRB

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**Review of potential conflicts of interest with initial approval**

When a potential conflict of interest has been identified, the IRB communicates closely with the appropriate COI point of contact and the investigator throughout the protocol review process. When appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict must be determined by the Conflict of Interest Program, in conjunction with the Conflict Review Board and accepted by the IRB. The IRB has the final authority to decide whether the potential conflict of interest and its management, if any, allows the research to be approved.

- When there are non-substantive outstanding COI matters, a protocol may be approved contingent upon the matters being resolved (e.g., requiring that the investigator modify the informed consent document to include verbatim language).
- When there are substantive outstanding COI matters, a protocol will either be tabled or precluded from possible approval until matters are resolved.

Only when COI matters are completely resolved is the study Final Approval Letter generated.
Review of conflicts of interest disclosed after IRB approval of research

When a potential conflict of interest arises and the investigator discloses it after the IRB has reviewed and approved a protocol, the investigator should immediately notify the IRB of the potential conflict and notify the IRB that enrollment and protocol procedures will stop until the conflict of interest has been reviewed and resolved by the Conflict Review Board as described above. The determination by the CRB is forwarded to the IRB.

When a known potential conflict of interest is discovered after the IRB review and approval, the IRB will ask the PI to file a conflict of interest disclosure as described above, and may, among other possible actions, ask the investigator to disclose the relationship to research participants. The IRB will assess whether any action should be taken in accordance with Non-Compliance with HRPP Requirements in Chapter 3.7.

Recordkeeping

Records on all disclosures of financial interests and all decisions to manage, reduce, or eliminate conflicts of interest are maintained within the electronic submission system. This information will be made available to DHHS upon request, while maintaining the confidentiality of all records of financial interest.

3.4 Institutional Conflict of Interest

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The University of Louisville has the following policies regarding institutional conflict of interest:

- Institutional Conflict of Interest Policy
- Addressing Potential Institutional Conflict of Interest Policy

An institutional conflict of interest (ICOI) is created if an investigator at University of Louisville undertakes human participants research on a drug, device, biologic or other item on which University of Louisville has a patent, has licensed the intellectual property, or receives royalties or other fees.

All new human participant research protocols submitted for IRB review must indicate the source(s) of all funding to be used in supporting the research, including unrestricted school, department or individual accounts, as well as the name of the manufacturer when applicable. When a protocol lists a manufacturer, or when other information indicates a potential conflict, the issues are handled as outlined in Addressing Potential Institutional Conflict of Interest Policy.

Decisions are communicated to the IRB, to the relevant offices within the University, and to the relevant dean or associate dean so that the recommendations can be implemented at the level of the individual schools as appropriate.

3.5 Non-compliance and IRB Report of Findings

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<td>The University of Louisville has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program</td>
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requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate.

Any situation of perceived or actual serious or continuing non-compliance jeopardizes the University of Louisville commitment to human subject research protection. Receiving information about possible non-compliance is essential for accountability and education purposes, correcting non-compliance, deterring it from occurring again, and attempting to mitigate any adverse effects on research participants.

Definitions and Examples

**Allegation of non-compliance**: A report of non-compliance that represents an unproven assertion.

**Continuing non-compliance**: A pattern of non-compliance that indicates a deficiency likely to result in further non-compliance (e.g., a pattern that indicates lack of attention to or knowledge or understanding about regulations or ethics) or a circumstance in which an investigator fails to cooperate with investigating or correcting non-compliance. Continuing non-compliance includes repeated failures to complete the continuation review process prior to study expiration.

**Finding of non-compliance**: Non-compliance that is true, or an allegation of non-compliance that is determined to be true based on a preponderance of the evidence.

**Non-compliance**: An action or activity in human subject research at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of the University of Louisville, or relevant state or federal laws. Non-compliance actions may range from minor to serious, be unintentional or willful, and may occur once or several times. The degree of non-compliance is evaluated on a case-by-case basis and will take into account whether participants were harmed or placed at an increased risk and as well as the willfulness of the non-compliance.

Examples of non-compliance include, but are not limited to:
1. Inadequate procedures for the informed consent process;
2. Inadequate supervision;
3. Failure to follow IRB policy;
4. Failure to report adverse events or protocol changes;
5. Failure to provide ongoing progress reports prior to study expiration;
6. Protocol deviations;
7. HIPAA breach.

**Serious non-compliance**: Non-compliance that affects the rights or welfare of human subject research participants.

Examples of serious non-compliance include, but are not limited to:
1. Conducting non-exempt research without IRB approval;
2. Human participants research conducted without appropriate informed consent, when consent could not have been waived;
3. Substantive changes to IRB approved research without IRB approval;
4. Serious protocol deviations that may place participants at risk from the research;
5. Incidences determined to be serious by the IRB.
Review of Allegations or Findings of Non-Compliance
Findings and allegations of non-compliance can come from a number of different sources, including investigators, members of the research team, study sponsors, regulatory bodies (OHRP, FDA), participants and their families, institutional personnel or committees, the media, the public, or anonymous sources. Additionally, the IRB can identify non-compliance during the review of research studies.

All reports of non-compliance are initially evaluated by the Assistant Director of Compliance Auditing. The Compliance Monitors, in conjunction with the Director or Associate Director, or the IRB Chair may consult with other institutional units or committees (such as the Research Integrity Program, the Privacy Office, Institutional Compliance Office, or the IBC) concerning the reported non-compliance. A report will either be designated as not requiring further action, or will be escalated for review by the Director, IRB Chair, or to the convened IRB.

The Director or Associate Director, the IRB Chair or their delegate ensures that immediate action is taken as necessary to prevent unacceptable risk to research participants.

If the instance of non-compliance involves research conducted without prior IRB approval, the Director, Associate Director, or the IRB Chair will order all research activities to stop. The Compliance Monitors may be requested to investigate and present findings to the convened IRB.

Investigation of Non-compliance
The Director or Assistant Director of Compliance Auditing reviews the report of non-compliance and chooses one of the following courses of action to investigate the allegation:

- Conducts the review alone;
- Conducts the initial review in coordination with the IRB Chair;
- Delegates some of the review to IRB staff;
- Delegates all of the review to IRB staff;
- Empanels a reviewing subcommittee of the IRB;
- Requests that legal counsel provide advice and conduct the review;
- Requests that the Research Integrity Program provide advice and conduct the review;
- Requests assistance from others at University of Louisville or outside consults as necessary.

The individual(s) or subcommittee conducting the investigation may take any of the following actions necessary to determine whether allegations are true, and to determine the seriousness or number of occurrences of the actions:

- Reviewing written materials;
- Interviewing knowledgeable sources;
- Collecting relevant documentation.

During the fact-finding process, the Director, IRB Chair, or delegate communicates as appropriate with the PI or representative about the progress of the review and investigation. A factual and objective written record of findings and evidence is made and stored in the appropriate files.

A report requires no further action if the non-compliance is:

1. A factual assertion of non-compliance (generally self-reported by the investigators);
2. Neither serious nor continuing; and
3. Addressed by the investigator through a corrective action plan to remedy the problem.
If a report of non-compliance does not require further action, the incident and corrective action plan will be documented in writing and stored in appropriate files.

**Serious or Continuing Non-Compliance Referred to the IRB**

Non-compliance that is believed to be serious or continuing is referred for review by the convened IRB. The report with relevant portions of the protocol is available to the reviewer(s). As a result of this review, the following actions may be taken:

- The IRB determines that additional information is needed and requests that such information be obtained before further action is taken.
- The IRB determines that non-compliance did not occur or that non-compliance occurred but was neither serious nor continuing, and either takes no action or requires or recommends an appropriate corrective action plan.
- The IRB determines that non-compliance occurred and that it was serious or continuing. The IRB:
  - Takes action appropriate to the situation.
  - Follows the internal reporting procedure required in Chapter 3.6 concerning determinations of serious or continuing non-compliance.

IRB determinations and actions are recorded, and communicated as appropriate to the relevant, involved individual(s), normally including the PI. IRB determinations of serious or continuing non-compliance are reported internally and externally as described in Chapter 3.6.

**Possible IRB Actions for Serious or Continuing Non-Compliance**

In considering actions for serious or continuing non-compliance, the IRB seeks to:

- Correct the non-compliance;
- Deter it from occurring again (e.g., hold the relevant individuals accountable for their actions and provide education on how to comply); and
- Attempt to mitigate any adverse effects on participants.

The IRB must consider:

- Suspension or termination of the protocol.
- Notification of current participants (required when such information may relate to participants’ willingness to continue to take part in the research).
- Other possible IRB actions include but are not limited to the following:
  - Monitoring of the research
  - Monitoring of the consent process
  - Referring to other organizational entities (e.g., legal counsel, risk management, institutional official)
  - Modifying the research protocol
  - Modifying the information disclosed during the consent process
  - Providing additional information to past participants
  - Requiring re-consent of current participants to continued participation
  - Modifying the continuing review schedule
  - Participation by research team members in additional training or education
  - When appropriate, applying any corrective action to all similar protocols.
If the IRB action will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB utilizes a process that takes into account the impact on their health and safety.

**Non-compliance Finding for Lapse in IRB Approval**

If an investigator has failed to provide continuing review information to the IRB by the date of expiration or the research has expired before the continued review approval has been issued by the IRB, all research activities must stop. This includes recruitment, research interventions or interactions, data sharing/reporting, data collection, and analysis of identifiable data. In addition, no new subjects may be enrolled. The investigator and any named team members will be sent a notice that the research has expired and that no human subjects activity, including enrollment or recruitment, may take place on or after the expiration date. The investigator will have thirty (30) days from the date of expiration to obtain continuing review approval for the research, or it will be administratively closed by the IRB and the Dean/department chair, facility, and Office of Sponsored Programs (if applicable) will be notified of the non-compliance.

If the study is closed by the IRB, the investigator has five working (5) days to contact the IRB office and request re-opening of the study. The request to the IRB must include the following information:

- the circumstances that led to the protocol closure;
- reasons why the investigator feels the research should be re-opened;
- corrective action the investigator has taken in order to avoid study expiration and closure in the future.

Once the request has been reviewed by the Assistant Director of Compliance Auditing, the PI will have two (2) working days to submit the continuing review. If the review is not submitted within two (2) working days the study will be closed permanently by the IRB.

If the above steps are not followed, the investigator must submit a new project application via the electronic submission system for IRB review and approval. The new submission must reference the study that was closed by the IRB due to non-compliance. If applicable, the new application will also require the IRB Initial Review fee to be paid.

The Compliance Monitors may also conduct audits on lapsed research to determine if there was any study activity conducted within the lapsed period.

**Consequential Actions for lapse in IRB Approval**

The IRB electronic submission system provides reporting on studies that have been closed by the IRB due to lapse of continuing review. The Compliance Monitors may review reports of studies closed by the IRB to ensure that continuing non-compliance does not occur. In addition, the Compliance Monitors may conduct audits on lapsed research.

**Suspension or Termination of Previously Approved Research**

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<td>The IRB has and follows written policies and procedures for suspending or terminating IRB approval of research, if warranted, and for reporting these actions, when appropriate.</td>
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The University of Louisville IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to participants or others. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action, and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.
Definitions:

**Suspension:** The temporary closing of a human research project or discontinuing an investigator’s or key personnel’s privilege to conduct or to participate in the conduct of human research at the University of Louisville. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the human research or related to the privilege to conduct or participate in the conduct of human research may proceed. The IRB will make this determination.

**Termination:** The permanent closing of all activities related to a human research project or an investigator’s or key personnel’s privilege to conduct or to participate in the conduct of human research at the University of Louisville except the continuation of follow-up activities necessary to protect participant safety.

The Director or Associate Director, the IRB Chair or their delegate ensures that immediate action is taken as necessary to prevent unacceptable risk to research participants.

Before ordering a suspension or termination of research, the convened IRB, IRB chair, HSPPO Director, or person ordering the suspension or termination must consider the effect of the suspension or termination on the rights and welfare of current participants, and consider whether procedures for withdrawal of current participants takes into account their rights and welfare such as:

a. Making arrangements for medical care outside of the research study;
b. Requiring follow-up by the current investigator;
c. Transferring responsibility for the protocol to another principal investigator;
d. Arranging for follow-up with another physician;
e. Arranging for the participant to stay on the study at another institution;
f. Informing current participants of the termination or suspension;
g. Submitting all reportable adverse events or outcomes to the IRB.

If a termination or suspension involves the withdrawal of current participants from the research, the investigator and key personnel must:

a. Respond immediately to any requests from the IRB for additional information;
b. Notify participants that their enrollment in the study has been terminated and inform the participants why their enrollment has been terminated. The reasons given will be those reasons determined to be appropriate by the IRB. The notice given may be oral but will also be in writing and copied to the IRB;
c. Inform the participants of any actions the investigator and key personnel will take to ensure their safety;
d. Participants should be requested to report any adverse events or unanticipated problems involving risks to them or others to the PI. Such reports will be reported to the IRB and others as required by the protocol and the University’s policies and procedures.

The Director, HSPPO, will inform the Executive Vice President for Research, the Principal Investigator, and key personnel of the suspension or termination determined by the IRB chair or Director, HSPP, as they occur, and by the convened IRB immediately after the meeting in which they occur.

The Director, HSPPO, will notify the PI when a human research protocol on which he/she is the PI has been suspended or terminated. If the Director, HSPPO cannot contact the investigator, the Director, HSPPO will inform the department chair, who will be responsible for taking further action to notify the PI, key personnel and participants.

Reporting of suspensions or terminations will be done in accordance with Chapter 3.6.
### 3.6 Internal and External Report of Findings

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<td>The IRB has and follows written policies and procedures for suspending or terminating IRB approval of research, if warranted, and for reporting these actions, when appropriate.</td>
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#### Event Reporting to the IRB

Events and information that must be reported to the IRB, along with the timelines for reporting, are listed in the Chapter 7.10. They should be reported to the IRB using the appropriate online IRB Form in the electronic submission system.

Suspensions and termination of research ordered by someone other than the IRB (e.g. the study sponsor, federal agency, etc...) must be reported to the IRB within 5 working days of site awareness through the electronic submission system (ESS). The submission should include all pertinent information related to the suspension or termination. Once received by the HSPPO office, the information will be reviewed by the IRB Chair/Vice Chair, HSPPO Director, convened IRB (when necessary), and/or specific institutional officials (as necessary).

#### Reportable Determinations, Distribution, and Reporting to Regulatory Agencies

If the convened IRB determines that:

- serious or continuing noncompliance has occurred as specified in Chapter 3.5; or
- an unanticipated problem involving risks to subjects or others (UPIRTSO) or some other reportable event has occurred as specified in Chapter 7.10; or
- suspends or terminates the approval of a protocol as specified in Chapter 3.5; then the following reporting process will be followed.

The Director or Assistant Director of Compliance Auditing, and/or the IRB Chair, will prepare a draft report promptly after the IRB meeting at which the determination occurred.

The report will contain:

a. A summary of the event,

b. The findings of the organization,

c. Actions taken by the organization or IRB,

d. Reasons for the organization’s or IRB’s actions,

e. Plans for continued investigation or action,

f. Project title,

g. Principal Investigator, and

h. Federal Support, if any.

The Director, HSPPO, in consultation with the IRB chair and the EVPRI will finalize the report within ten (10) working days after the IRB meeting at which the final determination occurred. The EVPRI will send the report to the following, as applicable and as determined by the IRB:
a. OHRP\(^1,2\),
b. FDA\(^1\) (whenever the research is subject to FDA regulation),
c. Other Federal Agencies\(^1,2\) that are a signatory to “The Common Rule” who conduct or oversee the research,
d. Investigator,
e. Department Chair/Division Chief/Program Director/Unit Head,
f. Dean/Research Dean,
g. Other organizations involved with the research,
h. The sponsor,
i. The funding agency,
j. The Office of Sponsored Program Administration and the Clinical Contracts Division, and other University of Louisville offices as applicable.

Suspensions and terminations of IRB approval are promptly reported (within 30 days) to OHRP (if applicable) and/or FDA (if research is FDA regulated).

For multicenter research projects, only the institution at which the reportable event occurred must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.103(b)(5)), if applicable.

\(^1\)Reporting is not required if the agency has already been made aware of the event through other mechanisms, such as reporting by the investigator, sponsor, or another organization.

\(^2\)Reporting to OHRP is not required for research approved on or after January 21, 2019 that is not funded or supported by a federal agency.

3.7 Research Compliance Monitoring Program Activities

<table>
<thead>
<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.5.A</td>
<td>The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary.</td>
</tr>
<tr>
<td>I.5.B</td>
<td>The Organization conducts audits or surveys or uses other methods to assess the quality, efficiency, and effectiveness of the Human Research Protection Program. The Organization identifies strengths and weaknesses of the Human Research Protection Program and makes improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program.</td>
</tr>
<tr>
<td>I.1.C</td>
<td>University of Louisville has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants.</td>
</tr>
</tbody>
</table>

The Post Approval Monitoring Program of the Human Subjects Protection Program Office (HSPPO) is designed to:

- Evaluate and monitor the effectiveness of the HSPP;
- Assess compliance with HSPP policies and procedures;
- Prepare and execute For-Cause assessments;
- Prepare and execute Not-For-Cause assessments;
- Identify areas and implement measures for improvement.
Compliance Monitoring

HSPP Compliance Auditors conduct periodic compliance reviews and for-cause assessments to evaluate adherence to applicable federal regulations, state and local laws and University of Louisville policies and procedures, and to verify that research is conducted in accordance with the IRB approved protocols.

- **For-cause Assessments**: The HSPPO Directors, IRB, and/or IRB chairs may direct the Compliance Monitors to conduct an assessment in response to a particular concern. Concerns that may prompt a for-cause assessment include but are not limited to:
  - Complaints or concerns initiated by a research participant, family member, or research team/workforce member;
  - Irregular receipt of required reports (Continuation Review reports, data safety monitoring reports, sponsor monitor reports, etc.);
  - Studies closed due to investigator failure to complete the continuation process prior to study expiration;
  - Reports of serious or continuing non-compliance.

- **Not-For-Cause Assessments**: Compliance Monitors regularly conduct reviews using systematic methods to assess the conduct of research studies to ensure compliance with federal regulations, state and local laws, and University of Louisville policies and procedures. Such not for cause assessments include but are not limited to:
  - Examinations of executed informed consent forms;
  - Observations of the informed consent process;
  - Review of training approvals for investigators and study personnel at initial submission and continuation review.

- **Periodic Compliance Reviews**: Periodic compliance reviews are conducted using systematic methods to assess IRB compliance with federal regulations, state and local laws, and University of Louisville policies and procedures. Periodic compliance reviews may include but are not limited to:
  - Reviews of IRB meeting minutes;
  - Detailed examinations of protocol files;
  - Review of determinations made for vulnerable populations;
  - Review of Exempt and Not Human Subjects Research determinations made by the IRB Chairs;
  - Review of turnaround times for IRB staff; and
  - Review of administrative approvals made by the IRB Staff.

**Observation of the Consent Process**

As part of the IRB oversight options, the IRB may require that a staff member or an outside third party observe the consenting of research participants to determine:

- Whether the informed consent process has been appropriately completed and documented;
- Whether the participant has had sufficient time to consider study participation, that no coercion has been used by the consenting staff; and
- That the information presented to the participant reflects the content of the consent form and is conveyed in understandable language.

The IRB may require that one or more informed consent process situations be observed for selected protocols. IRB considerations used to choose such protocols include:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
• Studies involving potentially vulnerable populations (e.g., ICU patients, children)
• Studies involving study staff with minimal experience in administering consent to potential study participants, or
• Situations when the IRB has concerns that the consent process is not proceeding well.

Reporting of Compliance Monitoring Results
Results of compliance monitoring activities are documented and reported to the Director, the IRB, Institutional Officials and other units within University of Louisville, as appropriate. These results, supplemented by other review results when available, provide a quantitative and qualitative measurement of compliance with the HSPP.

Other Review Activities
Depending on the results of annual risk assessments, the University’s Office of Audit Services may conduct additional reviews of the IRBs and the various schools and departments within the institution that conduct or review human subject research activities.

Research Community Feedback
Compliance Monitors are asked to share comments, questions and issues received from the University of Louisville investigators and participants to identify areas for potential improvement in the effectiveness of HRPP policies and procedures and for ensuring the protection of human subject research participants. The Principal Investigator and key study personnel receive a request to respond to a survey after approval of most events by the IRB. A customer service survey and submission form for questions, complaints, or concerns is available on the HSPPO Website.

Additionally, proposed policy and procedure changes are typically prepared as drafts to get feedback from HSPPO staff, Investigators, IRB members, coordinators and/or others as applicable.

IRB Performance Metrics
The HSPPO Directors review periodic metrics and analysis of the IRB operations and functions, including detailed measurements of activity volume.

Based on the results of the aforementioned assessments and feedback received from the communities served by the HSPPO, the HSPPO staff may partner with other components of the University of Louisville to identify root causes of problems, recommend action plans to correct issues, and provide education, tools and outreach to promote effectiveness of improvements.

3.8 Investigators’ Input to the HSPP

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<tr>
<td>I.5.C</td>
<td>University of Louisville has and follows written policies and procedures so that Researchers and Research Staff may bring forward concerns or suggestions regarding the Human Research Protection Program, including the ethics review process.</td>
</tr>
</tbody>
</table>

There are a variety of mechanisms available for contacting relevant individuals to bring concerns and suggestions, including:
• Reporting possible non-compliance as described in HSPP Chapter 3.6;
• Reporting possible unanticipated problems as described in HSPP Chapter 7.10;
• Making general comments and suggestions and expressing concerns about other matters, issues or processes involving the HRPP, including IRB review and operations to any person in the HSPPO or to the Executive Vice President for Research and Innovation.
• Reporting of any financial irregularities to the Office of Audit Services.
• A customer service survey and submission form for questions, complaints, or concerns is available on the HSPPO Website.

The Director, HSPPO, receives and evaluates the input from any of these sources, with review by other individuals, as needed.

3.9 Inspection by a Federal Agency

Inspection of IRB
For IRB inspections, FDA will determine if the IRB is in compliance with its own SOPs and with FDA regulations. FDA inspections are either surveillance (periodic, routinely scheduled every 5 years) or directed (unscheduled, following a complaint, PI misconduct, or safety issues pertaining to a study or a site). FDA usually (but not always) will make an appointment for a suitable date to start the inspection. An unannounced inspection is possible (typically for cause, such as a complaint). Once the UofL IRB is notified of an inspection the following individuals should be notified.

• IRB Chairs and Vice Chairs
• EVPRI
• Assistant Vice President Risk and Compliance
• University Counsel assigned to EVPRI

Any additional notifications to University personnel will be handled by the EVPRI.

Certain preliminary steps are followed for all inspections. The FDA investigator will ask to see the person in charge, typically the IRB Chair, HSPPO Director, or designated individual. Upon arrival the Institutional representative will be given a Form FDA 482, Notice of Inspection, by the FDA inspector. The person who receives the Form 482 should be sure to see the FDA investigator’s credentials and photo identification card. This starts the inspection.

Inspections typically will include interviews, a review of IRB policies and SOPs, evaluation of the IRB’s performance through inspection of selected records, and facility tours (particularly with regard to IRB record storage). FDA will determine an IRB’s compliance with regulations based on these activities.

Documents that are inspected typically include policies and SOPs; records of IRB membership; IRB reports; IRB approvals and corresponding documentation; study folders; meeting minutes; significant risk (SR) vs non-significant risk (NSR) device determinations; correspondence to/from sites, sponsors, and FDA; organizational charts; emergency use approvals; complaints from subjects; training/qualification records; and IRB study databases.

Research Site Inspection
The following describes the process to be followed when the principal investigator (PI) is notified by a federal regulatory agency (e.g. FDA, OHRP, DOD, NIH) that an inspection or an audit will occur. It is important to notify University offices as soon as the site is aware to ensure availability of personnel and time to assist with a pre-audit review, if needed.

1. PI must notify the IRB in writing about inspections/audits being conducted by a federal regulatory agency, as soon as possible. This notice is emailed to HSPPO@louisville.edu. This notice should include:
   • IRB number
   • Protocol
   • Date and location of planned inspection
   • Name of agency conducting the inspection
   • Type of audit: random or for cause
2. In addition, the PI should notify the Institutional Compliance Officer and their Department Chair.

3. If time allows, the Compliance Monitor will conduct a comprehensive review of the IRB file, research participant records, and regulatory files in advance of the inspection to ensure compliance with IRB policies and federal regulations.

4. The PI should notify the HSPPO Director or Assistant Director as soon as the exit interview is scheduled. The HSPPO will send at least one representative to be involved in the exit interview.

5. Any report issued by the federal regulatory agency as a result of the inspection/audit must be submitted to the IRB for formal review within 5 business days of receipt.

6. The PI must notify the IRB immediately by phone and writing, if any federal agency suspends a study or requests a clinical hold on the study.

7. Within 10 working days of receipt of the final agency report, the PI must submit any written response to the IRB for its review and approval BEFORE sending that final response to the federal agency.

8. Once the final letter from the federal agency it must be submitted to the IRB, through the electronic submission process within 5 working days.

Inspection information listed above should be submitted to the IRB using the Amendment form in the electronic system.
In this chapter:

4.1 **Education of Individuals Responsible for Human Subjects Research Review**
   - Human Subjects Protection Program Office (HSPPO) Staff
   - Evaluation of Qualifications
   - Contributing to the Improvement of Expertise
   - Educational Materials and Resources
   - Education Planning
   - Attendance at Local, Regional and National meetings

4.2 **Required Training in Human Subjects Protections**
   - Investigator and Study Personnel Required Training
   - HSPPO and IRB Staff Required Training
   - IRB Member Required Training
   - Institutional Officials Required Training

### 4.1 Education of Individuals Responsible for Human Subjects Research Review

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<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
<tr>
<td>I.1.E.</td>
<td>The University of Louisville has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.</td>
</tr>
</tbody>
</table>

Education and training are provided to all individuals involved with the HSPP. The HSPP Policy Manual specifies education requirements for IRB members, IRB staff, and key personnel on the research team (see Chapter 4.2).

Education is offered in many areas of research, including ethical standards, related both to research and to professional conduct, University of Louisville policies and procedures, and applicable federal, state, and local law.

The foundation of ethical training at University of Louisville is the Belmont Report, which is made available at training sessions and on the HSPPO website.

**Human Subjects Protection Program Office (HSPPO) Staff**

The HSPPO has staff dedicated to developing and providing education for IRB Chairs, IRB members, HSPPO and IRB staff, and the research community regarding human subjects’ protections.

**Evaluation of Qualifications**

In addition to receiving training on human subject research protections (described in Chapter 4.2), IRB members and IRB staff are reviewed periodically to evaluate their understanding of the HSPP (ethical principles, policies and procedures, and regulations).

IRB staff qualifications are reviewed during the hiring process and annually or as needed to ensure a high level of commitment to the HSPP.

IRB member qualifications are reviewed by the HSPPO Director or Associate Director during the recruitment process, and IRB members are formally appointed by the Executive Vice President for Research and Innovation. IRB members, including IRB Chairs, are evaluated yearly to ensure that their service on the IRB contributes to the ethical and regulatory...
review of research at University of Louisville. Investigators at the University of Louisville are evaluated according to individual institution, school, and department policies.

**Contributing to the Improvement of Expertise**

New IRB members and HSPPO staff receive orientation to the University of Louisville HSPP. All IRB Chairs, IRB members, and HSPPO staff receive regular, ongoing training, and continuing education. Opportunities for continuing education in human research protections are announced on a regular basis. IRB members and HSPPO staff attendance is encouraged at regulatory and professional meetings and conferences, both locally and nationally, for web broadcasts and seminars at University of Louisville, and in the greater community. Educational presentations and articles of interest are also presented at IRB meetings and documented in the meeting minutes. Additionally, the HSPPO supports and encourages professional certification for qualified IRB staff.

IRB staff and IRB Chairs are encouraged to take the certification examination for designation as a Certified IRB Professional.

**Educational Materials and Resources**

The University of Louisville research community, IRB members, HSPPO and IRB staff and other individuals responsible for the protection of human research participants have access to a wealth of educational material, available online and in printed format, or offered as courses or workshops. They include, among others:

- The HSPPO website, with links to the University of Louisville HSPP Policy Manual, instructional information, educational material, document templates, forms, and guidance.
- Access to required training through the interactive online Collaborative Institutional Training Initiative (CITI) Course: Human Subjects and HIPAA Research Training. This course combines human subjects protection training with HIPAA research training.
- Regular and ad hoc communications from the HSPPO.
- The Research Integrity Program website.
- The IRB electronic submission system, iRIS, providing instructional text and explanation as part of the application.
- The University of Louisville Research Handbook, in particular, Chapter 9.1, Research Regulations, Human Subjects Protection Program Office.
- A copy of IRB: Management and Function, Robert Amdur, MD and Elizabeth Bankert, is provided to each new IRB member, and to HSPPO staff.
- A copy of Protecting Study Volunteers in Research, Cynthia Dunn, MD and Gary Chadwick, PharmD, MPM, CIP, is provided to each new IRB member, and to HSPPO staff.

**Education Planning**

Routinely HSPP staff meet to design the education plan for the research community. The plan incorporates input received from IRB members, IRB staff and investigators, and from the compliance monitoring program. Trends in research at University of Louisville are considered, and new federal, state or local regulations (or published guidance) are integrated. Compliance activities (e.g., internal and external audits) also provide input into the education plan, which is presented to the HSPPO Director and other senior managers for review and approval. The HSPP office hosts routine educational sessions for research staff including open office hours, presentations, and workshops.

**Attendance at Local, Regional and National meetings**

HSPPO staff, IRB Chairs/Vice Chairs and IRB members are provided the opportunity to attend local, regional or national meetings. The Executive Vice President for Research and Innovation supports attendance at these meetings.
4.2 Required Training in Human Subjects’ Protections

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<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
<tr>
<td>I.1.D</td>
<td>The University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to sponsors, researchers, research staff, research participants, and the Institutional Review Board, as appropriate.</td>
</tr>
<tr>
<td>III.2.A</td>
<td>Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization’s policies and procedures regarding the protection of research participants.</td>
</tr>
</tbody>
</table>

University of Louisville employs the Collaborative Institutional Training Initiative (CITI) course as its training program. Required CITI training for investigations includes, but is not limited to, modules on the history and ethical principles of human subject research, basic IRB regulations and review process, informed consent, HIPAA regulations, and research with vulnerable participants. University of Louisville requires a refresher training course to be completed every four years. Completion of the required training is a condition for exempt, expedited, or full board IRB approval of protocols, regardless of the project’s source of funding.

**Principal Investigator and Study Personnel Training**

University of Louisville requires that PIs and other key personnel involved in the conduct of a project confirm completion of training in the protection of human research participants. Individuals involved in the design or conduct of a project include co-PIs, research coordinators, professional staff, persons administering informed consent or surveys, post-docs, and students. Collaborating individuals operating under the University of Louisville’s FWA and third party (subcontract) research personnel or consultants must also comply with this education requirement.

Principal Investigators (PIs), as part of the protocol submission process, acknowledge their obligation to protect the rights and welfare of research participants. It is the responsibility of the PI to ensure completion of the required training by all study personnel at all times during the study.

The IRB required training of investigators and other key personnel must be completed prior to submission of an Initial Study Application, Continuing Review, or Personnel change amendment for approval. Training information electronically transmitted by CITI posts to the IRB electronic submission system. Workflow for the above processes will not allow submission of Initial Study Application unless the appropriate training is documented within the IRB electronic submission system. If Human Subjects and HIPAA Research training have not been completed, the study will not be approved.

**Key personnel** are research personnel who are directly involved in conducting the research with human subjects through an interaction or intervention for research purposes, including participating in the consent process by either leading it or contributing to it; OR who are directly involved with recording or processing identifiable private information, including protected health information, related to those subjects for the purpose of conducting the research study.

The IRB training requirement applies to individuals working under the auspices of University of Louisville, whether at University of Louisville facilities or at another location, and regardless of their institutional affiliation or source of funding. In the event that individuals from other institutions (“third-party” or contract employees) conduct research...
under the auspices of University of Louisville, they must complete human subjects’ protections training, but may do so at their home institution. A letter, certificate, or email notification by a representative from their home institution will satisfy this requirement. For example, when the University of Louisville is the IRB of Record (IOR) for another institution, and an IRB Authorization Agreement has been signed, individuals from the relying institution may provide proof of training (as noted above) to satisfy the training requirement. Similarly, new University of Louisville employees can meet the training requirement if they have completed human subjects’ protections training at their prior institution within the applicable timeframe. Third-party individuals and new University of Louisville employees may also take the University of Louisville CITI modules, if desired.

Electronic feeds of course completion information from CITI are received by University of Louisville. Training records of IRB Chairs and Members, HSPPO staff, and Institutional Officials are also maintained through the IRB electronic submission system.

### HSPPO Required Training

<table>
<thead>
<tr>
<th>Training</th>
<th>IRB Staff, HSPPO Staff</th>
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<tbody>
<tr>
<td>Human Subjects and HIPAA Research Training (CITI)</td>
<td>Required</td>
</tr>
<tr>
<td>Continuing HSPP education</td>
<td>Required</td>
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</tbody>
</table>

For newly hired HSPPO or IRB staff, HSPP orientation and training is a process managed by the HSPPO Directors(s). Combined CITI Human Subjects and HIPAA training must be completed within 30 days of employment in HSPPO, and must be renewed every four years.

### IRB Member Required Training

<table>
<thead>
<tr>
<th>Training</th>
<th>Medical and SBE IRB Members and Chairs</th>
<th>Ex-Officio IRB Members</th>
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</thead>
<tbody>
<tr>
<td>HSPP orientation for new members</td>
<td>Required</td>
<td>If needed</td>
</tr>
<tr>
<td>Human Subjects and HIPAA Research Training (CITI)</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Human Subjects and HIPAA Research Continuing education (CITI Refresher course)</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>IRB Administration</td>
<td>Required for Chairs</td>
<td>Not required</td>
</tr>
</tbody>
</table>

### Institutional Officials Required Training

Institutional officials at University of Louisville University must take CITI Institutional Official modules. If an institutional official is also an investigator or an IRB member, additional CITI modules would be required.
In this chapter:

5.1  Research with Test Articles
5.2  Research with Drugs
5.3  Research with Devices
   - Significant Risk Device Research
   - Non-significant Risk Device Research
   - Exempt Device Research
   - In Vitro Diagnostic Device Research
5.4  Radiology Devices and Radioactive Materials
5.5  Research with Biologics
5.6  Sponsor-Investigator Research
5.7  Internal Handling of Test Articles
5.8  Expanded Access to Investigational Drugs and Devices for Treatment Use
   - Drugs
   - Devices
5.9  Emergency Use of a Test Article
5.10 Humanitarian Use Device (HUD); Orphan Drugs
5.11 Planned Emergency Research

<table>
<thead>
<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
<tr>
<td>I.7.A</td>
<td>When research involves investigational or unlicensed test articles, University of Louisville confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.</td>
</tr>
</tbody>
</table>

This chapter outlines policy for:

- research using investigational drugs, devices, or biologics (in this chapter, the term investigational means unapproved drugs, unapproved devices or devices not cleared to market, or unlicensed biologics)
- research with FDA-approved drugs, approved/cleared devices, or licensed biologics (sometimes called “commercially available”)
- sponsor-investigator research
- radiation devices and radioactive materials
- handling (inventory control and storage) of investigational drugs, devices, or biologics
- emergency, humanitarian, or compassionate use of investigational drugs, devices, or biologics

FDA regulates clinical investigations (research) “that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.” (See 21 CFR 56.101)

All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.
Required Study Registration

**ClinicalTrials.gov:** Applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), must be registered on ClinicalTrials.gov; clinical trial information must be submitted for inclusion in the clinical trial registry databank (Public Health Service Act, section 402(j)) and a corresponding statement added to the consent form.

Applicable clinical trials are:

- Drug or biologic studies, with or without IND (except Phase 1, expanded access/compassionate use, or drug being used as part of routine care and not under study)
- Device studies, with or without IDE (except small feasibility studies, expanded access/compassionate use, or device being used as part of routine care and not under study)

University of Louisville guidance for clinicaltrials.gov registration can be found at: https://louisville.edu/research/ccd/investigators/clinicaltrials-gov-registration.

Comparison of FDA and HHS Regulations

The FDA web page Comparison of FDA and HHS Human Subject Protection Regulations outlines differences between FDA regulations and OHRP 45 CFR 46 regulations for the protection of human subjects. Where regulations differ, the IRB applies the stricter one.

5.1 Research with Test Articles

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Research with FDA-regulated test articles may commence only after the IRB has approved the protocol and:

- receives documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); The IND goes into effect generally 30 days after the FDA assigns the IND, unless the sponsor receives earlier notice from the FDA; or
- formally determines and documents that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or
- formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

For research requiring an IND, the IRB will not issue final approval of the study until the valid IND is in place. The researcher must not begin recruiting, obtaining consent, and/or screening participants for the study until the valid IND is in effect and final IRB approval letter has been received.

Definitions

**Biologic:** A biological or related product, regulated by the FDA, including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a
medical device. FDA regulates biologics general use and licensing under 21 CFR 600 and 601, (42 U.S.C 262 of the Public Health Service Act.

**Clinical investigation**: Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug and Cosmetic Act (FD&C Act), or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part. (See 21 CFR 56.102)

**Combination product**: A product containing a combination of a drug, a device, or a biological product. Studies of combination products are regulated according to the IND or IDE regulations, depending on the components of the product. The FDA determines which of its organizational components has primary jurisdiction for the premarket review and regulation of products that are comprised of any combination of a drug, device, and/or biological. (See 21 CFR 3.2(e))

**Human subject**: An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A participant may be either a healthy individual or a patient. (See 21 CFR 56.102)

**Off-Label**: Use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications. See FDA "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices.

**Test article**: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (See 21 CFR 56.102)

**Compassionate use/Expanded Access**: A potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Prior IRB approval is required. See FDA Expanded Access.

**Humanitarian Device Exemption (HDE)**: A Humanitarian Device Exemption (HDE) is an application that is similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

**Non-significant Risk (NSR)**: An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the IRB regulations to identify certain studies that may be approved through an "expedited review" procedure.

**Significant Risk (SR) Device**: An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.
5.2 Research with Drugs

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Clinical investigations of drugs are subject to the Investigational New Drug Application (IND) regulations, 21 CFR 312. An investigational new drug application (IND) is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met.

Applications for research on the use of a drug, unless that research is exempt from the IND regulations, must be accompanied by documentation from the FDA that includes a valid IND number. The IND number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IND numbers may not be validated with an Investigator Brochure (which may serve multiple INDs).

As stated in 21 CFR 312.2(b), clinical investigation of a drug is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.8 (promotion and charging for investigational drugs).

Additionally, a clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR 312 if the investigation does not otherwise require submission of an IND. Clinical investigations that are exempt from IND regulations still require IRB review and approval.

Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of off-label uses of approved drugs or biologics should contact the FDA regarding obtaining an IND before submitting a protocol to the IRB.

See the FDA guidance for FDA’s current thinking on exemptions from IND regulations for oncology combination protocols. See the FDA guidance IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products.
5.3 Research with Devices

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<tbody>
<tr>
<td>I.7.A</td>
<td>When research involves investigational or unlicensed test articles, University of Louisville confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.</td>
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Clinical investigations of devices are subject to the Investigational Device Exemptions (IDE) regulations, 21 CFR 812. An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, PMA) or cleared to market (via 510(k)) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk investigational devices must have an IDE issued by FDA before they can be shipped. Non-significant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a non-significant risk device.

Research with devices falls into three categories:

- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of non-significant risk devices to determine safety and effectiveness of the device
- Investigations exempted from the IDE regulations

See:

- Guide-028 - Significant Risk (SR) and Non-significant Risk (NSR) Medical Device Studies
- Frequently Asked Questions Medical Devices [FDA],
- Significant Risk and Non-significant Risk Medical Device Studies [FDA]

Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure.

Initial review by the expedited procedure might also be designated for certain NSR device studies involving no more than minimal risk and satisfying criteria for expedited review categories 1 or 4.

**Significant Risk Device Research**

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. The IDE number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs).

**Non-significant Risk Device Research**

When research is conducted to determine the safety or effectiveness of a device, the organization confirms that the device fulfills the requirements for an abbreviated IDE (21 CFR 812.2(b)(1)):

- The device is not a banned device;
- The sponsor labels the device in accordance with 21 CFR 812.5;
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
• The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, consent under 21 CFR 50 and documents it, unless documentation is waived;
• The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
• The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
• The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7); and
• The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

If the investigator applies to the IRB for a non-significant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB shall notify the investigator and the sponsor, if appropriate.

Exempt Device Research
Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories (Criteria in 21 CFR 812.2(c)):

• A device legally marketed in the US that is used or investigated in accordance with the indications in the FDA-approved labeling.
• A diagnostic device (that is, an in vitro diagnostic device) if the testing:
  o Is non invasive,
  o Does not require an invasive sampling procedure that presents significant risk,
  o Does not by design or intention introduce energy into a participant, and
  o Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
• A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
• A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.
• A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
• A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

A clinical investigation involving an in vitro diagnostic biological product (i.e., blood grouping serum, reagent red blood cells, or anti-human globulin) is exempt from IND requirements if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21CFR312.160.

In Vitro Diagnostic Device Research
In vitro diagnostic (IVD) device investigations may be exempt from the IDE requirements of 21 CFR 812 if the devices are properly labeled and meet the criteria set forth in 21 CFR 812.2(c)(3). However, such studies are still subject to the FDA regulations and IRB review requirements if the research is to support an application for research or marketing of the
device (see 21 CFR 50.1). This is true regardless of whether the samples to be used are individually identifiable or not. The FDA regulations define a participant to include a human on whose specimens an investigational device is used (21 CFR 812.3(p)). Thus, an IVD study to support a premarket submission to the FDA is considered a human subject investigation and is subject to IRB review under 21 CFR parts 50 and 56. IVD research may be eligible for expedited review and conducted without informed consent if the study involves leftover human specimens and as long as participant privacy is protected by using only specimens that are not individually identifiable, when appropriate.

In addition to the above, FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable makes clear that IRB review is one of several criteria for IVD studies using leftover specimens that are not individually identifiable.

5.4 Radiology Devices and Radioactive Materials

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The FDA regulates radiology devices and radioactive materials used in research. Oversight for issues of radiation safety at the University of Louisville is handled by the Radiation Safety Committee (RSC). RSC membership includes representatives of both the faculty and administration. The RSC sets University policies and oversees the implementation of all aspects of the safe use of radioisotopes and radiation on the Belknap campus, the Health Sciences Campus, the Shelby Campus and the U of L Hospital.

5.5 Research with Biologics

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Clinical investigations of biologics are regulated in the same way as clinical investigations for drugs, and require an IND, unless the biologic is part of a combination product that the FDA has assigned for premarket approval to the Center for Devices and Radiological Health (CDRH). In such cases, the biologic/device combination product would require an IDE prior to research approval by the IRB.

Generally, protocols using biological agents or recombinant DNA vectors are reviewed by Biomedical IRB and the Institutional Biosafety Committee (IBC).

5.6 Sponsor-Investigator Research

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<tr>
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<td>University of Louisville has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.</td>
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</table>

_Sponsor-Investigator (IND):_ means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under FDA regulation, include those applicable to both an investigator and a sponsor.
**Sponsor-investigator (IDE):** is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

In reviewing research involving test articles, the IRB determines if a University of Louisville investigator holds his or her own IND or IDE. If so, the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA. See FDA Investigational New Drug Application and IDE Application.

**Sponsor-investigators** who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE and any University of Louisville required approvals for applying for an IND or IDE. Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate policies and procedures in place to comply with the FDA regulatory requirements.

**Investigator-held INDs**
A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities. Check with the Office of University Counsel for any University guidance that may be required.

**Investigator-held IDEs - Significant Risk Devices**
A sponsor-investigator for an IDE protocol must follow the FDA regulations in 21 CFR 812. Check with the Office of University Counsel for any University guidance that may be required.

**Non-significant Risk Device Studies when Investigator Acts as Sponsor**
Investigators studying non-significant devices, regulated by the abbreviated IDE regulations, have abbreviated sponsor responsibilities when there is no industry sponsor.

## 5.7 Internal Handling of Test Articles

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For clinical investigations, University of Louisville promotes researchers’ adherence to ICH guidelines as presented by the FDA in the form of the Consolidated Guidance for Good Clinical Practice (GCP).

All studies submitted to the University of Louisville IRB that involve an investigational drug or device must have a dispensing plan in place. Those studies that are not utilizing pharmacy oversight must submit their dispensing plan to the IRB prior to receiving approval.

## 5.8 Expanded Access to Investigational Drugs and Devices for Treatment Use

Expanded access to investigational drugs and devices requires prior IRB review and approval (with the exception of Emergency Use).
Drugs

*Expanded access*: Use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition. [*21 CFR 312.300 (Subpart I)*]

*Expanded Access Programs (EAPs)*: The FDA uses this term to refer to the various types of allowable expanded access use.

*Immediately life-threatening disease or condition*: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

*Serious disease or condition*: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

There are 3 categories of expanded access program (EAP) for investigational drugs:

I. Single patients, including for emergency use (*21 CFR 312.310*).
II. Intermediate-size patient populations (*21 CFR 312.315*).
III. Treatment IND or “treatment protocol” for widespread treatment use (*21 CFR 312.320*).

Devices

The FDA may make an unapproved device available under several mechanisms:

- *Emergency Use*
- *Compassionate Use* (or Single Patient/Small Group Access)
- *Treatment Use* (Larger Group/More Widespread Use)
- *Continued Access*

5.9 Emergency Use of a Test Article

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<tr>
<td>I.7.C</td>
<td>University of Louisville has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.</td>
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</tbody>
</table>

*Emergency Use*: Use of a test article on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (*21 CFR 56.102(d)*). Specific additional requirements apply; see HSPP guide 009, *Emergency Use of a Test Article* and FDA *Emergency Use of an Investigational Drug or Biologic*. 

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Louisville KY 40202-1798
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Service Acct: hsppofc@louisville.edu
5.10 Humanitarian Use Device (HUD); Orphan Drugs

**Humanitarian Use Device (HUD)**
A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. The regulations under [21 CFR 814 (Subpart H)](https://www.accessdata.fda.gov/cdrh_docs/regulatory.html) were designed to promote the development of devices for diseases affecting these populations.

**Orphan Drugs**
The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S. These drugs are not expected to recover the costs of developing and marketing as treatment drugs.

5.11 Planned Emergency Research

**Planned emergency research**: Planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived ([21 CFR 50.24](https://www.accessdata.fda.gov/cdrh_docs/regulatory.html)).

The research plan must be approved in advance by the FDA and IRB. The research plan must also be disclosed to the communities where the research will be conducted and from where participants will be drawn, including presentation of the risks and expected benefits of the research. An independent data monitoring committee (DMC) must be established to exercise oversight of the research. Advance notice of these protocols will be provided to the Office for Human Research Protections pursuant to federal regulation 45 CFR 46.101(i).

PIs who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB.

Planned emergency research is usually not eligible for emergency use approvals.

See [Exception from Informed Consent Requirements for Emergency Research](https://www.accessdata.fda.gov/cdrh_docs/regulatory.html) [FDA]. Full details are listed in chapter 12.6.
In this chapter:

6.1 **Authority of the Institution and Authority of the IRB**
   - Authority of Institution
   - Authority of IRBs
   - Purpose of the IRBs
   - Prohibition against Others Using IRB Approval Authority or Using Undue Influence
   - Decisions of the IRB
   - Responsibilities to Regulatory Agencies

6.2 **Review of IRB Composition, Members and IRB Chairs**
   - Appointment of Members and Length of Service
   - Appointment of IRB Chair and Length of Service
   - Compensation of IRB Members
   - Alternate IRB Members
   - Administrative Designees
   - Ex Officio IRB Members
   - Removal of IRB Members
   - Liability Coverage for IRB members

6.3 **IRB Member Duties and Responsibilities**

6.4 **Scientific and Scholarly Expertise of IRB Members**

6.5 **Obtaining Additional Expertise – Consultants and Ad Hoc Reviewers**

6.6 **IRB Member, IRB Staff, and Consultant Conflicting Interest**

6.7 **Separating Competing Business Interests from Ethics Review Functions**

6.8 **Assessment and Evaluation of the IRB**

6.9 **Relationships with Other Affiliated Institutions**
   - Jefferson County Public Schools
   - UofL Health and Norton Healthcare
   - Veteran Affairs Medical Center (VAMC)

6.10 **Review by Other University Committees**
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   - Radiation Safety Committee

6.11 **Review by Other University Offices**
   - Conflict of Interest and Commitment Office
   - Office of Sponsored Program Administration (OSPA)
   - OSPA Negotiation Core
   - Commercialization EPI-Center (EPI-Center)
   - Privacy Office
   - Office of Research Integrity

6.12 **Relationships with Industry Sponsors and Other IND or IDE Holders**
6.1 Authority of the Institution and Authority of the IRB

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<tr>
<td>I.1.A</td>
<td>The University of Louisville (UofL) has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.</td>
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<tr>
<td>I.1.C</td>
<td>The University of Louisville (UofL) has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants.</td>
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**Authority of the Institution**

The President of the University of Louisville has delegated the authority and responsibility to establish, maintain and oversee the HRPP to the Executive Vice President for Research and Innovation (EVPRI).

The Executive Vice President for Research and Innovation delegates independence and authority to the IRBs. UofL has demonstrated a commitment to human subject protections by establishing a human subjects protection program led by a University of Louisville official, the Executive Vice President for Research and Innovation (EVPRI), with sufficient standing, authority and independence to ensure implementation and maintenance of the program. The University utilizes a centralized program to review all human subjects’ research. The University of Louisville, at present, operates two Institutional Review Boards (IRBs), Biomedical IRB and Social Behavioral Educational (SBE) IRB, that review projects in a wide range of medical, biomedical, social, education and behavioral fields. As a part of the University of Louisville’s continued commitment to human subjects’ protections, the resources allocated to the IRBs are constantly monitored to ensure the existence of adequate support of IRB functions (See Chapter 2, Resources Supporting the Human Subjects Protection Program).

All human subject research conducted by or under the auspices of the University of Louisville will be performed in accordance with Title 45 Code of Federal Regulations, Parts 46, 160 and 164 and Title 21 Code of Federal Regulations Parts 50, 56, 312, and 812. In addition, the actions of the Institutional Review Boards (IRBs) at the University of Louisville will also conform to all applicable Federal (Food and Drug Administration, National Institutes of Health, Department of Education, Department of Energy, Office for Human Research Protections (OHRP), etc.), regulations, guidance, state and local laws.

Activities that constitute human subject research are determined by the University of Louisville IRBs. The IRBs delegate this decision to the IRB chair or experienced member designee. The decision by the chair or designee is based on whether the activity:

1. Represents “research,” involves “humans” as participants, and “engages” the University of Louisville (as defined in 45 CFR 46.102(d), 45 CFR 46.102(f), and the OHRP guidance document “Engagement of Institutions in Research” respectively).

2. Represents a clinical investigation of a test article involving one or more humans as participants (as defined in 21 CFR 50.3(c), 21 CFR 50.5(j), and 21 CFR 50.5(f) respectively) or individuals (humans) on whose specimens an investigational device is used (21 CFR 812.3(p)).

**Research** is defined in federal regulations as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

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1 45 CFR 46
Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

Clinical Trial (for studies approved on or after January 21, 2019) is defined in the “Common Rule” as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Human subjects (for studies approved prior to January 21, 2019) are defined in the “Common Rule” as “living individuals 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.” The FDA regulations define human subjects as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control or individuals on whose specimens an investigational device is used. A participant may be either a healthy human or a patient. The appropriate definition depending on the type of human research will generally apply to all human research conducted by investigators at the University of Louisville.

Human subjects (for studies approved on or after January 21, 2019) are defined in the “Common Rule” as living individuals about whom an investigator:

- Obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. All human subjects research carried out at the University or under its auspices must be reviewed and approved by an IRB prior to the start of the research. The IRBs are guided by the principles of The Belmont Report and the regulations and policies set forth by the DHHS and its subordinate agencies and offices in reviewing all human subjects’ protocols.

University of Louisville IRBs review human subject’s research projects when:

1. the research is sponsored by the institution or one of its affiliated institutions,
2. the research is conducted by or under the direction of any employee or agent of the institution in connection with his or her institutional responsibilities,
3. the research is conducted by or under the direction of any employee or agent of the institution using any property or facility of the institution,
4. the research involves the use of the institution’s non-public information to identify or contact human subjects, or
5. any research determined by the Institutional Official (IO).

The EVPRI has the authority to review decisions of the IRB. In the case of an approval decision, should the EVPRI conclude that a project does not fully comply with policies or obligations of the University of Louisville, the project may be disapproved, suspended, or terminated on behalf of the institution. In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the EVPRI or any other officer or agency of the University of Louisville, state government, or federal government may not reverse the decision. Affiliated Institutional Officials retain the same authority as the University’s Institutional Official for their respective organizations. Affiliated institutions will utilize their own internal policies and procedures to manage conflicts of interest unique to their institution.

If a project does not fully comply with policies or obligations of the University of Louisville, the project may be disapproved, suspended, or terminated on behalf of the institution.
Research covered by this policy that has been approved by a University IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, as per 45 CFR 46.112 and 21 CFR 56.112, those officials may not approve the research if a University of Louisville IRB has disapproved it.

Authority of the IRBs
The authority conveyed to the Biomedical and SBE IRBs includes the following:
1. review and approve all non-exempt human subject research in which it is determined that the risks to participants are reasonable in relation to potential benefits to participants and society;
2. review and determine the exempt status of new research projects;
3. approve the research contingent upon receipt of specific modifications requested by the IRB. The HSPP/IRB will draft correspondence to investigators requesting specific modifications to the application, protocol, study documents or the informed consent form. The requested modifications must be specific enough to allow the IRB chair to determine whether the responsive materials provided by the investigator match the modifications required by the IRB. The IRB will be informed of these approvals at the next regularly scheduled meeting.
4. defer the research pending further communication between the investigator and the IRB. Studies are deferred when the IRB has substantive concerns or significant requests for clarification. Responses to the IRB correspondence in this category must be returned to the full IRB for deliberation and review;
5. review and disapprove the initiation of new research projects in which it is determined that the risks to participants are not reasonable in relation to potential benefits to participants and society;
6. require from investigators revisions in research protocols and informed consent documents as a condition for initial or continuing approval;
7. monitor the activities of approved projects including regularly scheduled continuing review as required, and verification of compliance with approved research protocols and informed consent procedures;
8. develop mechanisms for prompt reporting to the IRB of any planned changes in approved projects prior to the implementation of those changes;
9. develop mechanisms for prompt reporting to the IRB of any adverse experiences occurring in approved projects, or reporting of unanticipated problems involving risks to subjects or others (UPIRTSO), in other projects related in context to the approved projects;
10. suspend or terminate previously approved research;
11. restrict aspects of research for the purposes of human subjects protection;
12. review and monitor the use of test articles (investigational drugs, biologicals and devices);
13. serve as the privacy board of the University of Louisville’s hybrid covered entity (HCE);2
14. recommend sanctions to the Office of the Executive Vice President for Research and Innovation (EVPRI) for cases of non-compliance investigated and found actionable by the IRBs; and/or
15. report human research violations to the appropriate officials.

Purpose of the IRBs
The purpose of the Human Subjects Protection Program and the University of Louisville IRBs is to protect the rights, dignity, welfare, and privacy of human research subjects at the University by adhering to the principles of the Belmont Report and the regulations of the Department of Health and Human Services (DHHS). The Program is committed to advancing responsible conduct in research, ethical treatment of human research subjects, and ensuring that the right of every human being to voluntary, informed consent to research is respected.

The purpose of the UofL IRBs is to:
1. Approve, modify (to secure approval), or disapprove all human research conducted by the organization,
2. Suspend or terminate research not conducted in accordance with the regulations, statutes, principles, or IRB’s requirements mentioned above or when unanticipated problems occur,
3. Observe, or to have a third party observe, the consent process,
4. Observe, or have a third party observe, the conduct of the research, and
5. Serve as the Privacy Board for the University of Louisville.

The Human Subjects Protection Program serves its purpose by:

1. Administratively supporting the University’s Institutional Review Boards,
2. Reviewing all research involving human research subjects before it is initiated,
3. Working to protect the rights and welfare of human research subjects by fostering and advancing the ethical and professional conduct of persons and organizations that engage in research with human participants,
4. Providing education to researchers, research staff and the public,
5. Conducting periodic reviews of research involving human subjects.

Prohibition against Others Using IRB Approval Authority or Using Undue Influence

“Undue influence” means attempting to interfere with the normal functioning and decision-making of the IRB or to influence an IRB member or staff, a PI or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision or action by the IRB or one of its members or staff.

To prevent undue influence of IRB members, the IRB preserves the anonymity of members assigned as reviewers to specific protocols or protocol events.

Any IRB member or staff who believes that they have been subject to inappropriate influence should report this immediately to the IRB chair or the Director, Human Subjects Protection Program, who will report the attempt to influence to the Executive Vice President for Research and Innovation (EVPRI). The EVPRI will investigate, or have investigated, the attempt to influence and determine an appropriate response to the attempt based on penalties similar to those outlined in the University’s Sanctions for Violations of University of Louisville Research Policies.

The types of response to attempts to unduly influence the IRB are determined as appropriate to the situation, by either the Director, Human Subjects Protection Program or the Executive Vice President for Research and Innovation.

The IRB has the statutory and institutional authority to take any action necessary to protect the rights and welfare of human research participants involved in research. For example, the IRB assesses suspected or alleged protocol deviations, participant complaints, or violations of external regulations or University of Louisville policies. The IRB has the authority to suspend or terminate the enrollment or ongoing involvement of research participants in research as it determines necessary for the protection of those participants. The IRB also has the authority to observe or monitor any human research to whatever extent it considers necessary to protect research participants, (45 CFR 46.109, 46.112, and 46.113).

Decisions of the IRB

IRB approval is always necessary before a research project involving research participants may begin. An IRB decision to not approve a human research project, or require modifications as a condition for approval, cannot be overturned by any University of Louisville official or University of Louisville committee.

The IRB must provide the investigator with a written statement of the reasons for not approving proposed research and must give the investigator an opportunity to respond in person or in writing. The IRB must carefully and fairly evaluate the investigator’s response in reaching a final determination.

If an investigator has concerns with respect to procedures or decisions of the IRB, the investigator may discuss his/her concerns with the Executive Vice President for Research and Innovation with the understanding that no University
official or committee may approve a protocol that has not been approved by the decision of one of the IRBs, nor apply undue pressure on the IRB(s) to reverse a decision. Investigators must first put their concern(s) in writing to the Executive Vice President for Research and Innovation, who may use his or her sole discretion to determine the process for responding to an investigator’s concern, including:

- Notifying the IRB of the concern and requesting a response and relevant information from its records
- Submitting the concern to mediation if the investigator agrees to participate
- Appointing a fact-finder to review the matter and report back
- Seeking assistance from consultants or internal administrative units such as the Office of Audit Services or Office of University Counsel.

Responsibilities to Regulatory Agencies
The IRB must comply with the requirements of all relevant federal regulatory and compliance enforcement agencies or offices, including OHRP and FDA, as well as relevant agencies of the Commonwealth of Kentucky.

6.2 Review of IRB Composition, Members and IRB Chairs

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<td>The IRB has qualified leadership (e.g., chair and vice chairs) and qualified members and staff. Membership and composition of the IRB are periodically reviewed and adjusted as appropriate.</td>
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Each IRB has a qualified Chair, members and staff whose membership and composition is reviewed and adjusted annually by the HSPPPO Director in consultation with the EVPRI and the IRB Chair(s). This review ensures that individual IRB Chairs and members have the knowledge, skills and abilities appropriate to their respective roles and perform their responsibilities in an acceptable manner.

University of Louisville policy requires that the IRB be constructed according to DHHS regulations and FDA regulations (45 CFR 46.107 and 21 CFR 56.107). Additionally, the IRB shall include a nonscientific IRB member. These individuals may not have meaningful scientific or medical training or experience. Health professionals, regardless of discipline, may not be considered nonscientists. At least one nonscientist IRB member must always be present to have a quorum.

Appointment of Members and Length of Service
IRB members are nominated from a variety of sources, including previous IRB members, division chiefs, department chairs, compliance administrators, faculty, hospital pharmacy and nursing staff, research laboratories, senior administrative IRB staff, and various public groups. Consideration is given to balancing race, gender, expertise, and cultural backgrounds. People with active licensure from various clinical disciplines are sought.

A background knowledge of and current familiarity with affiliated institutional concerns helps ensure that the local research context is brought to IRB deliberations. Newly identified nominees are contacted by the HSPPPO Director (or delegate) about their willingness to voluntarily serve on the IRB and their availability for the coming year. When a nominee agrees to serve on the IRB, his or her CV and any relevant correspondence are reviewed by the HSPPPO Director and the appropriate IRB Chairs/Vice Chairs.

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To avoid any possible conflicting interests or influence on IRB determinations due to competing business interests, individuals who are responsible for development activities (including raising funds), or are in a position to influence programmatic and budgetary decisions may not serve as IRB Members. See Chapter 6.7.

University of Louisville IRB members or alternates (hereafter referred to collectively as members) will be appointed by the EVPRI in accordance with 45 CFR 46 and 21 CFR. Committee members, chairs, and vice-chairs serve at the discretion of the EVPRI.

IRB members are appointed utilizing the following criteria:

1. Each IRB will consist of at least five and not more than twenty-one voting members, with varying backgrounds to promote complete and adequate review of human research activities commonly conducted by the institution.

2. Each IRB will be sufficiently qualified through the experience, expertise, and diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

3. The IRB will consist of both male and female members, otherwise qualified for the positions.

4. Each IRB will consist of members of various professions including at least one scientist, one nonscientist, and one member who is not otherwise affiliated with the institution, and who is not part of the immediate family of a person who is affiliated with the institution (community member).

5. No IRB will consist entirely of members of one profession. Each IRB will consist of members of various professions including at least one scientist, one nonscientist, and one member who is not otherwise affiliated with the institution, and who is not part of the immediate family of a person who is affiliated with the institution (community member).

After an extensive review of a potential member’s education, experience and other characteristics that might add diversity to the IRB, a new IRB member is formally appointed by the EVPRI. Members serve five-year renewable terms (from date of appointment). At the conclusion of the fiscal year, members’ contributions are evaluated by the IRB Chair with the HSPPO Director. If their service is satisfactory, and continued membership is mutually desired, they are eligible for reappointment. All members may be re-appointed at the end of their terms without lapse in service.

Members are expected to attend IRB meetings on a regular basis, serve as primary reviewers for research within their areas of expertise, and serve as general reviewers on all research. Members may also be asked to participate in subcommittees, ad hoc committees, audits, and education, as long as there is no conflict of interest with their IRB responsibilities or their other personal or professional roles.

Once appointed, the IRB member will complete an Attestation and Disclosure Form (ADF) that requires updating annually (at a minimum). The IRB members will be reminded to complete the ADF by electronic reminder messages sent through the IRB electronic submission system.

IRB Member Non-Disclosure Agreements (NDAs) will be given to the members at time of appointment (or if NDA language is revised) and IRB staff will ensure that the NDAs are signed and returned.

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3 45 CFR 46.107, 21 CFR 56.107
Appointment of IRB Chair and Length of Service

IRB Chairs are nominated by previous and current IRB members, division chiefs, deans, department chairs, and compliance administrators. In addition to the characteristics sought in an IRB member, these individuals possess demonstrated skills in leadership and group process. Typically, they have served on an IRB previously.

IRB Chairs are formally appointed by the EVPRI. Chairs serve five-year renewable terms. At the conclusion of the IRB fiscal year (and on an interim basis if needed) the IRB Chairs’ contributions are evaluated by the HSPPO Director. If their service is satisfactory, and their continued service is mutually desired, they are eligible for reappointment. Chairs are eligible to serve two consecutive terms.

These individuals are respected, active members of the University community who are well informed in regulations relevant to the use of human subjects in research. The term of service is at the discretion of the EVPRI. Whenever the chair or vice chair is not available to conduct IRB business, the chair or vice chair may designate a board member to assume his/her responsibilities during the period of his/her absence.

IRB chairs and vice chairs should have experience in conducting human subjects research, have thorough knowledge of federal regulations and state statutes concerning human subjects research, and understand University of Louisville research policies, conflict of interest policies, and knowledge of ethical guidelines governing research.

Responsibilities of the chair, or their designee, include: determining the type of review (exempt, expedited, full board), running full board meetings, reviewing minutes prepared by staff, reviewing specific revisions to protocols/consent documents that are required as conditions of approval, and reviewing local serious adverse event reports and any reports of unanticipated problems involving risks to subjects or others. In addition, they serve as a resource for investigators and IRB members regarding issues related to University, state and federal policies on human subjects’ research.

The IRB Chair works with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research participants are adequately protected.

Compensation of IRB Members

IRB Chairs’ departments receive a percentage of their salaries to offset the time dedicated to IRB duties. IRB Vice Chairs receive an hourly rate to offset the time dedicated to IRB duties. IRB members who are affiliated faculty or staff members generally do not receive monetary compensation for their service on the IRB. However, it is recognized that service on the IRB requires a significant investment of time for all members.

IRB members who are not otherwise affiliated with the University of Louisville or its collaborating institutions who are not compensated by their sponsor or employer will be paid for their service on the IRBs at the rate of $25.00 per hour, unless waived by the committee member. As stated in OHRP guidance, compensating unaffiliated members in this way does not create an affiliation or cause a conflict of interest.

Alternate IRB Members

Alternates replace regular IRB members who are unable to attend convened meetings of the IRB. They are required to have the same qualifications and characteristics of expertise and diversity as the regular IRB members for whom they substitute. When an alternate substitutes for a regular member, the alternate member has access to the same materials that the regular member would have access to through the Electronic Submission System (ESS).

IRB membership rosters specify which regular member each alternate member is qualified to replace. The expertise or qualifications of alternate members are similar to those of the regular member they replace, and in some case, alternate
members are able to represent similar interests or a specific vulnerable population. Terms of appointment, length of service, and duties are exactly as for regular IRB members. Alternate members must adhere to the same conflict of interest standards and documentation requirements as regular IRB members.

If an alternate member attends a convened meeting at which his or her regular member is in attendance, one of them does not vote. Ad hoc substitutions for regular or alternate IRB members are not permitted.

The HSPPPO Director, HSPPPO Associate Director, IRB HIPAA Analyst, and selected IRB Analysts serve as alternate members of both the Biomedical IRB and the SBE IRB.

Administrative Designees
The HSPPPO IRB Analysts perform pre-review of all items submitted to the IRB for review and approval. They are considered Administrative Designees. Administrative Designees may also request administrative modifications to submitted materials prior to assignment of submissions to IRB Chairs, Vice Chairs and IRB reviewers.

IRB Analysts have permission to approve the following items administratively. Upon analyst review, if there are concerns related to participant safety, non-compliance, or other issues, an IRB chair/IRB member is assigned to review.

1. Study Personnel Changes (excluding PI changes)
2. Non-complicated study closure to enrollment (for example if closed due to safety issue)
3. Non-complicated study closure (for example if closed due to safety issue, non-compliance, etc.
4. Study closures when PI withdraws submission pre-IRB approval
5. Changes to HIPAA documents requested by HIPAA reviewer when the Primary Reviewer has “approved as submitted” or “approved with changes” and the only changes were HIPAA related.
6. Grammar/formatting changes in documents that do not change the content or meaning of the document
7. Additions/Deletions of study sites
8. IRB Authorization Agreements (IAA). These can be processed in coordination with HSPPPO Director and/or Associate Director, including amendments for IAA continuing review letters where another institution is the IRB of record.
9. Enrollment changes (increases/decreases)
10. DSMC letters that indicate no changes
11. Submissions that the reviewer “approves with changes” and the only requested change is adding specific section(s) of the IRB template language such as the 1099 language, Clinicaltrials.gov language, or other verbatim section of the current IRB template.
12. Submission response forms when the submission has been approved with changes and the only change was to update CITI training, upload CVs, and/or ADF completion (ADF completion may need to go to a reviewer/board meeting if there is a conflict).
13. Submission response forms when the IRB reviewer indicated on their previous review checklist that the analyst could process the response administratively.

HIPAA Analyst (as an IRB Member) can serve as the Primary Reviewer on:
- Case Reports
- NHSR with de-identified data (not quality improvement submissions)
- Submissions only related to HIPAA documents
Ex Officio IRB Members

An ex officio member is designated as an IRB member by virtue of that individual’s office. Some ex officio members serve on other University of Louisville compliance committees and may provide expertise to IRB members. Ex officio members may participate in the IRB deliberations to provide information and expertise as requested by the IRB. Ex officio members are expected to adhere to the same conflict of interest standards and documentation requirements as regular IRB members and alternates. Ex officio members may not vote on any IRB action or determination, and for this reason are sometimes referred to as “non-voting” members.

The Biomedical IRB accepts permanent ex officio representatives from the following areas:

- Office of University Counsel
- Associate Vice President for Research and Innovation (Chief of Staff)
- Institutional Biosafety Committee
- Radiation Safety Committee
- Research Officials from Affiliated Hospital Organizations

The SBE IRB accepts permanent ex officio representatives from the following areas:

- Office of University Counsel
- Associate Vice President for Research and Innovation (Chief of Staff)
- Research Officials from Affiliated Hospital Organizations where behavioral research sites are located

The IRB may accept additional permanent ex officio members with the agreement of the IRB Chair and the HSPPO Director.

Removal of IRB Members

Members of the IRB may be removed before the end of their term. Removal is at the sole discretion of the EVPRI, at the recommendation of the chair of the IRB on which the member participates, or the chair of the member’s department or dean of the college or school the member represents.

Liability Coverage for IRB members

University of Louisville provides liability coverage under its insurance programs for IRB members acting in good faith in the performance of their IRB duties. The University of Louisville Office of Risk Management provides liability coverage of volunteer individuals, including community IRB members. All University of Louisville, University-related faculty, staff, and students are likewise covered in their capacity as employees and students.

6.3 IRB Member Duties and Responsibilities

Duties of members include reviewing human subject application materials in advance of meetings and being prepared to discuss issues related to human subjects protections, serving as primary reviewer when requested by the chair, and having an understanding of the specific requirements of human subjects regulations. Member duties include:

1. Protecting the rights and welfare of research subjects.

2. Determining that risks to subjects are minimized.

3. Ensuring that the investigators:

   a. use procedures that are consistent with sound research design and that do not expose subjects to risk,
b. whenever appropriate, use procedures already being performed on the subjects for diagnostic or treatment purposes, and

c. follow a procedure for properly documenting informed consent (IRB members are encouraged to review chapter 4, Informed Consent in the University of Louisville Investigator’s Guide for a comprehensive review of the informed consent process).

4. Determining that risks to the subjects are reasonable in relation to the anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB member should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB member should not consider possible long-range effects of applying knowledge gained in the research.

5. Determining that selection of subjects is equitable. In making this assessment, the following should be taken into account:

a. The purpose(s) of the research and the setting in which it is conducted.

b. Special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.

c. Women and members of minority groups and their subpopulations must be included in all clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the IRB that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

d. The inclusion (recruitment process) of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

6. Determining if the informed consent is adequate and contains all other federally or locally mandated elements, and if not, request clarifications and changes in the consent form in order to adequately explain the purpose of the research, the risks and benefits entailed therein.

7. Determining that the research plan makes adequate provision for ensuring the safety of the subjects.

8. Determining that there are adequate provisions to protect the privacy of subjects and to maintain the privacy of the subjects and confidentiality of the data, in accordance with the DHHS and FDA regulations. Investigators who conduct research under the direction of the University of Louisville must develop a plan for each protocol submitted to protect the privacy and confidentiality of subjects. The conditions for maintaining confidentiality of

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4 45 CFR 46, 160, 164 and 21 CFR 50
the subjects and the research records are required for the life of the data. The assigned protocol reviewer is responsible for assessing the efficacy of the plan.

9. Ensuring additional safeguards are in place to protect the rights and welfare of subjects that are likely to be vulnerable to coercion or undue influence, such as children, students, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.5,6

10. Before the IRB meeting, the IRB member should:

   a. Review all required documentation in the application submission package.

   b. Discuss any questions about the assigned projects with the investigator, other IRB members, or consultants.

   c. Decide whether the investigator should attend the meeting to discuss any problems or concerns noted with the project.

   d. Determine if specific changes are needed in the application, protocol or consent form, and come to the meeting with recommended wording to be transmitted to the investigator.

As soon as deemed appropriate by the IRB chair, the committee member may prepare and present initial submission reviews at full-committee meetings, review and present continuation and review materials at full-committee meetings, present local serious adverse event reports or reports of unanticipated problems at full-committee meetings, and recommend any changes, additions, deletions or actions in any of the above.

6.4 Scientific and Scholarly Expertise of IRB Members

Wide-ranging scientific or scholarly expertise among IRB members allows the IRB to review the broad variety of research in which University of Louisville investigators are engaged. These policies and procedures require IRB members to be knowledgeable about all relevant regulatory requirements, and to strive to remain impartial and objective during protocol review, deliberation and voting. The IRB includes several members who are particularly knowledgeable about research ethics and the vulnerable research participants included in University of Louisville research.

The IRB uses a “primary reviewer” system. The IRB Analysts, in consultation with the HSPPO Associate Director and/or IRB Chair where appropriate, assign protocols to primary reviewers, based on each individual’s scientific, scholarly, professional, or clinical expertise. Primary reviewers must have the relevant expertise to conduct an in-depth review of the protocols to which they are assigned. If the HSPPO Associate Director/IRB administrator cannot identify a primary reviewer with the appropriate scientific or scholarly expertise, the IRB administrator arranges for expert consultation and will not place the protocol on an agenda until appropriate expertise is made available. Primary reviewers are expected to conduct an in-depth review, and it is the responsibility of primary reviewers to notify the IRB Chair or IRB staff should they feel unqualified or unable to do so. In such cases, the IRB Chair will assign primary review responsibilities to another member who is appropriately qualified or obtain consultation from one or more experts outside the IRB.

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process includes one or more individuals who are knowledgeable about or experienced in working with these participants (children, pregnant women, adults unable to consent, students, etc.). The IRB staff reviews each application to determine whether it involves participants vulnerable to coercion or undue influence, and considers the participant population when assigning reviewers.

5 45 CFR 46.111(a)
6 21 CFR 56.111(a)
The IRB is constituted to possess and make use of collective knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites, and their capabilities and limitations; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants’ perspectives.

6.5 Obtaining Additional Expertise – Consultants and Ad Hoc Reviewers
The IRB Chair or IRB staff reviews the proposed convened meeting agenda and determines whether the IRB has the required expertise to review upcoming research. If not:

- The IRB Administrator, in consultation with the IRB Chair, will invite individuals with competence in the specific areas needed to assist in evaluating issues that require expertise beyond or in addition to that available on the IRB.
- On an as-needed basis, an IRB primary reviewer may invite individuals with competence in special areas to assist in evaluating specific issues.

Reasons for seeking additional or special competence from outside experts may include (but are not limited to) the need for additional scientific, clinical, or scholarly expertise; the need for particular knowledge and understanding about potentially vulnerable populations of subjects; the desire to ensure appropriate consideration of race, gender, language, cultural background, and sensitivity to such issues as community attitudes.

The IRB Administrator, or the IRB Chair makes initial contact with a proposed consultant and notifies the consultant of the IRB member conflict of interest policy. When a consultant is used, that fact, and the pertinent information gained from the consultant’s assessment, is documented at the time of the protocol discussion, and recorded in the IRB minutes. In some cases, a consultant may provide the IRB with a written report of his or her assessment which is kept with the protocol file. The IRB staff can assist in making the consultation arrangements and in obtaining the required conflict of interest documentation.

All consultants, internal or external to University of Louisville, must comply with the IRB conflict of interest policy. They are not considered ad hoc IRB members, and cannot vote with the IRB.

6.6 IRB Member, IRB Staff, and Consultant Conflicting Interest

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<td>II.1.D</td>
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See 45 CFR 46.107(e); 21 CFR 56.107(e).

IRB Member’s Disclosure of a Conflicting Interest
Conflicting Interests may be declared when:

- Protocols and reports are first received by members assigned to review;
- During discussion and voting in convened meetings; and
- When consultants are asked to advise the IRB.
This policy applies to all projects reviewed by the IRB, regardless of whether the project is exempt or considered during full Board review, expedited, or continuing review. This policy also applies to reviews of non-compliance reports and unanticipated problems involving risks to participants or others.

IRB intake procedures take into account conflicts of interest when assigning new protocols to an IRB, such as when any IRB member is named in the research protocol or has a spousal relationship with any research personnel.

IRB members who realize they have a conflicting interest when they are first assigned a protocol or report for review must notify the IRB staff or IRB Chair immediately so that the protocol can be reassigned.

IRB members review the Agenda before a convened meeting with the issue of conflicts in mind. Any conflicting interest for protocols to be voted on must be reported to the IRB Chair or HSPPO Director before the meeting whenever possible.

The IRB Chair begins each meeting with a reminder that proceedings are confidential. This is followed by a reminder of the requirement that each member must disclose any conflicting interest and recuse him or herself from the discussion of and vote on the project by leaving the room, except if the member is providing information at the IRB’s request.

If other IRB members need to request information about the project from the IRB member with the conflicting interest, the IRB member may remain in the room during the presentation of the project. The IRB member must then leave the room during the IRB’s discussion and vote.

IRB staff will record in the minutes a recusal based on a conflicting interest. The IRB member will not be counted as part of the quorum for review of the protocol. (Should the quorum fail, the IRB may not take further action or vote on the project.)

An abstention may be acknowledged at any time when an IRB member has any other concerns that in his or her own judgment warrant abstaining from review, deliberation, and voting on a project.

Consultant’s Disclosure of a Conflicting Interest
The definition of conflicting interest as defined in the Guidelines for IRB Members on Conflicting Interest extends to any consultant who may be asked to review a protocol. The IRB Administrator who contacts a consultant to inquire about review of a project is responsible for asking if the consultant has a conflicting interest in the project. If such an interest exists, then the protocol will not be assigned to the consultant.

If the consultant is internal to the University of Louisville, the HSPPO will reach out to the COI Office to ensure that a current ADF is on file and request any management plans. If the consultant is external to the University of Louisville, a Non-Disclosure Agreement (NDA) will be sent to the consultant via email. The consultant will answer the same questions and provide the same information that a regular IRB member would be required to make in their ADF. The consultant’s NDA must be completed and returned to the HSPPO prior to the contracted consultant’s review. A statement will be added to the minutes indicating that a completed disclosure has been received for the consultant and it is on file with the HSPPO.

If a consultant with a conflicting interest is the only appropriate resource for the IRB, (e.g., is the only scientist with sufficient technical understanding of the project) and if that consultant has been asked to provide information to the IRB, then the conflict of interest must be disclosed to the IRB members reviewing the protocol or present in the convened meeting where the information is presented. Such a consultant is excluded from discussion except to provide information requested by the IRB, and must leave the meeting room during discussion and voting.
IRB Staff and Conflicting Interest

IRB Staff must not participate in the review of research protocols, and must not make exempt determinations for research protocols in which they have a conflict of interest. IRB staff who realize they have a conflicting interest when they are first assigned a protocol or report for review must notify their supervisor immediately so that the protocol can be reassigned.

The University of Louisville Attestation and Disclosure Form is completed annually by IRB Staff who are involved in protocol review.

6.7 Separating Competing Business Interests from Ethics Review Functions

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The University of Louisville recognizes that officials who administer research programs, and individuals who are responsible for development activities (including raising funds), may represent competing business interests, or be in a position to influence programmatic and budgetary decisions and exert undue influence on IRBs or individual IRB members. To avoid such influence on IRB determinations, the Executive Vice President for Research and Innovation, School Deans, Institute or Center Directors and other University of Louisville officers will not serve as voting members of the IRBs, unless there are compelling reasons to do so. Such reasons must be justified in writing and include specific measures to manage any conflict of interest or the possibility of undue influence.

Due to their supervisory and institutional decision-making functions, these individuals frequently encounter conflict of interest situations beyond those faced by most covered individuals. They often do not directly conduct sponsored activities, teach or conduct outreach in their administrative capacities but may be in a position to influence how these activities are conducted and reported. Their external interests and activities must be disclosed to prevent any real or perceived institutional conflicts of interest.

Thus, the institutional leaders, as described above, do not serve as members on the IRB or carry out day-to-day operations of the research review process.

6.8 Assessment and Evaluation of the IRB

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The composition and membership of each IRB is evaluated annually by the HSPPO Director and the IRB Chairs and is adjusted as needed to ensure appropriate knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites and their capabilities; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants’ perspectives. Due to the increased complexity of human research protocols submitted, this often results in adding members. The composition of each IRB may change as often as needed. Education, training and periodic evaluation of IRB members, IRB Chairs, and IRB staff is discussed in Chapter 4.
6.9 Relationships with Other Affiliated Institutions

The University of Louisville IRBs coordinate IRB reviews with the affiliated institutions listed below. None of these affiliated institutions are a formal part of the UofL IRB structure, but there is communication between the institutions regarding status of review and/or conditions of approval. These institutions all have their own Federal-wide Assurances and they name the University of Louisville IRBs as IRBs who may review research for their facilities.

Jefferson County Public Schools (JCPS). When possible, a representative of the Jefferson County Public Schools serves on the SBE IRB. The SBE IRB may provide informal expertise and consultation to the JCPS IRB. JCPS has procedures that must be followed in order to conduct research in the school system. Information can be found on the JCPS website at https://www.jefferson.kyschools.us/departments/research-systems-improvement.

UofL Health, including James Graham Brown Cancer Center, and Norton Healthcare. The University of Louisville’s IRBs provide IRB review and oversight for human subjects research conducted at the above sites by University affiliated investigators.

The respective hospital research offices reviews each study for completeness and issues a site approval letter for all research approved for their facilities. Investigators may not initiate research at the sites until site approval is given.

Veterans Affairs Medical Center (VAMC). The VAMC Research and Development Committee (R&D) reviews and approves all research conducted at the VAMC. For guidance on submitting a research study to the VA R&D, see Guide 039 Studies involving the Robley Rex VA Medical Center.

6.10 Review of Research by Other University Committees

The IRB is required at times to participate with other University committees that also have responsibility for the ethical oversight of research within the HSPP. In some cases, the approval of another University of Louisville body may be required prior to or in addition to IRB review.

Institutional Biosafety Committee: Protocols involving biosafety materials and requiring review by the Institutional Biosafety Committee (IBC) must be reviewed and receive an approval letter in addition to review by the IRB. The HSPP Director and Associate Director are ex-officio members of the IBC and receive communications directly from the IBC regarding submitted protocols.

The IBC is administratively located in the DEHS and ensures that research involving recombinant DNA complies with the National Institutes of Health (NIH) guidelines. All such research that is not exempt from NIH recombinant DNA guidelines must be registered with the University of Louisville DEHS. It is the Principal Investigator’s responsibility to ensure these registration documents are reviewed and approved by the IBC prior to initiation of research.

Radiation Safety Committee: If a study involves any investigational radioisotopes or radiation-producing machines, the Radiation Safety Committee must certify that it has reviewed a protocol using investigational radioisotopes or radiation machines and recommends it for approval. It is the Principal Investigator’s responsibility to ensure review and approval from the RSC is obtained prior to conducting research. The RSC must have the IRB approval in order to issue RSC approval.

If RSC review is completed after the IRB review, the IRB chair reviews any RSC comments. If the chair believes the suggested changes are appropriate and qualify as minor modifications, the IRB chair reviews these through an expedited process. If changes exceed minor modifications, the IRB chair refers the application back to the full board for review. If the chair determines that full-committee review is necessary, the HSPP will notify the investigator and the RSC that the study has been placed on administrative hold until the concerns are addressed by the IRB.
6.11 Review by Other University Offices

Conflict of Interest and Commitment Office: All investigators’ conflicting interests are managed via the Conflict of Interest Office (COIC Office) and its associated Conflict Review Board (CRB). Information concerning Conflicts of Interest and Commitment is available within the integrated research administration system software utilized by the compliance units at the University of Louisville. The IRB will not approve a protocol until any disclosed COI has been reviewed and resolved by the CRB, and as appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict has been determined by the CRB. Staff of the HSPPO and the COIC share conflict of interest information as well as individual and institutional significant financial conflict of interest management plans.

Office of Sponsored Programs Administration (OSPA): Staff of the HSPPO and IRB may consult with the OSPA when questions arise concerning whether appropriate clearances have been received for the human subjects research involved in a grant application or award. Consultation is on an as-needed basis.

OSPA Negotiation Core: The Negotiation Core of OSPA provides support services to faculty and staff conducting clinical trials and other research involving human subjects. The Negotiation Core supports research sponsored by industry, both nonprofit and for-profit organizations, as well as funded research that flows through third parties and federal and state funding contracts. This includes governmental flow-through if funding to the university is via industry sponsors and non- or for-profit organizations.

The Negotiation Core’s support services include negotiation of contracts/agreements and the review and submission of proposals and applications. The IRB is notified once contracts are executed and IRB Compliance staff review the sponsored contracts to ensure research injury language presented in the executed contract matches the context of the language in the informed consent document(s). Additionally, the Nonfinancial Agreement Core negotiates Data Use Agreements when those are required.

Commercialization EPI-Center (EPI-Center): Staff of the HSPPO and IRB may consult with the EPI-Center, UofL’s technology transfer office, concerning Material Transfer Agreements which may be associated with the shipment of blood, specimens, or data to another institution.

Privacy Office: Staff of the HSPPO and IRB members often consults with the University Privacy Officer on matters concerning the management of personal health information (PHI) as it relates to the enforcement of Health Insurance Portability and Accountability Act (HIPAA) of 1996 research regulations. Consultation is on an as-needed basis and may be initiated by the IRB, the HSPPO, or the Privacy Officer. Additionally, the HSPPO employs a HIPAA Analyst for review of submissions where HIPAA regulations apply. The HIPAA Analyst sends administrative modifications to the investigator for required modifications in authorizations or waivers.

Office of Research Integrity: The HSPPO and ORI work together and share information concerning possible research misconduct and violations of University of Louisville research oversight policies.

6.12 Relationships with Industry Sponsors and Other IND or IDE Holders

Unless specifically required by the FDA or requested by the sponsor, the IRB will not routinely provide written notification of IRB decisions to industry sponsors and other holders of INDs or IDEs (University of Louisville sponsor-investigators excepted). For FDA-regulated research, clinical investigators generally serve as the link between the IRB and the sponsor, and are required to do so by the FDA in compliance with their obligations as clinical investigators. This relationship is agreed to by investigators when they sign FDA Form 1572 (for drug and biologic studies) or an investigator agreement for device studies.
There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The IRB staff may engage in such direct communication on behalf of the IRB when the IRB Chair or the HSPPO Director considers it desirable. The clinical investigator will be kept apprised of such communication.

The FDA indicates that direct communication between the sponsor and the IRB may be appropriate when the IRB does not accept a sponsor’s Non-significant Risk (NSR) designation of a medical device (21 CFR 812.66). Direct communication between the sponsor and the IRB is required for the waiver of informed consent in planned emergency research relative to (a) the public disclosures required under 21 CFR 56.109(a)(7)(ii),(iii); or (b) disapproval of such a waiver under 21 CFR 50.24(e). See Chapter 5.11.
In this chapter:

7.0 **FUNCTIONS OF THE IRB: SYSTEMATIC REVIEW OF SUBMISSIONS TO THE IRB**
- Ethical Principles Governing Human Subjects Research
- Scientific and Scholarly Merit and Departmental Review
- Essential Definitions and Determinations of Research Covered by the HSPP
- Implementation of the Revised Common Rule

7.1 **Use of Decision Trees and Guide for Determination of Is It Research?**

7.2 **Protocol Review**
- Requirements to be Satisfied to Approve Research
- Fundamental Considerations for Approval of Research
  * Study Design
  * Risks and Benefits
  * Equitable Selection of Subjects
  * Informed Consent/Assent
  * Monitoring for Data Safety
    - Review of Data Safety Monitoring Plan
    - IRB Continuation Review and Data Safety Monitoring Findings
  * Privacy and Confidentiality
  * Special Considerations for Projects Involving Vulnerable Populations
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7.3 **Levels of IRB Review**
- IRB Exemption Determination
- IRB Expedited Review by Chair(s) and Senior Members
- IRB Full Board Review
- IRB or Administrative Determination of Not Human Subjects Research (NHSR)
- Administrative Determination of Not Engaged in Research (NEIR)

7.4 **Types of IRB Study Applications**
- IRB Submission Application
- Case Report Application
- Emergency Use (EU) Application
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7.5 **IRB Applications - Electronic Submission System (ESS)**

7.6 **Receipt of Submissions**
- Intake process
- Administrative Review by IRB Analysts Prior to Assignment to Primary Reviewer
- Assignment of Primary Reviewer
- Approval Criteria

7.7 **Review of Initial Submissions by the Convened IRB**
- Quorum
- Materials Available at Convened Meetings
- Meeting Deliberations
- Utilizing Guidance Documents for Special Findings When Approving a Protocol
- Range of Actions on Research Protocols at Convened Meetings
7.0 Systematic Review of Submissions

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<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
<tr>
<td>I.1.A</td>
<td>The University of Louisville has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.</td>
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<tr>
<td>I.1.D</td>
<td>The University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Subjects Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate.</td>
</tr>
<tr>
<td>I.1.F</td>
<td>The University of Louisville has and follows written policies and procedures for reviewing the scientific and scholarly validity of a proposed research study.</td>
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Ethical Principles Governing Human Subjects Research

The primary ethical principles applied to research covered by the HSPP, including protocols “exempt” under federal regulations pertaining to human subject research, are those set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The three main principles are:

1. **Respect for persons** (e.g., applied by obtaining informed consent, giving consideration to privacy and confidentiality, and adding protections for vulnerable populations)
2. **Beneficence** (e.g., applied by weighing risks and benefits)
3. **Justice** (e.g., applied by the equitable selection of subjects)

All parties involved in the conduct of research (researchers and research staff, IRB members and Chairs, HSPPO and IRB staff, employees and students) are expected to also adhere to the principles of expertise (“competent to do the work”) and integrity (“faithfully adhere to professional principles”). Ethical principles from other sources (e.g., International Conference on Harmonization) may also be applied to research covered by the HSPP, for example:

- To an individual protocol because its particular circumstances raise a type of ethical issue that most other protocols do not,
- When they are recognized by the federal or other funding source or the state or country where the research will occur,
• When they have been developed for specific areas or types of subjects (e.g., embryos and fetal tissue, illiterate subjects).

Scientific and Scholarly Merit and Departmental Review (SSMR)
The University of Louisville is committed to protecting the rights and welfare of human subjects involved in research. Protection of subjects includes an assessment of the benefits of the research and of the risks, and the determination of an appropriate and favorable ratio between the two. The scientific or scholarly merit of a research activity may affect the benefits that could result from the research and therefore impact the risk benefit equation.

To determine that the approach is sound and the research design will yield valid results, research projects involving human subjects and conducted by University of Louisville faculty, staff, or students, or for which the University is responsible, will be reviewed prior to its submission to the IRB.

When the SSMR and Department Chair/Unit Head are completing the departmental scientific or scholarly merit review, the following areas should be considered. The SSMR should make evaluative statements about the strengths and weaknesses of the proposal.

a. **Significance:** Does this study address an important problem? If the aims of the project are achieved, how will knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

b. **Innovation:** Does the project employ novel concepts, approaches, or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

c. **Approach:** Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project (please consider the appropriateness of the proposed budget and duration relative to the proposed research)? Does the principal investigator acknowledge potential problem areas and consider alternative tactics? If the research involves activities that could have an adverse effect on humans, are the proposed means adequate for protecting against or minimizing such effects.

d. **Principal Investigator:** Is the principal investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

e. **Environment:** Does the environment in which the work will be done contribute to the probability of success? Does the research take advantage of unique features of the environment or employ useful collaborative arrangements? Is there evidence of institutional support?

Reviewers should consider all or part of the following factors:

a. **Scientific or scholarly merit of the proposal.**
   1. Conceptual adequacy of hypothesis;
   2. Clarity and delineation of objectives;
   3. Adequacy of the description of the undertaking and suitability and feasibility of methodology;
   4. Demonstration of feasibility through preliminary data (if available);
   5. Probability of success of project;
   6. Novelty, uniqueness and originality; and

b. **Qualifications of proposed project personnel and adequacy of facilities.**
1. Training and demonstrated awareness of previous and alternative approaches to the problem identified in the proposal, and performance record and/or potential for future accomplishments;
2. Time allocated for systematic attainment of objectives;
3. Institutional experience and competence in subject area; and
4. Adequacy of available or obtainable support personnel, facilities, and instrumentation.

The following should be taken within the context of the research, the researcher’s qualifications (faculty, graduate student, or student) and the purpose of the research.

a. Is the Scholarly Activity likely to make a new and/or significant contribution to theory, method, or information?
b. Is the need for Scholarly Activity adequately demonstrated in a review of the literature?
c. Are the aims of the Scholarly Activity sufficiently clear?
d. Is the methodology clearly stated and does it relate to both need and aims?
e. Is the scope, time-scale, and planning of the work appropriate and realistic given the aims of the Scholarly Activity?
f. Does the applicant's Scholarly record (CV) support the likelihood of a tangible result?
g. Is there potential for publication or, where appropriate, some other tangible result which serves as an indicator of scholarly or professional achievement in the applicant’s discipline?

The SSMR will summarize the review by answering the following three questions and provide comments concerning each.

a) Will the research design yield valid results?
b) Does the research utilize acceptable practice for the discipline?
c) Does/Do the investigator(s) possess adequate qualifications to conduct the research?

The scientific merit and departmental review process takes place within the IRB ESS or by using the paper form located on the IRB website.

Submissions to the IRB that fall within an exempt, expedited, or full board review category must have SSMR and Department Chair signoff prior to IRB approval.

Responsibility for conducting such a review may be delegated to another committee provided that the circumstances and the identity of the committee is specified.

**Essential Definitions and Determinations of Research Covered by the HSPP**

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<td>I.1.A</td>
<td>The University of Louisville has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.</td>
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</table>

All human subject research conducted by or under the auspices of the University of Louisville will be performed in accordance with Title 45 Code of Federal Regulations, Parts 46, 160 and 164 and Title 21 Code of Federal Regulations Parts 50, 56, 312, and 812. In addition, the actions of the Institutional Review Boards (IRBs) at the University of Louisville will also conform to all applicable Federal (Food and Drug Administration, National Institutes of Health, Department of Education, Department of Energy, Office for Human Research Protections, etc.), regulations, guidance, state and local laws.
Activities that constitute human subject research are determined by the University of Louisville IRBs. The IRB delegates this decision to the IRB chair. The decision by the chair is based on whether the activity:

represents “research,” involves “humans” as participants, and “engages” the University of Louisville in research (as defined in 45 CFR 46.102(d), 45 CFR 46.102(f), and the OHRP guidance document “Engagement of Institutions in Research” respectively). The University of Louisville’s employees or representatives refers to individuals who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. “Employees and agents” can include staff, students, gratis faculty, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

represents a clinical investigation of a test article involving one or more humans as participants (as defined in 21 CFR 50.3(c), 21 CFR 50.5(j), and 21 CFR 50.5(f) respectively) or individuals (humans) on whose specimens an investigational device is used (21 CFR 812.3(p)) .

Research is defined in federal regulations as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Systematic Investigation is defined as a methodological procedure or plan, carried out in an organized manner, involving testing and evaluation, designed to develop or contribute to generalizable knowledge. A process that entails going from identification and articulation of the scientific or technological obstacles/uncertainties, hypothesis formulation, through testing by experimentation or analysis, to the statement of logical conclusions. A predetermined method for answering certain questions or studying a specific program or topic.

Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

Human subjects are defined in the “Common Rule” as “living individuals 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.” The FDA regulations define human subjects as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control or individuals on whose specimens an investigational device is used. A participant may be either a healthy human or a patient. The appropriate definition depending on the type of human research will generally apply to all human research conducted by investigators at the University of Louisville.

When following FDA regulations: Research means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505 (i) or 520 (g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration
as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. (21 CFR 50.3(c), 21 CFR 56.102(c)).

Implementation of the Revised Common Rule
The revised common rule applies to federally funded or supported projects approved on or after the implementation date of January 21, 2019.

All projects reviewed and approved prior to the implementation date remain under the old rule. These projects retain their existing level of review and all other IRB requirements, including continuing review requirements.

Implementation Date: January 21, 2019
The following table describes the regulations that apply to the various categories of research before and after the January 21, 2019 implementation date.

<table>
<thead>
<tr>
<th>Research approved before Jan 21, 2019</th>
<th>Research approved on or after Jan 21, 2019</th>
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<tbody>
<tr>
<td>FDA regulated research</td>
<td>FDA Regulations</td>
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<tr>
<td>Research regulated by federal</td>
<td>Revised Common Rule</td>
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<tr>
<td>department or agency (other than</td>
<td></td>
</tr>
<tr>
<td>DOJ)</td>
<td>Use UofL ICF template</td>
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<tr>
<td>Unregulated research</td>
<td>Original Common Rule</td>
</tr>
<tr>
<td></td>
<td>Use UofL ICF template</td>
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<tr>
<td>Consent form exceptions that</td>
<td></td>
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<tr>
<td>are recommended, not required:</td>
<td></td>
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<tr>
<td>-Consent summary information</td>
<td></td>
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<tr>
<td>-Consent new elements</td>
<td></td>
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<tr>
<td>-Posting consent on public website</td>
<td></td>
</tr>
<tr>
<td>Research regulated by DOJ</td>
<td>Original Common Rule</td>
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<tr>
<td></td>
<td>Use UofL ICF template</td>
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7.1 Decision Trees and Guide for Determination of Is It Research?
The University of Louisville requires that human subject research be submitted to the IRB for review. Investigators may use the OHRP Decision Trees to guide them on whether their research can be expedited, exempted, or will require full Board Review.
7.2 Protocol Review

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<tr>
<th>AAHRPP Std./Element</th>
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<tr>
<td>II.2.E</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by the convened IRB:</td>
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<tr>
<td>II.2.E.1.</td>
<td>Initial review</td>
</tr>
<tr>
<td>II.2.E.2.</td>
<td>Continuing review</td>
</tr>
<tr>
<td>II.2.E.3.</td>
<td>Review of proposed modifications to previously approved research</td>
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<tr>
<td>II.2.F</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used.</td>
</tr>
<tr>
<td>II.2.F.1.</td>
<td>Initial review</td>
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<tr>
<td>II.2.F.2.</td>
<td>Continuing review</td>
</tr>
<tr>
<td>II.2.F.3.</td>
<td>Review of proposed modifications to previously approved research</td>
</tr>
</tbody>
</table>

All new human research at the University of Louisville and modifications to approved research (except when the modification is necessary to eliminate apparent immediate hazards to participants) must be prospectively reviewed by the IRB. In addition, no previously approved human subject research may be continued beyond the expiration date without prospective approval (continuing review). If a researcher does not provide continuing review information to the IRB or the IRB has not approved a study by the expiration date, all research activities must stop. Interventions and interactions on current participants must stop, unless there is an over-riding safety concern or ethical issue involved so that it is in the best interests of individual participants to continue participating. Enrollment of new participants must not occur.

Requirements to be Satisfied to Approve Research

In order to approve research, the IRB shall determine that all of the following requirements are satisfied:

1. Risks to participants are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to participants are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within its responsibility.

3. Selection of participants is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective participant or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

**Fundamental Considerations for Approval of Research**

Based on information provided by OHRP, the FDA, and other federal agencies, the IRB must consider the submission in its entirety prior to making a determination of approval, disapproval, and to defer. The following areas must be considered when reviewing IRB submissions:

**Study Design**

The IRB will consider the study design as described in the IRB review application and protocol insofar as it impacts the rights and welfare of the human subjects. The Office for Human Research Protections indicates in the *Protecting Human Subjects: Institutional Review Board Guide Book* that “...if a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even inconvenience them through participation in such a study.” Many experts agree that the IRB should approve only research that is both valid and of value. The IRB may request an expert consultant review or defer to scientific review committees, including the investigator’s departmental review, in order to determine whether a study design places subjects at unnecessary risk. The federal regulations allow the IRB to approve a study design that involves deception or withholding of information, if the strategies are justified and the protocol provides for a post-study debriefing of the subjects.

**Risks and Benefits**

The IRB will assess whether the risks to subjects are reasonable in relation to the anticipated benefits, if any, to the subjects, and the importance of the knowledge reasonably expected to result from the research. The IRB will consider only those risks and benefits that may result from the research. The federal regulations do not allow the IRB to evaluate the possible long-range effect of applying the knowledge gained through the research.

The IRB is required to review any possible benefits a participant may derive from participation in research, and/or the benefits of new knowledge that may justify asking a person to undertake the risks of the study¹.

**Considering Risk**

Assessing risk is an important component of the review process. As stated earlier, one aspect is to ensure that risks have been minimized, risks are appropriate given the expected benefits, and benefits are maximized. Each greater than minimum risk protocol submitted must contain a data and safety monitoring plan (DSMP) detailing how confidentiality is protected and, to the extent possible, risks are reduced to a minimum. This plan must be appropriate for the risks associated with the study.

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¹ Payment for participation in research is not considered a benefit.
The IRB determines the level of risk for all protocols and assigns the risk level to the study.

a. The research does not involve more than minimal risk to the participant;

b. The research is likely to benefit the participant directly, even if the risks are considered to be more than minimal;

c. The research involves greater than minimal risk with no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition; or

d. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the participant. Requests for approval of any research that exposes vulnerable populations to risks that do not meet a. through c. of the above criteria must be submitted to the United States Secretary of Health and Human Services for review and approval.

**Minimal Risk**

An especially prominent concept is that of minimal risk. By statute and custom, the IRB may consider studies, of only minimal risk as exempt from IRB approval, eligible for expedited review, or appropriate for alternatives to the requirement of written informed consent. According to the federal regulations, a risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychology examinations or tests.

Additional details on risk considerations and steps to minimizing risks is addressed in Chapter 9.

**Benefits**

The benefits of research fall into two categories: benefits to individuals and benefits to society. Research frequently provides subjects with treatment, diagnosis or examination for an illness or abnormal condition. In these cases, the research involves evaluations that may benefit the participants by improving their condition or providing better understanding of their disorder. Investigators should clearly detail those potential benefits for the IRB in the protocol, and subjects in the consent form, while not over stating these benefits. The investigator should attempt to maximize benefits to the greatest extent possible for potential subjects. The investigator should clearly state that the participant may receive no benefit from participation in the study.

Where research does not provide direct benefit to potential subjects, this should be stated in the protocol and in the informed consent form.

Although research may not always provide a benefit to society, researchers are encouraged to design research projects so that information, in the form of generalizable knowledge, can contribute to societal benefit whenever possible. Investigators should clearly detail these potential benefits for the IRB in the application, and for subjects in the informed consent form, while not overstating these benefits. Research that does not provide benefit to individuals is required to provide a reasonable likelihood of resulting in benefits for society.

**Equitable Selection of Subjects**

The selection of subjects should be equitable and free of any coercion, both explicit and implied. The IRB will consider the purpose of the research and the setting of the research. The IRB will determine if the burden placed on research subjects is disproportionate to the possible benefits of the study and that the inclusion and exclusion criteria are justified.
The IRB will closely examine research involving vulnerable participant populations, such as children, prisoners, subjects with cognitive disorders, or economically or educationally disadvantaged subjects. Primary reviewers who have expertise in representing vulnerable populations will be assigned to review research when subjects from these populations are to be included in the research. Other IRB members who may have expertise in a particular area related to the research will be asked to comment on the appropriateness of the research in the particular population. Protocol specific findings related to the research and the approvable category will be recorded in the minutes of the IRB meeting.

Women and members of minority groups and their subpopulations must be included in all clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the IRB that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

**Informed Consent/Assent**

In order to give informed consent to treatments or procedures involved in research, a person must be legally competent to do so and be eighteen years old (federal regulation and Kentucky statute requirement) or be legally competent and meet the definition of an emancipated child in the Commonwealth of Kentucky statutes.

The IRB will carefully review the informed consent process; when, where and how consent is obtained, and any provisions for the on-going consent of subjects.

Informed consent of the participant is one of the fundamental principles of ethical research with human subjects. While the IRB reserves the right to observe the consent process, the signing of the consent form, and the research procedures, such audits are rare and the IRB relies on a thorough review of the proposed consent process and form, as well as on the integrity of the investigator and their staff.

It is understood that informed consent will always involve or be based on one or more conversations between the investigator and the participant and/or the subject’s legally authorized representative (LAR) or research LAR. This is true if the requirement for written consent is waived, if a short form or oral consent process is used, or if full written consent is sought. In the case of short form and written consent, the written document that the participant signs serves as documentation that a dialogue has taken place and as a record that the participant has agreed to participate in the research. In addition to providing the participant with a signed copy of the consent form, the investigator must retain a copy of the consent form and, as necessary, document the consent process. University of Louisville IRB policy dictates that an investigator on the study must sign and date these consent forms within two weeks of obtaining the subject’s signature.

Regulations prohibit any investigator from involving a human being as a participant in research unless the investigator has obtained the legally effective informed consent of the participant or the participant's LAR. The FDA (drug or device studies) explicitly requires that consent forms be dated as well as signed by the participant or the participant's legally authorized representative. The DHHS regulations do not explicitly require consent forms to be dated. To avoid confusion between
DHHS and FDA regulated studies, the University of Louisville IRB has adopted the policy that subjects or their LAR will sign and date the consent form. The University of Louisville IRB has also adopted the policy that subjects will sign and date the assent form when University of Louisville is the IRB of record.

For additional information on informed consent, see Chapter 12.

**Monitoring for Data Safety**

To approve research, the IRB must determine that, when appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants [45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6)]. The IRB has authority to observe or have a third party observe the research [45 CFR 46.109(e)].

**Review of the Data Safety Monitoring Plan (DSM)**

The IRB primary reviewer reviews and evaluates the proposed DSM Plan and the administration and composition of the monitoring entity (ME) when applicable. The DSM Plan should include the appropriate elements and address required reporting. If additional expertise is needed, the IRB consults with individuals with appropriate clinical, scientific, or biostatistical knowledge.

The IRB may specify the timeframe for reporting the ME findings to the IRB, for example, for continuing review in less than a year, after a specific number of participants are enrolled, or after a serious adverse event has been reported.

**IRB Continuing Review and Data Safety Monitoring Findings**

The IRB considers relevant information since the previous IRB review and approval. The IRB pays particular attention to risk assessment and monitoring, and ensures that the conditions satisfied in order for initial IRB approval of the research are still fulfilled. It also may be appropriate for the IRB to confirm that any previously approved provisions for monitoring the research data have been implemented and are working as intended. If no DSMB reports have been submitted for a study where an established DSMB exists, PIs will be asked to submit any DSMB reports that have been submitted to date.

**Privacy and Confidentiality**

The IRB is required to review the method for prospective identification of subjects. The IRB will examine the means of identifying and contacting potential subjects and the methods for ensuring the subjects’ privacy and confidentiality are effective. Investigators are required to submit plans for ensuring the confidentiality of subjects.

**Special Consideration for Projects Involving Vulnerable Populations**

The IRB considers certain groups of human subjects to be particularly vulnerable in a research setting. The IRB considers additional protections for research activities involving pregnant women, human fetuses and neonates, prisoners, children, and cognitively impaired persons. In certain projects, special classes of subjects may also require additional protections. In reviewing these research projects, the IRB ascertains that the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population.

**Students and Employees as Research Participants**

Investigators should detail any extra precautions taken to safeguard the rights and welfare of subject populations. In the case of using employees or a student “participant pool,” the IRB should ensure that consent for participation is sought.

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3 45 CFR 46, Subparts B, C and D

4 Special classes include, for example: traumatized and comatose subjects, terminally ill subjects, elderly and aged persons, minorities, students, employees, normal volunteers, and international research subjects.
only under circumstances which minimize the possibility of coercion or undue influence, and that genuinely equivalent alternatives to participation are available.

Additional details on risk considerations and steps to minimizing risks for vulnerable populations are addressed in Chapter 9.

7.3 Levels of IRB Review

All human subject research conducted by or under the auspices of the University of Louisville will be performed in accordance with Title 45 Code of Federal Regulations, Parts 46, Subparts A-E of Part 46, 160 and 164 and Title 21 Code of Federal Regulations Parts 50, Subparts A,B, and D of Part 50, 56, 312, and 812. In addition, the actions of the Institutional Review Boards (IRBs) at the University of Louisville will also conform to all applicable Federal (Food and Drug Administration, National Institutes of Health, Department of Education, Department of Energy, Office for Human Research Protections, etc.) regulations, guidance, state and local laws.

<table>
<thead>
<tr>
<th>Exempt Review</th>
<th>The IRB determines whether the request for exemption is appropriate and whether it will be granted. Exemption from IRB continuing review continues unless the protocol is to be modified such that it no longer will meet the criteria for exemption. Exempt review is considered minimal risk and the determination of exemption is normally made by the IRB Chairs/Vice Chairs or designated IRB member. These studies are exempted from IRB continuing review - not from initial review.</th>
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<tr>
<td>Expedited Review</td>
<td>Minimal risk studies meeting specific criteria. Protocols are generally reviewed by one primary IRB reviewer. Protocols approved under Expedited review are subject to IRB continuing review. For expedited studies approved on or after January 21, 2019 where the reviewer determines continuing review is not required, the IRB analyst will set an expiration date of three years minus a day from the approval date. If the study is still open at that time, the investigator will be required to submit a continuation request to extend the study. Research approved by Expedited Review is considered minimal risk. Approval by Expedited Review is normally carried out by an IRB Chair/Vice Chair or designee (such as a senior IRB member).</td>
</tr>
<tr>
<td>Full Board Review</td>
<td>Protocols that involve more than minimal risk or do not meet the criteria for Exempt or Expedited. They are reviewed at a convened IRB meeting. Examples of protocols requiring initial regular review are studies using FDA investigational test articles, randomized double-blind placebo-controlled studies, Phase I, II, III and IV clinical trials, and studies using x-rays and other significant risk devices. Such studies are reviewed by the IRB Analysts for completeness and then assigned to an IRB Member and scheduled for full Board convened review.</td>
</tr>
<tr>
<td>Determination of Not Human Subjects Research (NHSR)</td>
<td>This application allows a PI to receive an official determination that the project does not meet the regulatory definition of “research” or “human subjects research”. This simple application allows the PI to submit the study application, have review by an IRB Chair/Vice Chair or designee, and receive a determination that the project does not require approval of the IRB. The information obtained from this application allows the institution to record their findings should a research activity be questioned in the future.</td>
</tr>
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</table>
| Determination of Not Engaged In Research (NEIR) | Normally, the request received from the external applicant is for the University to allow recruitment of study subjects on University of Louisville campuses or clinics. The external individual must have an appropriate IRB approval from their home institution. The IRB requests the same type of supporting documentation of the external applicant (materials that were submitted for review at the other IRB, copy of approval letter from other institution, certification of human subjects’ protection training at the
The determination of NEIR is made by the HSPPO Director or Associate Director.

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<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tr>
<td>II.2.A</td>
<td>The IRB has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB. Such policies and procedures indicate that exemption determinations are not to be made by researchers or others who might have a conflict of interest regarding the studies.</td>
</tr>
<tr>
<td>II.2.B</td>
<td>The IRB has and follows written policies and procedures for addressing protections of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB.</td>
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</table>

**IRB Exemption Determination**

All applications are assigned to full board review unless they meet the criteria for exemption or for expedited review. All projects involving the use of investigational drugs, devices, or biologics for which an IND/IDE is required receive full board review.

A claim of exemption means that the researcher believes that a proposed research activity does not require IRB review and approval. The university, however, is still obligated to review all such activities, whether funded or not, and certify that the research meets the federal, state, local and UofL IRB requirements for exemption. In order to fulfill requirements for the proper review of research, investigators cannot “self-exempt” from IRB review. The University Institutional Review Boards have determined that evaluation and certification of exemption status will be performed by the Chair/Vice Chair or chair’s designee. In order for the chair or designee to make this determination, the PI must submit the appropriate application for IRB review best descriptive of the type of study to be conducted (e.g., Risk vs. Benefit, Survey/Questionnaire/Interview, Specimen).

The IRB chair or designee will make a determination of exemption from IRB review. The reviewer completes the IRB Reviewer Form (Biomedical or Behavioral, depending on the type of research) that documents the status of the submission (exempt or not exempt), the category of exemption (if applicable) and any additional requirements (informed consent, HIPAA, etc.) that are applicable.

The IRB chair or designee will review the proposed research and will validate or decline the investigator’s claim for exemption, ensure that risks to individuals are minimized, and confirm that the research meets ethical standards. The IRB will document the review and action of the IRB Chair or designee including the category specified in 45 CFR 46.104 or 21 CFR 56.104 justifying the classification of exempt.

Experienced, qualified IRB member designees may also be utilized to make a determination of exemption if the chair is not readily available or if the chair determines that s/he has a conflict of interest, the appearance of a conflict of interest or a member is better qualified to make the determination. The UofL IRB does not currently conduct “limited review” as allowed in the revised common rule as all exempt determinations are made by an IRB chair or IRB member (Element II.2.C). The IRB will promptly notify the PI electronically through the IRB ESS of its decision regarding the research. If it is determined that the research is not exempt or if modifications are required such as submission of a consent document or strengthening of protections in place to minimize risks to participants, the IRB will include in its written notification a statement of the reason for its decision and give the PI an opportunity to respond in person, in writing, or electronically.
through the IRB ESS. Final approval of exempt research is pending resolution of all stipulations identified by the IRB reviewer.

If the IRB chair or member determines that an application does not qualify for exemption, the application will be processed either through Expedited Review or by full IRB review.

At the time of approval of exempt protocols, PIs are reminded of the responsibility to report all modifications that could affect the exempt status and unanticipated problems involving risks to subjects or others in accordance with the HSPPO Policy Manual.

Applications for exempt research are reviewed in the same manner as expedited protocols. All determinations made by the IRB Chair or designee regarding exemptions are reported to a full board committee.

**Exempt research fulfills the institution’s ethical standards, such as:**

- The research holds no more than minimal risk to participants.
- Selection of participants is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- If there are interactions with participants, the IRB should determine whether there should be a consent process that will disclose such information as:
  - That the activity involves research.
  - A description of the procedures.
  - That participation is voluntary.
  - Name and contact information for the researcher.
- There are adequate provisions to maintain the privacy interests of participants.

**Exempt Criteria**

Research will be determined to be exempt only when the sole involvement of human subjects will be in one or more of the categories listed in 45 CFR 46. The IRB will not create new categories of exempt research.

For studies exempted prior to 01/21/2019, details on the exempt categories can be on the HSPPO website, Guide 10 Exempt Review Categories.

For studies exempted on or after 01/21/2019, details on the exempt categories can be on the HSPPO website, Guide 10a. Revised Common Rule Exempt Categories.

Exempt review does not apply to the following categories of clinical investigations regulated by the FDA (21 CFR 56):

- a. Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.
- b. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.
- c. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.
d. Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed; (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Services of the U.S. Department of Agriculture.

Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy. The University of Louisville, an institution with a DHHS-approved assurance on file, will abide by provisions of Title 45 CFR Part 46 Subparts A-D and Title 21 CFR 56.

The IRB retains the right to require oversight and continuing review when warranted by the nature of the research and/or inclusion of vulnerable populations even though it may not be required by federal regulation.

This right may be exercised in situations when the IRB:

1. Has sufficient reason, through anonymous reports, to suspect that the research is not being conducted as described in the submitted protocol and no amendments to the protocol have been received noting changes in the protocol; or
2. Receives a complaint from a participant about the conduct of the research; or
3. Receives a complaint from another investigator or associate of the researcher; or
4. Believes that the research, while meeting the exempt research criteria, could unfairly embarrass individuals, the University or the University’s research affiliates; or
5. For other reasons yet to be determined.

If, in the opinion of the IRB chair/vice chair who reviews exempt research, a protocol that meets the exempt criteria may conflict with the University’s ethical standards for research, then that individual can seek counsel from the full IRB, HSPPO staff, Office of University Counsel, members of the University of Louisville Institute for Bioethics, Health Policy and Law, or the other schools and colleges of the University who teach ethics in research. The chair should be prepared to discuss the issues of concern with those with whom s/he consults. After consultation, a summary of the discussion and the final decision will be reported to the appropriate IRB and recorded in the minutes of that meeting.

Studies that meet exemption criteria do not necessarily mean that the investigator is exempt from the need to obtain informed consent from a participant or HIPAA requirements.

The IRB may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency, but not otherwise covered by this policy, comply with some or all of the requirements of this policy. Projects involving classified research cannot be completed by exempt review. University of Louisville officials\(^5\) may restrict, suspend, terminate, or choose not to authorize an IRB’s use of the exemption review procedure.

Investigators who conduct research exempt from IRB oversight must report changes in their protocol that might increase participant risks or change the exempt determination. The exemption granted is only for the protocol as written at the time of the initial review.

Changes should be reported utilizing the Amendment Form found within the IRB ESS. If the protocol remains exempt, the investigator will be notified of the decision through the IRB ESS. If the change(s) require(s) that the research may be

\(^5\) Institutional Official (EVPRI), or designee
considered under Expedited Review criteria, the investigator will be asked to modify the submitted application to indicate which expedited review category the study falls under, and if necessary to request the appropriate additional documentation for this review.

If the submitted application change(s) require(s) that the research be reviewed by the full board IRB, the investigator will be asked to modify the application, and if necessary, to provide additional documentation for this review. Once those modifications are received, the submission will be routed to the full board IRB for review.

Studies submitted and determined to be Exempt are not subject to annual review.

**Additional Definitions and Considerations for Exempt Research**

**Anonymous Data**
Investigators should note that a survey is anonymous when there is no possible way to identify the participants from the data collected. Data are not anonymous if anyone or any procedure such as accessing a computer database will identify the participant. In most instances, the omission of names or other specific identifiers, such as social security numbers, is insufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject’s anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small or the research setting is identified, anonymity can be threatened or compromised even when the names are removed from the data.

**Observational Research**
Observational research involving sensitive aspects of subjects’ behavior, or in settings where subjects have a reasonable expectation of privacy, is not exempt. Similarly, sensitive survey research is seldom exempt from IRB review (see below for exceptions). A sensitive survey includes questions about illegal activities, or highly personal aspects of the subject’s behavior, life experiences, or attitudes. Examples include chemical or substance abuse, sexual activity or attitudes, sexual abuse, criminal behavior, sensitive demographic data, detailed health history, etc. The potential for provoking a negative emotional reaction from subjects is a principal determining factor in sensitive survey research. In addition, observation of children is not exempt from IRB review if the researcher participates in or influences the observed activities.

**Breach of Confidentiality**
Additional consideration for exemption includes whether there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review of exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of participant identifiers may be a decisive factor.

**Questionnaires/Surveys/Interviews**
Questionnaires or surveys covering sensitive topics may qualify for a request for exemption if they fulfill the following:

a. anonymity of the participant is guaranteed,
b. potential subjects are fully informed of the sensitive nature of the topics prior to their participation,
c. the study does not exceed minimal risk; and

b. potential subjects are fully informed of the sensitive nature of the topics prior to their participation,
Existing Data, Documents, and Human Biological Specimens for Non-genetic Research

The source of the data, documents, pathological specimens, or diagnostic specimens must be provided to the IRB, along with the name of the gatekeeper of the data, documents, or specimens. The term “existing” refers to the time period that the data and/or material was obtained and does not necessarily mean that the data and/or material were obtained for clinical or diagnostic purposes. OHRP indicates that the term “existing” refers to data, documents, biological material and/or tissue “archived” or “on the shelf” prior to the conceptualization of the research project and prior to review by the IRB.

Many agencies and/or departments routinely collect data or information as part of an ongoing quality-control, quality improvement or quality assurance process. In most situations, the collection of such information does not constitute research and is, therefore, not reviewable by the IRB. In addition, educational agencies may collect information related to student progress or to assess the effectiveness of new programs or projects. Investigators at the University of Louisville submit an NHSR application for a determination of the NHSR status.

Archived pathology or diagnostic specimens that are considered residual biological material and are destined to be destroyed can be used in research and are considered exempt from IRB review if there are no patient identifiers (HIPAA de-identified) linked to the specimen and if the data is not intended to be used in the diagnosis or treatment of a patient. If either of these conditions applies, consent of the research participant is required and the study is not exempt from IRB review. If the data/specimens are collected after the submission of the IRB application, the data is not pre-existing or “archived.” When the data/specimen is not “archived” or if the information is recorded with direct or indirect identifying links to subjects, the protocol requires IRB review and may require written informed consent.

Research which includes review of private records involving access to and recording of identifiable information is not exempt from IRB review or HIPAA standards and may require prior written consent of the subjects. Records considered private based on federal and state statutes, including medical records, insurance records, and educational records, may require written authorization by the individual participant or waiver of authorization by the IRB, written assurance to the gatekeeper of the record and IRB review, in order to be used in research.

Specimen Protocols Ineligible for Exemption

The IRB is required to review research requesting the use of residual biological material, i.e., blood, tissue, other bodily fluids, etc., that is no longer needed for clinical/diagnostic purposes (“archived” or “on the shelf”) if the material or tissue is not archived prior to submitting the protocol to the IRB.

The IRB is also required to review research with residual material where the investigator intends to identify the patient/participant donor with the acquired sample, either for future purposes or with the intent that the research results may have implications for diagnostic or clinical decisions.

Requests for additional material, i.e., blood, tissue, bodily fluid, from a patient or participant who is scheduled for a diagnostic or clinical procedure are not exempt from IRB review. This type of study would need prospective review and approval, in order to obtain the extra material or tissue. IRB review is required regardless of the amount of extra material requested and regardless of the purpose for which it is procured.

Research involving human ova (fertilized and unfertilized) is not exempt.

Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not pre-existing or “archived” and thus require written informed consent from the participant and review by the IRB.
there is a link to the patient’s identity and a possibility that the patient may be contacted in the future, an informed consent document is required. Furthermore, informed consent is required if there is a link to the patient’s identity and a possibility that the research may result in commercial or economic value.

The federal regulations also require that the IRB distinguish between residual material and/or tissue and extra material and/or tissue gathered from diagnostic or clinical procedures to be used in research.

This section does not apply to human biological specimens collected or used for genetic research. There are additional ethical concerns for genetic research that may apply for other types or research with biological specimens. Please contact the IRB for additional information.

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<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tr>
<td>II.2.E</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by the expedited procedures if such procedures are used.</td>
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<tr>
<td>II.2.E.1</td>
<td>Initial review</td>
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<tr>
<td>II.2.E.2</td>
<td>Continuing review</td>
</tr>
<tr>
<td>II.2.E.3</td>
<td>Review of proposed modifications to previously approved research</td>
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</table>

**IRB Expedited Review by Chair(s) and Senior Members**

All studies received by the IRB are evaluated for possible expedited review. Under an expedited review procedure, the review may be carried out by the IRB chair utilizing the IRB Reviewer Form within the IRB ESS (Biomedical or SBE, depending on the nature of the research), or by one or more experienced reviewers designated by the chair from among members of the IRB as authorized by 45 CFR 46 and 21 CFR 56.110. When a reviewer cannot approve the research under expedited review, the study is sent to the full IRB for review at its next scheduled meeting. An experienced or senior member or designee is an individual who has completed training in reviewing submissions with an emphasis on determining if the submissions meet the criteria for approval by expedited review, determination of exemption based on the exempt review criteria, or do not meet the definition of human subjects research (NHSR).

The expedited review process may be used in accordance with federal regulations for applications that qualify for expedited or exempt. IRB chairs or their designees are responsible for these reviews. Only those projects involving no more than minimal risk are considered for expedited review.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

Projects involving government classified research cannot be completed by exempt or expedited review.

The chair or designee has the ultimate responsibility for making the decision whether to review through the expedited process or refer to the full board. A complete submission for an expedited review approval includes the same items required for full board review.

If the application is incomplete or otherwise not fully prepared for review, it is returned to the investigator or a request for administrative modifications is made for necessary changes or to provide additional information. The IRB Analysts
may contact the investigator by phone or correspondence through the IRB ESS requesting clarification of submission forms, protocol issues or revisions in consent document(s) prior to referral to the IRB.

The categories eligible for expedited review in accordance with 45 CFR 46.110 and 21 CFR 56.110 are found on the HSPPO website, Guide 11 Expedited Review Categories.

The IRB retains the right to require additional oversight and more frequent continuing review when warranted by the nature of the research and/or inclusion of vulnerable populations even though it may not be required by federal regulation. This right may be exercised in situations when the IRB:

1. Has sufficient reason, through anonymous reports, to suspect that the research is not being conducted as described in the submitted protocol and no amendments to the protocol have been received noting changes in the protocol,
2. Receives a complaint from a participant about the conduct of the research,
3. Receives a complaint from another investigator or associate of the researcher,
4. Believes that the research, while meeting the exempt research criteria, could unfairly embarrass individuals, the University or the University’s research affiliates,
5. Has other reasons yet to be determined.

The chair or designee may approve projects as submitted or require modifications prior to approval. They are not empowered to disapprove projects reviewed through the expedited process; in such cases, the application must be submitted for full board review along with the comments and recommendations of the chair or designee. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b). In cases where the full board concurs with the recommendation, the investigator may appeal.

Initial review, continuing review and minor changes in research protocols that are reviewed and approved through the expedited process are reported to all IRB members, usually at the next convened meeting of the appropriate IRB, by circulation of report of expedited items.

Studies approved by the Expedited Review process prior to 01/21/2019 are subject to at least annual review. This information is communicated electronically to the principal investigator in the approval letter sent through the IRB ESS.

Studies approved by the Expedited Review process on or after 01/21/2019 may no longer be subject to a continuing review, unless the IRB finds and documents the need to require a continuing review to enhance the protections of research subjects.

The IRB requires continuing review for minimal risk research when:
• The research is regulated by the FDA or Dept. of Justice/National Institute of Justice or other agency that has not adopted the revised common rule;
• The Principal Investigator (PI) has a corrective action plan issued within the past two years;
• The project involves deception;
• A conflict of interest management plan exists related to the research; OR
• Determined by the IRB Chair/Vice Chair for oversight of participant enrollment or other concern that requires increased oversight.
For expedited studies approved on or after January 21, 2019 where the reviewer determines continuing review is not required, the IRB analyst will set an expiration date of three years minus a day from the approval date. If the study is still open at that time, the investigator will be required to submit a continuation request to extend the study.

**IRB Full Board Review**

All applications are assigned to full board review unless they meet the criteria for exemption or expedited review. All projects involving the use of investigational drugs, devices, or biologics for which an IND/IDE are required, receive full board review.

Reviewers are expected to document their review comments utilizing the appropriate Reviewer Checklist provided in the IRB ESS.

**IRB or Administrative Determination of Not Human Subjects Research (NHSR)**

The following are examples of the types of studies which may be found to be NHSR. An NHSR application should be submitted to the IRB for review and final determination.

- Pilot Studies
- Student Projects
  - Research Practica
  - Directed or Independent Research Projects
- Case Studies
- Oral Histories
- Quality Assurance/Quality Improvement Projects
- Surveillance Projects
- Research Involving Coded Private Information or Specimens
- De-identified data files

**Pilot Studies**

A pilot study is a preliminary investigation of the feasibility of a study, usually done on a small scale (usually fewer than 10 subjects) and exploratory in nature. It is designed to help the investigator refine data collection procedures and instruments or prepare a better, more precise research design. At the point of academic discussions, e.g., "how could this survey question be misunderstood?" such a pilot would not contribute to generalizable knowledge and therefore is not considered research and does not require IRB review. Feasibility information might also involve retrospectively reviewing medical records to see how many eligible subjects were seen in a clinic during a specific period of time. Extrapolating retrospectively collected data for feasibility is not considered human subjects research. Data collection forms to obtain this type of feasibility information should not include the collection of any of the 18 HIPAA elements considered to be protected health information. Information could also be collected prospectively from patients presenting to a clinic who meet the eligibility criteria. If the data were collected without identifiers, and the researcher collected information consisted of whether or not the patient met eligibility criteria, eligibility data could be collected and used to support feasibility of recruitment.

**Medical interventions or interactions for research purposes, especially those involving invasive procedures, do require IRB review regardless of the size of the study.**

**Student Projects**

The University of Louisville supports a wide range of both undergraduate and graduate student research projects involving human subjects -- from course-related research exercises to Ph.D. dissertation studies. Generally, student
research involving human subjects falls into one of two categories, research practica and directed, independent research projects.

1. Research Practica

Research Practica are class projects designed to provide students an opportunity to practice various research methods such as interview, observation and survey techniques, as well as data analysis. Such projects typically do not lead to generalizable knowledge and are not undertaken with that goal in mind. Research practica do not require IRB review. Data that are collected during a research practicum project may be used in independent research projects at a future time. In such a case, the IRB should be consulted, because an IRB application for use of existing data may be required.

Although the IRB does not review such class projects, we strongly encourage instructors to become fully familiar with each student’s project(s) and to discuss it with the student. Explicit recognition of the existence of the IRB and discussion of its goals and concerns should be an integral part of introducing students to research methodologies.

2. Directed or Independent Research Projects

Directed or Independent Research Projects are any research conducted by students, graduate or undergraduate, which involve human subjects, employs systematic data collection, is intended to contribute to generalizable knowledge, and does not fall under the definition of research practicum. These projects include, but are not limited to, independent undergraduate research projects and honors theses, masters' theses and dissertations. Student projects in this category must be reviewed and approved by the IRB. It is possible that a research project may be exempt from ongoing IRB review, but it must meet explicit criteria and the IRB must certify the exemption. Questions regarding the distinction between these categories should be directed to the HSPPO.

Case Reports

Case reports by University of Louisville definition are medical information collected and presented on up to five patients to highlight an interesting treatment, presentation, or outcome. They generally result from retrospective review of the medical record. In this regard, case reports differ from research in which data are collected with intent to evaluate a specific hypothesis.

If an author develops a case report, with no prior research intent, IRB review is still required. University of Louisville research policy requires review, if the report is presented, published, or used to fulfill the requirement for scholarly activity outside this university.

In addition, when one of the following occurs, the IRB considers this research. IRB review, written informed consent, and HIPAA Authorization may be required if the review

1. is accepted as a fulfillment of a “research requirement” or,
2. acknowledges in the report that it is “research” or,
3. attempts to answer a question, or
4. uses an intervention to prove/disprove a hypothesis, or
5. requires treatment or record keeping modification for research rather than clinical purposes or,
6. becomes a case series greater than five (5) cases, with no prior research intent.
In many instances, case reports do involve a human subject(s) by definition, and may contribute to generalizable knowledge by presentation or publication. A case report (5 or fewer patients) generally does not meet the definition of a systematic investigation and thus does not meet the definition of research either in 45 CFR 46.102(f) or 21 CFR 56.102(e). A case report describes an interesting treatment, presentation or outcome. A critical component is that nothing was done to the patient(s) with prior “research” intent. University of Louisville research policy requires submission to and approval from the IRB prior to submission for publication.

The author of a case report is required to enter the report through the IRB ESS.

Author(s) must ensure that the article does not contain any of the 18 protected health information identifiers noted in the HIPAA regulations unless authorization from the individual(s) has been obtained. If the individual(s) is/are deceased, and no information is obtained from living individuals (e.g. relatives) HIPAA authorization is still required from the personal representative of the individual’s estate, in order to include protected health information in the report.

The IRB Chair or designee will review the request of an author who submits a case report to the IRB or, who has been asked by a journal to provide documentation of IRB approval prior to publication of a submitted case report. If the report is about five (5) or fewer individuals, meets the definition of a case report, and does not meet the definition of human research, the IRB will provide a form letter that submitted application does not meet the definition of human research and IRB review is not required for this activity.

If it is the conclusion of the IRB Chair or designee that the submitted proposal is research, the IRB will not provide “after the fact” approval of the research as this is prohibited by federal regulation. Authors are encouraged to seek advice from the IRB or the Human Subjects Protection Program Office prior to developing a case report when difficult questions arise about whether IRB review may be required.

**Oral History**

Oral history clearly involves historical research and interviews can lend themselves to generalizations. However, oral historians’ standard operating procedures do not fit the type of research defined by federal regulations. An oral history study may not require IRB review because it is not generally thought to be a systematic investigation designed to contribute to generalizable knowledge beyond the individual being interviewed. However, when using oral history as a technique in human subject research it may require IRB review. Individually-tailored interviews with narrators’ informed consent do not meet the federal definition of “research,” nor do they contribute to “generalizable knowledge within the context of the federal definition.”

Researchers proposing such work are strongly encouraged to contact the IRB to determine whether their project requires approval.

**Quality Assurance or Quality Improvement Projects**

Research conducted in conjunction with program evaluations or quality assurance measures may or may not fall under the jurisdiction of the IRB. If such a project is conducted with the intent to develop or contribute to generalizable knowledge, it should be submitted for IRB review. The University of Louisville utilizes the OHRP Quality Improvement Activity FAQs to make this determination.
Quality Assurance or Improvement – There is no regulatory definition but often QA/QI is described as “systematic, data-guided activities designed to bring about immediate (or nearly immediate) improvements in health care delivery”, and the combined efforts of everyone to make changes that will potentially lead to better patient outcomes, better system performance, and better professional development. In medical institutions, QA/QI is a necessary, integral part of hospital operations and is not subject to review as research, as defined under federal regulation. Rather, it is governed by Joint Commission and hospital standards.

Examples of QA-QI projects that are not human subjects research:

- Data collection for internal departmental, school, hospital, or other university administrative purposes (such as teaching evaluations, customer service surveys, or customer satisfaction surveys).

- Service surveys issued or completed by university or hospital personnel for the intent and purposes of improving services and programs, or for developing new services or programs for students, employees, or alumni, as long as the privacy of the subjects is protected, the confidentiality of individual responses are maintained, and survey participation is voluntary. This would include surveys by professional societies or university consortia.

Surveillance Projects
Some surveillance projects, emergency responses, and evaluations are research involving human subjects; others are not. Each project must be reviewed on a case-by-case basis. Although general guidance can be given to assist in classifying these activities as either research or non-research, no one criterion can be applied universally. The ultimate decision regarding classification lies in the intent of the project. If the primary intent is to generate generalizable knowledge, the project is research. If the primary intent is to prevent or control disease or injury, to improve a public health program, or to document the existence of a public health problem, and no research is intended at the present time, the project is non-research.

If the intended benefits are primarily or exclusively for the clients of the project or the clients’ community and 1) data collected are needed to assess and/or improve a program or service, the health or welfare of the clients or the clients’ community; 2) knowledge that is generated does not extend beyond the scope of the activity, and 3) project activities are not experimental, then the activity would not be classified as research utilizing human subjects and would not require IRB review prior to initiation.

Surveillance - The ongoing, systematic collection, analysis, and interpretation of outcome-specific data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease or injury.

Emergency Response - A public health activity undertaken in an urgent or emergency situation, usually because of an identified or suspected imminent health threat to the population, but sometimes because the public and/or government authorities perceive an imminent threat that demands immediate action. The primary purpose of the activity is to document the existence and magnitude of a public health problem in the community and to implement appropriate measures to address the problem.

Evaluation - The systematic application of scientific and statistical procedures for measuring program conceptualization, design, implementation, and utility; making comparisons based on these measurements; and the use of the resulting information to optimize program outcomes.
Examples of Center for Disease Control (CDC), Public health, and local surveillance, emergency responses, and evaluation activities that are not research utilizing human subjects:

**Surveillance: Non-research**
1. National Notifiable Diseases Surveillance System (NNDSS)
2. Diabetes Surveillance Report
3. All federal or state required reports
4. Infection rates in a neo-natal ICU
5. Pathogen sensitivity to an antibiotic in various units of a health care facility
6. Reporting of lead levels in children

**Emergency Response: Non-research**
1. Outbreak of a communicable or non-communicable disease
2. Drug or device recall
3. Effectiveness of local emergency response to a chemical spill or industrial accident.

**Program Evaluation: Non-research**
1. Evaluation of School-based HIV Prevention Program
2. Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT) progress reports
3. Effectiveness of a diabetic monitoring class as determined by aggregate data in the diabetic population served by the program.

Examples of Center for Disease Control (CDC), Public Health, and local surveillance, emergency response, and evaluation activities that are research utilizing human subjects:

**Examples of Surveillance: Research**
1. A Sentinel Surveillance System for Lassa Fever in the Republic of Guinea
2. Developmental Disabilities in Very Low Birthweight Children: Linkage of the Georgia Very Low Birth Weight Study and the Metropolitan Atlanta Developmental Disabilities Surveillance Program

**Examples of Emergency Response: Research**
1. Childhood Exposure to Nicotine-Containing Products in Rhode Island
2. Azithromycin Used as Prophylaxis Against the Spread of Illness Due to Mycoplasma Pneumonia in the Setting of an Outbreak

**Examples of Program Evaluation: Research**
1. Evaluation of Community Based Organization Intervention to Reduce Sexually Transmitted Disease (STD) Rates Among STD Patients in Miami
2. A Comprehensive Evaluation for Project DIRECT (Diabetes Intervention: Reaching and Educating Communities Together)
3. Effectiveness of a “Monitoring your diabetes for a better outcome” class.
OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

2. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because:
   a. the key to decipher the code is destroyed before the research begins;
   b. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
   c. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
   d. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This policy applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research:
1. medical records; and
2. on-going collection of specimens for a tissue repository.

**Coded** - identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code) and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

**De-Identified Health Information** - De-identified health information neither identifies nor provides a reasonable basis to identify an individual. There are two ways to de-identify information; either: 1) a formal determination by a qualified statistician; or 2) the removal of specified identifiers of the individual and of the individual’s relatives, household members, and employers is required, and is adequate only if the covered entity has no actual knowledge that the remaining information could be used to identify the individual.

**Non-Identifiable Tissue** - tissue that has been de-identified by the investigator(s) or tissue supplier(s) in preparing the tissue for research requiring no identifiable connection to the donor.

Additional information can be obtained at the following URL:  [http://www.hhs.gov/ohrp/policy/cdebiol.html](http://www.hhs.gov/ohrp/policy/cdebiol.html)

**De-identified Data Files**
Use of publicly available data, such as census data or labor statistics, may not require IRB review. If a data set is not available to the general public (i.e. you have to request access), then it may not be a public use dataset. An IRB application must be completed for review.

An investigator who wishes to make files available as public use files or de-identified datasets should submit a Not Human Subjects Research application to the IRB for review. This review will ensure that files intended to be made public do not include individually identifiable information.

**Publicly Held Data Set** - a non-identifiable file made available from investigators or data suppliers through a repository, via the internet, or by some other means to any person who wishes to use it.

**Non-Identifiable Data** - data that have been de-identified by the investigator(s) or data suppliers in preparing public use data files.

**IRB or Administrative Determination of Not Engaged in Research (NEIR)**

Individuals involved in research at other institutions may request access to recruit faculty, staff or students from the University of Louisville into research projects approved by external IRBs. In this case, no University of Louisville faculty, staff, or students are considered to be “engaged in the research” as defined by OHRP's policy, dated 10-16-2008 Guidance on Engagement of Institutions in Human Subjects Research. If the University of Louisville receives such a request, the Director or Associate Director, HSPPO, or the contacted IRB Analyst, requests the following items be forwarded to the UofL IRB office by the requesting external investigator:

- Copy of complete protocol submission from the IRB of Record (the approving IRB).
- Approval letter or Certificate of Exemption from the institution that will be the IRB of Record that includes the submission number of the project submitted at the IRB of Record.
- Consents/HIPAA waiver(s)/Research Authorizations approved by the other institution.
- Data collection forms, advertisements, or other supporting information, if applicable.

Once all documents are received, the information is reviewed and processed by the Director, Associate Director or IRB Analyst.

Correspondence is prepared to the requestor that indicates:

- Title;
- Project status at UofL;
- Name of the Requesting investigator;
- The name of the IRB of Record for the study;
- A statement that the University of Louisville is not engaged in the research;
- A statement of which section in the OHRP Guidance the study would fall under; and
- A statement that the requesting investigator is responsible for complying with their reviewing IRB decisions and to report any changes to their reviewing IRB.

When/if the University of Louisville HSPP office receives questions from individuals within the University community concerning whether such a study has IRB approval, the IRB office is able to respond to questions concerning the study and to let the individual know the status of IRB approval at the Reviewing Institution and that the University of Louisville is not engaged in the research.

### 7.4 IRB Application Types – IRB ESS
There are five types of applications within the IRB ESS.

- IRB Application
- Case Report Application
- Not Human Subjects Research (NHSR)
- Emergency Use (EU) Application (Prior to or After Use)

**IRB Application**

A regular IRB application includes the following sections that must be completed by the investigators, as applicable:

- Name of the proposed research study, department(s) involved in the research, listing of study personnel, study location, funding, resources, collaboration/multi-site, participant population, purpose, procedures, background, use of radiation producing machines, use of drugs (investigational and commercial) and devices (non-significant risk and significant risk), recruitment methods and screening procedures, inclusion and exclusion criteria, inclusion of vulnerable populations, potential risks and benefits, procedures to protect privacy and maintain confidentiality of data, conflict of interest, consent and assent, and HIPAA. A “check for completeness” feature requires that each question applicable to the study is answered before submission to the IRB is permitted.

Depending upon the particulars of the research study, other documents that may be required at initial review submission are:

- Final study protocol version (including IND #, if applicable)
- Investigator’s drug/device brochure
- Recruitment materials, including copies of ads, flyers, etc.
- Telephone scripts
- Pamphlets and study handouts (e.g. participant diary, wallet medication card)
- Questionnaires and survey instruments (excluding standard questionnaires that would be done outside of the research study)
- Focus group or interview guides
- Federally funded studies only: Human Subjects section of grant, proposal, or progress report
- Data collection sheets
- IRB approval letters and/or letters of support from collaborating or cooperating sites
- Notes on difficult ethical issues, special considerations for review, or requests for special handling (optional)
- Combined Consent & Research Authorization form(s) (if viewing/collecting/disclosing PHI), including any parental consent forms
- Assent form (if applicable, for pediatric studies)
- Preamble Letter of Information (if applicable, e.g., survey study)
- HIPAA Partial Waiver (if requesting access to view PHI to screen appropriate subjects)
- HIPAA Complete Waiver (if requesting a waiver of HIPAA authorization, e.g. chart review studies)

**Case Report Application**

This application is used when an individual investigator requests to describe for the literature up to five patients to highlight an interesting treatment, presentation, or outcome. A copy of the written case report must accompany the Case Report application. The Case Report application contains the following sections: Name of the proposed Case Report, department(s) involved, listing of study personnel, research nature (biomedical or SBE), study type, explanation of how the case report defines an interesting treatment, presentation or outcome, confirmation of the number of
records reviewed (five or less), confirmation there was no “research intent”, and attachment of the written Case Report.

**Emergency Use (EU) Application**
This application can be completed either prior to administration or after administration of the test article within 5 days of use. Chapter 5.9 describes the requirements for the emergency use of an investigational drug, device, or biologic under FDA regulations at 21 CFR 56.104(c), and materials which must be submitted to the IRB. The EU application contains the following sections: Name of the proposed emergency use, department(s) involved, listing of study personnel, research nature (biomedical or SBE), study type, sponsorship information (if applicable), funding (if applicable), EU details, EU determination, consent and HIPAA document attachment section, and other study documents attachment section.

The submitted material is assigned to the Biomedical IRB. If the IRB Administrator or the assigned reviewer has comments, they are sent to the investigator for response. Responses are reviewed and additional comments sent if needed. The reviewer documents his/her findings on the IRB Reviewer Feedback Form. At the convened meeting, the IRB notes the emergency use of the test article, which is reflected in the minutes.

An IAA is an agreement signed between two institutions to allow one of the IRBs to be the IRB of Record for the study. An IAA application is submitted when an external institution will be the IRB of Record. The HSPPO works with the other institution to ensure that the IAA is approved and recorded. The IAA application contains the following sections: Name of the proposed research study, department(s) involved, listing of study personnel, research nature (biomedical or SBE), study type, study sites, other institution information, FWA number, IRB identification number, status of whether the institution is AAHRPP accredited, rationale for the oversight responsibility to be ceded to another institution, IRB study number at other institution, and required documents including a copy of the qualified IRB approval letter and other submission documents.

**Not Human Subjects Research (NHSR) Application**
Some protocols submitted for review do not meet the federal definition of “human subjects research”, e.g., some quality Improvement/quality assurance activities, review and use of publicly available datasets, case reports (usually reporting unusual findings for up to 5 patients), and oral history projects. Investigators should submit these proposals to the IRB for verification that they do not meet the DHHS definition of human subjects’ research. The NHSR application contains the following sections: Name of the proposed research study, department(s) involved, listing of study personnel, research nature (biomedical or SBE), study type, determination of whether the study meets the federal research definition and the human subjects definition, a description of the proposed project, and any other documents relevant to the submission.

**7.5 IRB Submission Types – IRB ESS**
Submission types available include applications for:

- Initial Submission
- Continuing Review Submission
- Amendment/Modification Submission
- Serious Adverse Event Submission
- Unanticipated Problems Submission
• Deviations/Violations/Misc. Submission

7.6 Receipt of Submissions

Intake Process
All submissions in the ESS are received in a centralized “Unassigned” mailbox within the ESS. The new submission remains in the unassigned area until the IRB Analyst assigns the protocol for administrative review of the submission. The IRB Analyst check the submission for completeness utilizing a checklist within the ESS.

Administrative Review by IRB Analysts Prior to Assignment to Primary Reviewer
IRB Analysts review the submission for completeness, consistency among the documents submitted, level of IRB review, and level of risk involved. During the review of the submission, IRB Analysts prepare their comments to be passed to the assigned IRB reviewer. This review includes a general review of the consent, whether the UofL ICF consent template/research authorization was used to prepare the informed consent, noting problems with the ICF so that these problem areas may be fixed at the same time the primary reviewer comments are sent to the PI. If the submission is not ready for review, the IRB Analyst will send a request for administrative modifications to the PI requesting any additional items or changes to submitted documents.

During the review of a protocol, the IRB staff and reviewer(s) enter any comments or questions or recommended changes to the protocol or associated documents (e.g. consent forms, advertisements) stemming from their review in the IRB ESS submission discussion and/or reviewer checklist. After reviewing and editing all comments received for consistency and duplication, the IRB staff sends the comments to the investigators. Investigators are notified via an email that stipulations have been sent on the submission. All comments are sent to investigators without referencing the author of the comment, thus preserving their anonymity. Comments are sent out with a request for response.

Upon receipt of the investigators’ responses to the comments and recommended changes to the protocol and associated documents, the IRB staff reviews the responses and changes for completeness then forwards responses to the reviewer. If additional questions remain or changes need to be made, another round of comments is generated and sent to the investigators for responses. This process is repeated as often as necessary, until all reviewer questions have been answered and requested changes to the protocol and documents have been made.

Protocols may be moved for review to a subsequent meeting pending receipt of additional substantive information or if the comments and response cycles are not completed prior to the convened meeting. The IRB ESS notifies the PI that the protocol was moved to a different agenda.

Assignment of Primary Reviewer

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<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tr>
<td>II.1.E</td>
<td>The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.</td>
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The biomedical and SBE IRBs utilize a parallel process of pre-review, which involves an interactive review process between reviewer(s), IRB analyst(s), IRB HIPAA reviewer, IRB compliance monitor and IRB Chair/Vice chair or designated...
IRB reviewer. IRB Analysts make the preliminary assignment to the primary reviewer. For protocols assigned to a convened meeting, this system allows all presented protocols to be fully reviewed by the reviewer(s), so that recommended changes have been documented.

Primary reviewer assignments are made with the objective of matching reviewer expertise and experience with protocol subject matter. See Chapter 6. “Nonscientific” members assigned to review protocols are valued for the community perspective they bring to the process of ensuring the protection of research participants. For approved protocols, an attempt is made to assign any subsequent protocol events to a member who was the primary reviewer when the study was first approved.

If the primary reviewer is unable to attend the regularly scheduled meeting, it is their responsibility to notify the HSPP Office as soon as possible so that the HSPPO can appoint a new primary reviewer in time to present at the meeting.

Once assigned, the IRB reviewer has access to all components of the submission. These include: the completed IRB application, an attached protocol, ICF/RA combined form(s), assent form(s), recruitment materials, questionnaires or survey instruments, focus group or interview guides, and any HIPAA waivers.

A primary reviewer for an initial submission is assigned in advance of a full board meeting. The chair may, at his/her discretion, serve as the primary reviewer. In selecting the primary reviewer, consideration is given to the individual’s knowledge of the subject area embodied in the proposal. If no IRB member has adequate knowledge or experience to review a given protocol, the IRB chair or IRB Administrator will engage a consultant with appropriate expertise and experience to conduct the review.

Primary reviewers are provided an initial review checklist within the IRB ESS to ensure that all criteria for approval of research have been fulfilled. The checklist is part of the electronic submission and is available to the reviewer any time they log into the system. The primary reviewer conducts in-depth review of all items required for IRB submission of a new application including the informed consent document(s), and all supplemental materials (including, if applicable, the entire grant application, protocol, and investigator’s brochure).

The primary reviewer is strongly encouraged to contact the investigator in advance of the board meeting for additional information or clarification if needed. The primary reviewer leads the discussion of the initial submission or continuing review submission. The primary reviewer may not have a conflict of interest regarding the project under review and must notify the chair of any conflict.

Approval Criteria
All proposed research must meet the University of Louisville ethical standards governing the conduct of research (e.g., acceptable risk-benefit relationship, equitable selection, informed consent, protections of privacy, maintenance of confidentiality, and protections for vulnerable populations). The reviewers consider the approval criteria set forth in 45 CFR 46 and 21 CFR 50 in reviewing and approving an initial submission, continuing review, or review of an amendment/modification when the modification affects a criterion for approval. The IRB confirms that proposed application, informed consent documents, and recruitment documents are accurate and complete.

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6 The requirement for IRB review of each application or proposal for HHS-support applies only to the awardee institution. The application or proposal need not be reviewed by the IRBs at non-awardee institutions participating in the research. However, appropriately redacted copies of funded applications or proposals should be made available to IRBs at participating institutions if requested. Additional information may be found in the OHRP Document: IRB Review of Applications for HHS Support.
The reviewers consider the regulations in reviewing and approving a protocol. They are aided in their consideration by regulatory guidance provided in the form of:

Criteria for IRB Approval of Research (See Chapter 7.2, Requirements to be Satisfied)
General Requirements for Informed Consent (See Chapter 12, Informed Consent and Assent); and IRB ESS generated Reviewer Checklist.

7.7 Review of Initial Submissions by the convened IRB

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<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tbody>
<tr>
<td>II.2.D</td>
<td>The IRB has and follows written policies and procedures for conducting meetings by the convened IRB.</td>
</tr>
<tr>
<td>II.2.E</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by the convened IRB.</td>
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</table>

**Quorum**

A quorum for the Biomedical IRB is eight or more voting members, including a member whose primary concern is in a non-scientific area. For the SBE IRB, a quorum is seven or more voting members, including a member whose primary concern is in a non-scientific area. When the agenda for a specific meeting includes a protocol enrolling prisoners, the prisoner representative must attend [and vote] on the prisoner protocol. Expert reviewers are not required to attend the convened meeting, although they are sometimes invited to do so, and they do not vote.

**Materials Available at Convened Meetings**

Prior to the convened meeting, all scheduled voting IRB members, including non-primary reviewers, are notified of electronic access to all protocols to be presented. This electronic access enables reviewers to see the entire protocol submission, including the application and any reports (e.g. modification, continuing review, reportable event), all comments and responses, assent and consent form(s), and all other documents associated with the protocol (e.g. telephone script, questionnaires or surveys, advertisements, and recruitment materials). Reviewers are expected to review the full protocol (or protocol summary), application, consent document, and recruitment materials containing the relevant information to determine whether the proposed research fulfills the criteria for approval. The assigned primary reviewer also reviews the investigator’s brochure when applicable. Reviewers are to provide comments (if any) before the meeting and during the meeting. All materials submitted supporting a protocol are also available to voting members during the meeting. These materials are provided to all IRB members to assist in their determination of whether the proposed research fulfills the criteria for approval.

In addition, all members are provided the meeting agenda, Expedited Review report (which includes protocols approved by expedited review, exempt review, and processed administratively), educational and informational items.

**Meeting Deliberations**

The primary reviewers are considered the lead reviewers on the IRB for protocols assigned to them. They are responsible for:

- Being thoroughly versed in all details of the research,
- Conducting an in-depth review of the research using the IRB reviewer forms and tools as guidance.
The primary reviewer designated as the presenter presents the protocol for discussion. All IRB members are afforded full opportunity to discuss each research protocol during the convened IRB meeting. The reviewers consider the approval criteria set forth in 45 CFR 46 and 21 CFR 50 in reviewing a protocol. The IRB confirms the proposed protocol application, informed consent documents, and recruitment documents are accurate and complete. Controverted issues that have not been resolved during the review prior to the convened IRB meeting are discussed.

**Utilizing Guidance Documents for Special Findings When Approving a Protocol**

The reviewers and voting members consider the following information and regulations to make any special findings in reviewing and approving a protocol. They are aided in their consideration by regulatory guidance provided in an “IRB Quick Reference Guide” including:

<table>
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<th>Frequently referenced guidances</th>
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<tbody>
<tr>
<td>Criteria for IRB Approval of Research</td>
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<tr>
<td>General Requirements for Informed Consent</td>
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<tr>
<td>Additional Protections for the Inclusion of Children in Research (OHRP)</td>
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<tr>
<td>When the protocol involves children as participants, the IRB considers all of the regulations of 45 CFR §46.404, 45 CFR §46.405, 45 CFR §46.406, 45 CFR §46.407, 45 CFR §46.408 to make the appropriate finding(s) under which the children may be included. <strong>Wards:</strong> When the protocol involves children who are wards of the state the IRB considers all of the regulations of 45 CFR §46.406, 45 CFR §46.407 and 45 CFR §46.409(a) to make the appropriate finding(s).</td>
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<tr>
<td>Additional Protections for the Inclusion of Children in Clinical Investigations (FDA)</td>
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<tr>
<td>When the protocol involves children as participants, the IRB considers all of the regulations of FDA 21 CFR §50.51, FDA 21 CFR §50.52, FDA 21 CFR §50.53, FDA 21 CFR §50.54, and FDA 21 CFR §50.55 to make the appropriate finding(s) under which the children may be included. <strong>Wards:</strong> When the protocol involves children who are wards of the state the IRB considers all of the regulations of FDA 21 CFR §50.53, FDA 21 CFR §50.54 and FDA 21 CFR §50.56(a) to make the appropriate finding(s).</td>
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<tr>
<td>Guidelines for IRB Members on Conflicting Interests</td>
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<tr>
<td>Regulations for Waiver or Alteration of Consent Requirements</td>
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<tr>
<td>When the investigator requests waiver or alteration of informed consent in the protocol application, the rationale for the waiver or alteration is considered by the IRB as it makes any finding of waiver or alteration of informed consent as required by 45 CFR §46.116(c) or 45 CFR §46.116(d).</td>
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<tr>
<td>Waiver of Documentation (Including Signature) of Consent</td>
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<tr>
<td>When the investigator requests waiver of consent documentation in the protocol application, the rationale presented for the waiver is considered by the IRB as it makes any finding of waiver of consent documentation under 45 CFR 46.117(c) and 21 CFR § 56.109(c).</td>
</tr>
<tr>
<td>Significant Risk and Non-significant Risk Medical Devices Studies</td>
</tr>
<tr>
<td>When the protocol uses an investigational device that the investigator considers to be a non-significant risk, the rationale for non-significant risk is included in the protocol application.</td>
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<tr>
<td>Research Involving Pregnant Women, Fetuses, and Neonates</td>
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<tr>
<td>When a protocol involves pregnant women, human fetuses and neonates, the IRB considers the investigator’s response to the items in 45 CFR 46.204, as well as the IRB’s review of the items, and makes a finding under 45 CFR §46.204, 45 CFR §46.205, 45 CFR §46.206, and 45 CFR §46.207.</td>
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<tr>
<td>OHRP Guidance on the Involvement of Prisoners in Research</td>
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<td>HIPAA and PHI</td>
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<td><strong>Waiver of HIPAA Authorization:</strong> When the investigator requests a complete waiver or alteration of HIPAA authorization for the study, or partial waiver of HIPAA authorization for activities such as recruitment, the IRB/Privacy Board considers the rationale presented for the waiver(s) to determine if all of the requirements of 45 CFR 164.512(ii)(2)(ii)(A), (B), and (C) are met, and if so, makes the required finding.</td>
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<tr>
<td>Emergency Use of a Test Article</td>
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<tr>
<td>Exempt Review Categories</td>
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</table>
Frequently referenced guidances

| Expedited Review Categories
| What Qualifies as Human Subject Research
| (1) Clinical Trials Terms (2) Commonly Used Acronyms

Range of Actions on Regular Protocols at Convened Meetings
The IRBs must systematically evaluate each protocol to ensure the protection of research participants and reach a decision. The possible decisions are:

**Approved as Submitted:** The research may proceed. Approval requires an affirmative vote by a majority of the convened quorum.

**Approved with Changes:** Approved at a convened IRB meeting contingent on the investigator making minor changes. Such minor changes must be clearly delineated by the IRB at the meetings and approval is contingent on the PI accepting the IRB stipulations or making any verbatim changes to documents requested by the IRB. The research may proceed after the IRB chairperson (or any other individual(s) designated by the IRB) has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB from the investigator. This review is carried out via the expedited process.

If during the meeting the members decide major changes are required, the protocol is deferred.

**Deferred:** Approvable with greater than minor changes to be reviewed by the convened IRB. The research may proceed only after the IRB has reviewed and approved the required changes to the research at a convened IRB meeting.

A protocol will be tabled until it is approved (or eventually not approved) by the voting members at a convened meeting. If initial reviewers are not available at subsequent meetings where a tabled protocol is reviewed, additional reviewers will be assigned to review and present the protocol.

**Not approved:** The IRB has determined that the research cannot be conducted by the University of Louisville (e.g., the regulatory requirements, the University of Louisville’s HSPP standards, or other stipulations have not been satisfied). The investigator is provided with correspondence from the IRB Chair notifying him/her that the protocol was not approved by the IRB, explaining the reason(s) the protocol was not approved, and giving the investigator an opportunity to respond in person or in writing.

The minutes of the IRB meetings document the deliberations, actions, and votes for each protocol undergoing convened Review.

**Approval Date and Determination of Approval Expiration**
The approval date for a protocol subject to regular review is the date of the IRB meeting where the protocol was approved. The approval date of a protocol or protocol event (modification or continuing review) subject to expedited review is the date the reviewer recommends the protocol or event for approval. Approval of a modification does not alter the expiration date.
Protocols are approved for a period of no more than one year and unless otherwise stipulated by the reviewers. The expiration date is the last day the protocol has approval (e.g., a protocol approved on January 1, 2018 will expire at midnight on December 31, 2018).

The IRB can approve a protocol for a shorter period if warranted by the risks presented to participants. The IRB may approve a study for 6 months or may stipulate the approval on further IRB review after a defined number of participants has been enrolled (e.g., review after the first three subjects receive a Phase I drug that has never been tested in humans).

If any of the following are true, the IRB may perform review more often than annually:

(a) novel high-risk study using new therapeutic modality;
(b) phase I studies of a new drug or biologic that has never been tested in humans;
(c) studies involving a novel significant risk medical device that has never been tested in humans; and
(d) other high-risk studies as IRB members deem appropriate (this includes research for which the IRB determines that reports to the IRB of monitoring data should be more frequent than annually).

Approval contingent on minor conditions: The protocol initial approval date is recorded as the date the convened IRB approved the study contingent on minor conditions being addressed. However, the “effective” date of initial approval is the date on which the IRB chairperson (or designee) has reviewed and accepted as satisfactory any documents or any other responsive materials required by the IRB. IRB Final Approval Letters are not ‘released’ until contingencies have been met and, for corporate sponsored research, not until the IRB Review Fee has been paid. No research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective. The expiration date is determined in reference to the date the study was approved by the convened IRB contingent on minor conditions being addressed.

Preparation of Final Approval
After all changes are approved, and the study is ready for final approval, approval correspondence is prepared within the IRB ESS that establishes:

- The date the study was approved;
- The date of approval expiration;
- A listing of the items reviewed and approved at the convened meeting;
- Information that site approvals may be required from affiliated hospital(s);
- A reminder of the Privacy and Encryption policy;
- A reminder that modifications must be submitted and approved prior to implementation, unless the change is made to ensure the safety and welfare of the subjects enrolled in the research;
- A reminder that any unanticipated problems must be reported to the IRB and other agencies (as noted in Chapter 7.10 and IRB http://louisville.edu/research/humansubjects/lifecycle/event-reporting);
- A reminder of continuing review requirements and a statement that allowing lapse of approval to occur is considered “significant non-compliance” which may require reporting to federal agencies and/or a program audit by compliance monitors; and a
- A reminder that all payments to research subjects must be reported to the University of Louisville’s Controller’s Office.

The IRB ESS stamps the study number and approval date on items requiring approval stamps.
Rebuttal or Appeal of an IRB Decision to disapprove

Investigators may appeal the IRB requirement for specific changes in the protocol and/or consent document(s). At the discretion of the chair, the investigator may make such an appeal in person, in writing, or electronically (e-mail or IRB ESS) to the IRB.

If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision, and give the investigator an opportunity to respond in person and/or in writing. An appeal of a disapproved research project must be reviewed at a full board meeting.

In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by the Executive Vice President for Research and Innovation or any other officer or agency of the University of Louisville, state government or federal government.

7.8 Continuing Review Procedures
Submission of an application for continuing review is required on all approved protocols where research activities are ongoing, including but not limited to continuing recruitment and enrollment of participants; research tests, procedures, and other interactions and interventions; review of identifiable information; data analysis; and follow-up of previously enrolled participants.

IRBs must review proposed research at a convened meeting at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas and an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year. The IRB should decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research subjects. When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the next continuing review must occur.

Sixty and thirty days before study expiration, an expiration reminder letter is sent to the investigator. Once completed continuing review materials are received, a determination is made whether the continuing review is eligible for expedited review or if it should be scheduled for convened IRB review. If the review is to be a convened IRB review, the continuing review will be scheduled for review at the first regular meeting within 30 days of the study expiration date.

At each meeting, members may conduct continuing reviews of ongoing, approved protocols. Continuing review of expedited or full board approved research will be conducted with the same diligence as utilized with the initial review of the research. The review should be substantial and complete.

Reviewers have access to the original submission, all documents submitted since the beginning of the research, and any new documentation submitted with the continuing review application through the IRB ESS. This substantial review is designed to ensure that the rights and welfare of subjects continue to be protected. Reviews include protocols that were determined to require more than annual review, as well as those with annual review requirements. Reviewers
receive the submitted Continuing Review Form, including a revised informed consent document and copies of the last five signed consents and research authorizations. The report includes information on the number of subjects enrolled, adverse reactions, and any protocol violations, proposed changes, confirmation on informed consent process, subjects not completing the study, and a brief description of the research project. These materials allow reviewers to determine that the project continues to conform to the study as approved and to any special conditions placed on it by the IRB.

Reviewers are asked to review the continuing review application and supporting documents, including the protocol and informed consent document(s), to ensure compliance with current regulations and standards. Reviewers should:

1. consider if new or additional risks have been identified (e.g. number of serious adverse reactions, review DSMB reports, if available) which would require changes to the protocol, consent form, review frequency, etc.
2. verify that applicable requirements of the HIPAA Privacy Rule have been met.
3. determine that changes in research were reported to and approved by the IRB.
4. identify protocols that should be suspended or terminated because research is not being conducted in accordance with IRB requirements.
5. identify studies that might require verification that no material changes have been made since the previous IRB review. Specific criteria used to make these determinations:
   a. randomly selected projects;
   b. complex projects involving unusual levels or types of risk to subjects;
   c. projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and
   d. projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.
6. determine if new IRB policies might necessitate changes in the protocol.

In conducting a continuing review, members should ensure that the same standards as applied in the original review are still valid (e.g., minimize risk, risks reasonable in relation to anticipate benefits, equitable selection, adequate informed consent process and documents, monitoring data (DSMB reports, etc.) to ensure participant safety, privacy protections, and appropriate safeguards for vulnerable populations).

If significant new findings or information are submitted as part of a continuing review, the IRB may require the reporting of this information to participants if the information could reasonably affect participants’ willingness to continue participation.

The continuing review provides an important opportunity to ensure that changes in federal or state policy or IRB practices and expectations are reflected in the protocol and especially the new consent form.

Investigators are notified electronically through the IRB ESS of the decision of the IRB and any changes required. Continued approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent a continuing approval letter indicating the date of the next approval expiration. The continuing approval letter reminds investigators that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.
For all protocols initially subject to full board review, the continuing review application undergoes full board review, unless it meets the criteria for expedited review (see below). Those which will undergo full board review are assigned to one reviewer who presents the protocol at the convened meeting.

For a protocol initially subject to regular review, the continuing review application undergoes expedited review if it meets the criteria for expedited category 8:

(i) the research is permanently closed to enrollment of new subjects;
(ii) all participants have completed all research-related interventions; and
(iii) the research remains active only for long term follow-up of subjects;

or no subjects have been enrolled and no additional risks have been identified;

or the remaining research activities are limited to data analysis.

Or for a protocol initially subject to full board review, the continuing review application undergoes expedited review, thus it must meet the criteria below for expedited category 9:

For continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Protocols subject to expedited continuing review are assigned to one reviewer and are not presented at a convened meeting.

7.9 Review of Amendment/Modification Submissions

No amendments/modifications may be implemented without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to participants. Investigators are required to complete an Amendment/Modification application setting forth a summary of the proposed modifications and indicating the change in the risks to participants associated with the modification (e.g. increase, decrease, no change). Modifications involving changes to previously approved or submitted documents, (e.g. consent forms, advertisements, sponsor protocol) or the addition of new documents, must be accompanied by the proposed revised versions (with tracked changed) of the previously approved or submitted documents and/or the new documents.

If approved research is changed to eliminate an apparent immediate hazard(s) to the participant, the investigator is required to notify the IRB of the change(s) promptly (within five (5) business days). The IRB will review at the next convened meeting to determine if the change(s) instituted were consistent with the subject’s continued welfare.

If significant new findings or information are submitted as part of an amendment/modification or continuing review, the IRB may require the reporting of this information to participants if the information could reasonably affect participants’ willingness to continue participation.

Amendments/modifications that are considered “Major”, as indicated below, are subject to full board review. They are assigned by the IRB Analyst to one reviewer who reviews and presents the protocol at the convened meeting:

**Major Modifications:** A major (substantive) modification is one in which there is an increase in the level of risks to participants or a greater than minor modification (see below) in any of the following:

- The consent form
- Research design or methodology
- The participant population enrolled in the research
• Any other factor which would warrant review of the proposed changes by the convened IRB.

The IRB reviewer makes the final determination of whether changes to the protocol are “major” or “minor.”

**Minor Modifications:** A minor modification is one in which all of the following are true in the judgment of the IRB reviewer:

- Any newly identified risk does not alter the risk/benefit ratio
- All additional activities or procedures would have been eligible for expedited review had they been part of the initial protocol review.
- Either the research is minimal risk or the proposed changes do not alter the study design.

Minor modifications may be reviewed by the Expedited Review procedures.
Examples of minor changes that would allow for expedited review and major changes that would require full board review:

<table>
<thead>
<tr>
<th>Minor Changes</th>
<th>Major Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Administrative changes</td>
<td>• Changes that adversely affect the risk/benefit ratio of the study or specifically increase the risk to subjects</td>
</tr>
<tr>
<td>• Minor consent form changes</td>
<td>• Changes in inclusion/exclusion criteria that impact the risk/benefit ratio of the study</td>
</tr>
<tr>
<td>• Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods</td>
<td>• Significant changes in study design, such as the addition of a new participant population or the elimination of study arm</td>
</tr>
<tr>
<td>• Minor changes to study documents such as surveys, questionnaires or brochures</td>
<td>• New risk information that is substantial or adversely affects the risk/benefit ratio of the study</td>
</tr>
<tr>
<td>• New study documents to be distributed to or seen by subjects that are similar in substance to previously approved</td>
<td>• Significant changes to the study documents to be distributed to or seen by subjects</td>
</tr>
<tr>
<td>• Changes in payment to subjects or the amount subjects are paid or compensated that are not considered coercive.</td>
<td>• New study documents to be distributed to or seen by subjects that include information or questions that are substantively different from materials already approved by the IRB</td>
</tr>
<tr>
<td>• Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study</td>
<td>• New or revised financial conflict of interest management plans.</td>
</tr>
<tr>
<td>• Editorial changes that clarify but do not alter the existing meaning of a document</td>
<td>• Changes in inclusion/exclusion criteria that impact the risk/benefit ratio of the study</td>
</tr>
<tr>
<td>• Addition of or changes in study personnel</td>
<td>• Significant changes in study design, such as the addition of a new participant population or the elimination of study arm</td>
</tr>
<tr>
<td>• Addition of a new study site (in many but not all cases)</td>
<td>• New risk information that is substantial or adversely affects the risk/benefit ratio of the study</td>
</tr>
<tr>
<td>• Translations of materials already reviewed and approved by the IRB</td>
<td>• Significant changes to the study documents to be distributed to or seen by subjects</td>
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</table>

7.10 Review of Reportable Events

<table>
<thead>
<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.2.D</td>
<td>Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; University of Louisville policies and procedures; and the IRB’s requirements.</td>
</tr>
</tbody>
</table>

Definitions of the types of events that can occur

**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 participant or requires medical intervention to prevent one of outcomes listed above.

**Unexpected adverse experience (UAE):** Any adverse experience associated with the use of the drug, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to subjects and the IRB.

**Unanticipated adverse device effect (UADE):** Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSOs):** 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 participant 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.

**PI Responsibilities for Reporting**

The PI is responsible for the initial assessment of whether an event is reportable to the IRB based on the reporting requirements in the table below.

PIs must assess each adverse event, whether received from a sponsor, monitoring entity, or occurring on a sponsor-investigator project, and promptly report to the IRB.

For industry sponsored projects, PIs are responsible for maintaining contact with the sponsor, and receiving reports from the sponsor, and if applicable, the monitoring entity (e.g., DSMB, DMC) and reporting suspected UPIRTSOs and other reportable information to the IRB. For sponsor-investigator projects, the PI is solely responsible for reporting UPIRTSOs and other reportable information to the IRB and FDA, if applicable. Routine, periodic reports (e.g., Data Monitoring Committee reports, annual progress reports) should be submitted to the IRB at Continuing Review.

Any adverse event or experience that meets the reporting requirements below must be submitted to the IRB within the timeframe listed. Any new or follow-up information related to an event that has been reported to the IRB must be submitted as a follow-up report in the ESS.
## Reporting Timeframes

Additional details and examples of reportable events listed on the HSPPO website at:

http://louisville.edu/research/humansubjects/lifecycle/event-reporting

### Local Adverse Events

<table>
<thead>
<tr>
<th>Event Description</th>
<th>When to Report</th>
<th>IRIS Form</th>
</tr>
</thead>
</table>
| Local Adverse Event PI determines to be:  
  - Definitely, Probably, or Possibly related to the research intervention,  
  - Serious, and  
  - Unexpected (in terms of nature, severity, or frequency) | Report within 5 working days of UofL site awareness | Complete the Serious Adverse Event (SAE) Reporting Form within the iRIS system |

### Unanticipated Problems (UPIRTSOs)

<table>
<thead>
<tr>
<th>Event Description</th>
<th>When to Report</th>
<th>IRIS Form</th>
</tr>
</thead>
</table>
| Local Event PI determines to be:  
  - unexpected (in terms of nature, severity, or frequency), and  
  - related or possibly related to a subject’s participation in the research, and  
  - suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized. | Report within 5 working days of UofL site awareness | Complete the UPIRTSO Reporting Form within the iRIS system |

### Deviations/Violations/Misc.

<table>
<thead>
<tr>
<th>Event Description</th>
<th>When to Report</th>
<th>IRIS Form</th>
</tr>
</thead>
</table>
| Major Deviations/Violations/Misc.  
  - The PI and/or study sponsor is responsible for determining if a deviation is major or minor  
  - Note: Intentional deviation from the inclusion/exclusion criteria should be submitted prospectively and include a copy of the sponsor’s approval. | Report within 5 working days of UofL site awareness | Complete the Deviation/Violation/Misc form in iRIS. Attach notification of deviation to the study sponsor (if applicable). |

<table>
<thead>
<tr>
<th>Event Description</th>
<th>When to Report</th>
<th>IRIS Form</th>
</tr>
</thead>
</table>
| Minor Deviations/Violations/Misc.  
  - The PI and/or study sponsor is responsible for determining if a deviation is major or minor | Report with the next continuation review application | Attach documentation with the continuation review application:  
  These can be combined on one document (e.g. an Excel file) |

### External Safety Reports

The majority of IND Safety Reports or MedWatch Reports do not need to be reported to the UofL IRB. The only reports that must be reported are those that reveal an unanticipated problem involving risks to participants and others.

We understand that some sponsors require submission of all reports to the board regardless of the nature of the event reported. If you are submitting to fulfill such a requirement, please indicate this in your submission.
Additional Examples of Events That Require Reporting to the IRB
The following are additional examples of events that require reporting to the IRB:

a) Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.
b) Any accidental or unintentional change to the IRB approved research protocol or plan that involved risks or has the potential to recur.
c) Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
d) Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff.
e) Involving an individual in research without first obtaining their informed consent and a signed informed consent document (unless the IRB has explicitly waived these requirements).
f) Involving an individual in research using a consent form other than the current IRB-approved form.
g) Situations where the PI believes informed consent documents have been lost, misplaced, or destroyed.
h) Any non-compliance or continuing non-compliance. See Chapter 3.5 – Non-compliance and IRB Report of Findings.
i) Any other event appropriate to the local context.

IRB Review of Event Reporting
When reportable events are received by the IRB, the IRB Analysts will route the events to the IRB Chair/Vice Chairs for review.

<table>
<thead>
<tr>
<th>Reportable Event</th>
<th>IRB Review Routing</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Adverse Event reported within 5 working days</td>
<td>IRB Analyst routes to IRB Chair/Vice Chair for review. IRB Chair may determine that convened meeting review is required.</td>
<td>IRB may require PI to change the protocol and informed consent to include new findings. IRB determines whether safety information should be sent to participating subjects. IRB determines whether study subjects should be re-consented using the updated informed consent.</td>
</tr>
<tr>
<td>Unanticipated Problems (UPIRTSOs) reported within 5 working days</td>
<td>IRB Analyst routes to IRB Chair/Vice Chair for review and places the UPIRTSO on the agenda for the next available IRB meeting.</td>
<td>IRB determines whether enrollment should be placed on hold until safety concerns are addressed. PI may be required to change the protocol and informed consent to include new findings. IRB determines what safety information should be sent to participating subjects. IRB determines whether study subjects should be re-consented using the updated informed consent. IRB, in conjunction with IO, will notify federal agencies of the occurrence of the UPIRTSO. OHRP will be notified when the research is covered by DHHS regulations. FDA will be notified when the research is FDA regulated and the local investigator is the IND holder.</td>
</tr>
<tr>
<td>Major Deviations/Violations/Misc. reported within 5 working days</td>
<td>IRB Analyst routes to IRB Chair/Vice Chair for review. IRB Chair may determine that convened meeting review is required. If so, event is placed on next available IRB agenda. Depending on nature of event, IRB may assign review to IRB Compliance Auditor for action.</td>
<td>Based on Audit Findings, IRB Chair/Vice Chair or convened IRB will determine the severity of the event and the course of action to be taken. IRB may require PI to submit a corrective action plan to ensure that such events do not occur in the future. IRB determines any institutional contacts need notification. If reporting to federal agencies is required, IRB in conjunction with IO, will notify federal agencies of the occurrence of the event, actions taken and corrective action plans initiated.</td>
</tr>
</tbody>
</table>
Minor Deviations/Violations/Misc. reported within 5 working days

IRB Analyst includes information at continuing review for Chair review.

IRB may require PI to submit a corrective action plan to ensure that such events do not occur in the future.

When Modifying the Protocol is Indicated

An event or new information might prompt a protocol modification (amendment) – either initiated by the PI, Sponsor, or specified by the IRB after reviewing a report. When an event or new information requires a modification to a previously approved protocol (e.g., new side-effect in the consent form or suspension of enrollment) a modification must be submitted for IRB review, and must be approved by the IRB prior to implementation of the proposed changes. The only exception to pre-approval is for modifications necessary to eliminate apparent immediate hazard to the research participants; in this case, the PI must submit the modification to the IRB within 5 days following its implementation. See Chapter 7.9.

Suspensions and Terminations

The IRB has the authority to suspend or terminate approval of human subjects’ research that is not being conducted in accordance with the IRB’s requirements or when unanticipated problems occur. In general, these may include any incident, experience, or outcome, which has been associated with an unexpected event(s), related or possibly related to participation in the research, and suggests that the research places subjects or others at a greater risk of harm than was previously known or suspected. Any suspension or termination of approval will include a statement of the reasons for the IRB’s action and will be reported promptly to the investigator, the investigator’s department chair, and the Office of Sponsored Programs Administration. Federal regulatory agencies are notified as required.

Suspensions and termination of research ordered by someone other than the IRB (e.g. the study sponsor, federal agency, etc...) must be promptly reported to the IRB. See Chapter 3.6 for reporting requirements.

7.11 Review of Study Closures

Study Closure Amendment

Upon completion of a research project, investigators are required to submit an amendment notifying the IRB of the completion of the project.

Closure amendments are required for:

- Research that was subject to regular convened review
- Research subject to expedited review

Study closure amendments are processed administratively by the IRB analysts, unless there are complicating factors or issues of non-compliance that need to be reviewed by an IRB chair/vice chair or member. Closure amendments are generally not presented at a convened meeting.

A study may require re-opening for reasons such as additional recruitment or additional data analysis. If the study has not passed the next continuing review cycle, the HSPPO will work with the investigator to submit an amendment requesting the re-opening of the study. If the next continuing review cycle has passed, a new initial submission will be
required. Once all documents have been approved and no further interaction or communication with the participants is needed, the site should proceed with study closure.

If a study has been closed with the IRB and additional communication with subjects regarding treatment disclosures or study results is necessary, the IRB will review the information as an amendment without requiring the study to be re-opened with the IRB. Upon review of the amendment the study status will be set back to “completed”.

Study Closure Due to Lapse in IRB Approval is covered in Chapter 3.5.
In this chapter:

8.1  Staff Support of IRB Membership
- IRB Roster Requirements
8.2  Quorum Requirements and Voting at IRB Meetings
8.3  Meeting Times, Materials and Preparation for IRB meetings
8.4  IRB Study Files
8.5  Records Retention
8.6  IRB Minutes

8.1 Staff Support of IRB Membership
The IRB has qualified staff, dedicated to supporting the IRB in its mission of protecting human participants in research. The staff has knowledge, skills and abilities appropriate to their respective roles. The staff are reviewed at least annually by the HSPPO Directors and the EVPRI to ensure they continue to provide appropriate support to the IRB. The HSPPO Director oversees the Associate Director (IRB Administrator), the Assistant Director of Compliance Monitoring, the Research Administrative Systems Analyst (IRB Module Administrator) and an administrative associate, and is responsible for the overall management of the HSPPO. The Associate Director is responsible for supervising the IRB Analysts. The Assistant Director of Compliance Monitoring is responsible for supervising the Compliance Auditor(s). For policies on qualifications, education and periodic evaluation of HSPPO staff, see Chapter 4.

IRB Roster Requirements

<table>
<thead>
<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.1.A</td>
<td>The IRB membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB roster. The IRB has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.</td>
</tr>
<tr>
<td>II.1.E</td>
<td>The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.</td>
</tr>
</tbody>
</table>

IRB Rosters are constituted to meet the requirements of 45 CFR 46.107 and 108; 21 CFR 56.107 and 108.

An IRB Member database is maintained by the HSPPO and used as the data source for all IRB membership roster needs. The IRB Member database includes all information required under FDA and DHHS regulations and OHRP guidance (45 CFR 46.107 and 108; 21 CFR 56.107 and 108) including:

- Names of members
- Names of alternate members (and regular members for whom they substitute)
- Gender
- Earned degrees
- Scientific status
- Representative capacity
Affiliation

Representative capacity is presented in enough detail to indicate which appropriate participants can be represented by each member (e.g., children, pregnant women, prisoners). When research protocols include vulnerable participants, a member who is knowledgeable about that population, or who has experience working with similar participants, should be assigned to the protocol review.

Scientific status, (including the designation of “nonscientist” – see Chapter 6.2), is determined during recruitment and annually upon evaluation of IRB members. Scientific status and area of scientific expertise (e.g., pediatrician, radiologist, psychologist, engineering, pharmacist) are presented in sufficient detail to allow appropriate protocol assignment and in-depth protocol review.

Affiliation is determined during recruitment and annually upon evaluation of IRB members. An IRB member is considered affiliated if he or she, or any member of his or her immediate family, has any employment or other relationship (e.g., current employee, consultant, Board of Directors, current volunteer, trainee or student) with any of the affiliated entities:

University of Louisville and the University of Louisville Research Foundation
UofL Health, Inc. which includes University of Louisville Physicians, Inc., University Medical Center, Inc. (including UofL University Hospital, University Hospital-Jewish, James Graham Brown Cancer Center, Frazier Rehab Institute, Rudd Heart and Lung Center), UofL Health Louisville (including Peace Hospital, Mary & Elizabeth Hospital, Medical Center Southwest, Medical Center South, Medical Center East, Medical Center Northeast and UofL Health Shelbyville (Shelbyville Hospital))
Norton Healthcare, Inc. (Norton Hospital, Norton Children’s Hospital and other clinical sites as named in the Norton’s FWA).

The role of unaffiliated members is to represent the general perspective of participants.

8.2 Quorum Requirements and Voting at IRB Meetings

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<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tr>
<td>II.1.A</td>
<td>The IRB membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB roster. The IRB has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.</td>
</tr>
<tr>
<td>II.2.D</td>
<td>The IRB has and follows written policies and procedures for conducting meetings by the convened IRB.</td>
</tr>
</tbody>
</table>

Maintenance of quorum and voting at convened meetings is based on the following:

1. A majority of the (voting) members of the IRB (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of such members present at the meeting.
2. **Members may be present in person or through audio (telephone) or audio-visual teleconference.** Members present via teleconference shall be noted as such in the meeting minutes, which shall also indicate that the members received all pertinent information prior to the meeting and were able to participate actively and equally in all discussions.

The standard for members participating by audio or video conferencing is the same for those attending in person, giving all members the opportunity to participate fully in IRB deliberations.

3. IRB minutes shall include documentation of quorum and votes for each IRB action and determination by recording votes as follows:

- Total number voting;
- Number for;
- Number opposed; and
- Number abstaining

**Members leaving the meeting room** due to a conflicting interest, or for any other reason, will not be recorded as part of the quorum for a particular protocol.

4. An **individual who is not listed on the official IRB membership roster** may not vote with the IRB.

5. A **non-voting ex-officio member** of, or representative to, a University of Louisville IRB may not vote with the IRB.

6. **Ad hoc consultants** may not vote with the IRB.

7. A **nonscientist** must always be present for any vote to be taken.

8. Regular attendance of **unaffiliated** members is strongly encouraged. Individual members of the IRB may satisfy more than one required type of member (i.e. a nonscientific member may also be the unaffiliated member).

9. **When a member and their alternate both attend a meeting,** either person (but not both) may vote on each protocol. Generally if one of these individuals was the primary reviewer of a given protocol for that review cycle, that person votes on the protocol at the convened meeting.

10. **Voting by proxy** is not permitted.

11. **If the quorum fails during a meeting,** due to lack of a majority of IRB members being present or an absence of a nonscientist member, the IRB cannot take any further actions or vote until the quorum is restored.

12. The **IRB Administrator, Administrative Associate, or delegated staff member is responsible for monitoring** the members present at a convened IRB meeting to ensure that at the beginning of the meeting and for each subsequent vote the meeting is appropriately convened.

13. When the IRB reviews research that **involves participants vulnerable to coercion or undue influence,** at least one member must be present who is knowledgeable about or experienced in working with these participants.
14. When the IRB reviews research that involves prisoners, a majority must have no association with the prison involved, apart from their membership on the IRB.

When the IRB reviews research that involves prisoners, at least one voting member at the IRB meeting must be a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity.

The Role of the Chair(s) and Vice Chair(s) and Their Voting Responsibilities

The IRB Chair and the IRB Vice Chairs are voting members of the IRB. The Chair determines that quorum is established and maintained, chairs the meeting discussions, and calls for votes as appropriate. The IRB Chair is counted in the quorum but typically abstains from voting during the meeting unless certain circumstances arise. For example, if quorum is at the minimum number, the IRB chair will vote.

The IRB Chair, the individual who chairs the scheduled IRB meeting, reviews the agenda prior to the IRB meeting. The IRB Chair notes and communicates with other reviewers any important IRB issues that may be resolved or identified prior to the scheduled IRB meeting.

The IRB Chair directs the proceedings and discussion of the full IRB meeting. This includes keeping the discussion focused on important IRB issues.

The Chair and Vice Chairs have an in-depth understanding of ethical issues, state laws, institutional policy, and federal regulations.

The Chair may assist in drafting letters from the IRB to researchers regarding IRB decisions. The Chair also represents the IRB in defending or discussing IRB decisions with researchers.

The Chair or Vice Chairs serve as the reviewer for research that is reviewed by the Expedited Review procedure. They may also serve as the final reviewer of revisions made by the researcher to determine that response includes the appropriate requested changes. Proscriptive changes made by the IRB at a full committee meeting may be reviewed by the IRB Chair, Vice Chairs, experienced IRB members and/or an appropriate IRB designee (HSPPO Director or Associate Director).

8.3 Meeting Times, Materials, and Preparation for IRB Meetings

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The IRBs meet according to a regular schedule. Some IRB members, who review protocols according to the expedited review procedure and confirm exemptions, meet on an ad hoc basis as needed.

Meetings may be rescheduled, or additional meetings may be held, as needed by agreement of the IRB Chair and the HSPPO Director.
Protocol materials are available online, via the IRB electronic submission system. All IRB Members in attendance have access to the IRB ESS, and pertinent material is also projected. A hardcopy set of the most commonly referenced guidance documents are maintained in the IRB Conference Room.

Protocol Materials
The IRB staff assigns protocols in sufficient time for them to be reviewed before the meeting. Assignment is done via the IRB electronic submission system. All submitted study materials are available to the primary reviewers through the IRB ESS. All IRB members are granted view access to the presented protocol materials, unless they have a conflict, prior to the convened meeting. Materials necessary for review may be presented to IRB members less than 72 hours prior to a meeting only where determined necessary by the IRB Chair or HSPP Directors.

For protocol materials provided to members, see Chapter 7.

Meeting Documents
Approximately five days prior to the IRB convened meeting, all members have access to the following electronically:

Agenda List for the coming meeting, typically containing:
- a statement on confidentiality of meetings,
- conflict of interest statement(s),
- vote on previous meeting minutes,
- education and information items (including reports to be discussed), and
- finalized minutes from previous meetings.

The Agenda details:
- Protocols (Initial Submissions, Continuation Reviews, Amendments) which will be presented at the meeting.
- Local Serious Adverse Event Reports that the Chair/Vice Chair has determined should be circulated to all IRB members.
- UPIRTSOs submitted by any investigator.
- A list of actions (referred to as an expedited review report) taken since the previous convened meeting is circulated with the meeting agenda.
- Other items, such as Compliance Auditor reports that are presented at the convened meeting or miscellaneous information shared by the HSPP Director or IRB Chair(s).

8.4 IRB Study Files

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<tr>
<td>II.5.A</td>
<td>The IRB maintains a complete set of materials relevant to the review of the research protocol or plan for a period to time sufficient to comply with legal and regulatory requirements, sponsor requirements, and organizational policies and procedures.</td>
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The HSPPO employs an electronic submission system, “iRIS”, called ESS within this Policy Manual. Copies of some documents are also maintained in hard copy files.
Electronic Submission System (ESS)
The ESS maintains electronic records of all documents submitted through the system for every protocol event. The ESS contains a search function for locating and retrieving studies by IRB number, protocol title, name of Principal Investigator (PI), names of co-investigators, sponsor, or any combination of the above categories. Electronic copies of all materials submitted to the IRB can be accessed through the ESS on an event by event basis through the ESS Submissions History function, thus all documents supporting each protocol event are accessible to reconstruct the entire history of a study.

A study file contains, as applicable to the research:

Application(s). The study file includes one or more of the following application types:
- Biomedical IRB or SBE IRB research application (Regular, Expedited and Exempt review) submitted for all new research projects;
- Amendment/Modification Form, submitted for modifications to approved research;
- Continuing Review Form, submitted for continuing review of research;
- Reports submitted for reportable events; and
- Final Report Form, submitted for closing Regular review protocols, if applicable.

Study Document(s). The study file includes the following documents as applicable to the research:
- The IRB-approved informed consent document(s). The study file includes all approved consent forms, including the currently approved consent form.
- The IRB-approved Assent form(s). If a study involves children from whom the investigators will obtain assent, copies of approved assent forms will be included in the protocol file.
- Scientific evaluations of the proposed research. Documentation of scientific review is included in the protocol file and is required in the ESS before the study can be submitted. See Chapter 7 for information on the SSMR/Department Chair Review.
- Sponsor Materials. For investigational drug studies, the Investigator’s Brochure and Sponsor’s Protocol, including current amended editions of these documents and all previous versions are included in the protocol file.
- For investigational devices, a report of prior investigations and the Sponsor’s Protocol are filed.
- Application for federal grant support. For research supported by federal funds, a copy of the grant proposal is included in the protocol file. If the federal funding is subcontracted through another institution, the sub-contract with that institution is noted in the protocol file. For initial submissions approved on or after January 21, 2019, grant applications are only necessary upon IRB request.
- Advertisements, phone screening scripts and non-medical oral scripts, flyers, website or other subject recruitment materials.
- Questionnaires, surveys, interview scripts, diaries or other documents used in the course of the study.
- Participant informational sheets, brochures and sponsor newsletters.
- Reports submitted for reportable events.
- Final reports submitted for regular protocols.
- Data and Safety Monitoring Board (DSMB) reports.
- Continuation Review reports.
- Conflict of Interest (COI) documents, when COI or ICOI is applicable.
- Correspondence and communication between IRB members, IRB staff and investigators.
• Other IRB correspondence related to the research.
• Documentation of all actions including approvals, disapprovals, waivers or alterations of consents and HIPAA authorizations (as documented in the protocol application forms).
• Approval letter (or Determination of Exempt Review for research subject to exempt review.)
• Documentation of protocol closeout if any, including Final Report forms for regular protocols.
• Expiration notices.
• Various IRB Checklists.

IRB comments and investigator responses that occurred during IRB review are included with each application. Comments and responses exchanged via email may also be included as attachments.

Other IRB-related Information
Other information is maintained by the Human Subjects Protection Program Office, such as correspondence between the IRB and outside agencies and institutions, IRB convened meeting documentation - minutes, minutes lists, agenda, and agenda lists, information about each IRB Member including: contact information, background and experience, curriculum vitae, etc.

8.5 Record Retention

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</table>

In accordance with the Common Rule and FDA regulations (45 CFR 46.115(b) and 21 CFR 56.115(b)), IRB records are retained for at least three years after the completion of the research, either electronically or as hard copy. In accordance with federal HIPAA privacy regulations, IRB records containing protected health information (PHI) are retained for at least six years after the completion of the research. It is University of Louisville policy to retain records for the greatest amount of mandated time. Thus, HSPPO retains all research records for at least six years. This policy applies to all research studies, whether or not participants were enrolled. Sponsored grants and contracts may require additional periods for record retention.

Other documents, such as meeting agendas, agenda lists, meeting minutes, and minutes lists for the current IRB year are maintained in the HSPP office.

General correspondence from investigators and other documents not specific to a particular research protocol are maintained for a period of three years in the HSPP office.

Maintenance of and Access to IRB Records
The ESS resides on a secured server, with password-protected access. Access to IRB records is routinely provided to the Executive Vice President for Research and Innovation, IRB Chairs, IRB members, and HSPPO staff to carry out HSPP/IRB operations. Research investigators are provided reasonable access to files related to their own research.
8.6 IRB Minutes

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<tr>
<td>II.5.B</td>
<td>The IRB documents discussions and decisions on research studies and activities in accordance with legal and regulatory requirements, sponsor requirements (if any), and organizational policies and procedures.</td>
</tr>
<tr>
<td>II.2.E</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by the convened IRB.</td>
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<tr>
<td>II.2.E.1</td>
<td>Initial review</td>
</tr>
<tr>
<td>II.2.E.2</td>
<td>Continuing review</td>
</tr>
<tr>
<td>II.2.E.3</td>
<td>Review of proposed modifications to previously approved research</td>
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</table>

The IRB documents discussions, decisions, and findings either through the IRB minutes or for studies subject to expedited review, through documentation in the study file or other records.

The IRB minutes document:
- Meeting attendees and invitees
- Discussions and actions taken by the IRB
- Determinations made by the IRB
- Votes for each action recorded as numbers for, against, or abstaining
- Other issues requiring convened IRB review.

**Attendance at an IRB Convened Meeting**
Attendance at an IRB convened meeting is recorded in the minutes by documenting:
- The IRB members (voting, non-voting, and ex-officios) who are in attendance. Non-voting members include ex-officio members or alternate members attending for informational purposes
- The IRB members who are not in attendance
- When an alternate member replaces a primary member in attendance and votes at the convened meeting
- The continued presence of quorum for all votes, including a member whose primary concern is in a nonscientific area
- Attendance of members and alternate members who participate through videoconference or teleconference, and documentation that those members received all pertinent material before the meeting and had the opportunity to actively and equally participate in all discussions
- The IRB members who leave the meeting because of a conflicting interest
- The IRB members who leave the meeting briefly, are not present during a vote, and are not counted as part of the quorum
- The IRB members who arrive late or depart early from the meeting and their arrival or departure times
- The Human Subjects Protections Program Office staff present
- Any others present (e.g., invited guests, investigators invited to address the IRB, and consultants)

**Discussions and Actions Taken By the IRB**
Discussions and actions taken by the IRB, and the separate deliberations and basis for each action are documented in the minutes, such as:
- Discussion of protocol events – new, continuing review, modifications, reports of unanticipated problems and events and information requiring prompt review
• Approval of research – including the approval period for research, at initial and continuing review, (and if appropriate to the degree of risk determination of an approval period of less than one year)
• Suspensions and terminations of previously approved research
• Disapproval of research
• Discussion of controverted issues and their resolution or disposition
• Requests for consultant review or input from an expert in the field (e.g. requests made during a convened meeting)
• Actions resulting from review of reports of unanticipated problems involving risks to participants or others, or other reportable events and information
• Actions resulting from determinations of serious or continuing non-compliance
• If a protocol is using a DHHS-approved sample consent:
  The justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample consent document

Determinations made by the IRB
Determinations made by the IRB are recorded in the minutes with documentation of the protocol-specific findings justifying those determinations as appropriate, such as:
• Significant risk and non-significant risk device determinations, pursuant to: 21 CFR 812.2(b), 21 CFR 812.150(b)(9) and considering FDA Information Sheet Significant and Non-significant Risk Medical Device Studies
• Approval of waiver or alteration of informed consent, pursuant to: 45 CFR 46.116(c) and 45 CFR 46.116(d)
• Waiver of informed consent documentation, pursuant to: 45 CFR 46.117(c) and 21 CFR 56.109(c)(1)
• Research involving adults with impaired decision-making
• Waiver of HIPAA Authorization, pursuant to 45 CFR 164.512(i)(2)(ii)
• Waiver of HIPAA Authorization for recruitment or screening, pursuant to 45 CFR 164.512(i)(2)(ii)
• Alteration of HIPAA Authorization, pursuant to 45 CFR 164.512(i)(2)(ii)
• Use of short form process for consent 45 CFR 46.117(b)(2) or 21 CFR 50.27(b)(2)

When research involves children, the following IRB decisions are documented:
Appropriate children finding applicable to research:

Whether the permission of one parent/guardian is sufficient or if permission from both parents/guardians is required. How assent is to be solicited or obtained, unless waived.

The participation of children who are wards of the state is approved under:
45 CFR 46.406, 45 CFR 46.407 only if 45 CFR 46.409(a) is satisfied, or
21 CFR 50.53, 21 CFR 50.54 only if 21 CFR 50.56(a) is satisfied

Appropriate involvement of pregnant women, fetuses, and neonates pursuant to:
45 CFR 46.204, 45 CFR 46.205, 45 CFR 46.206, and 45 CFR 46.207

Approval of research involving transplantation of fetal tissue:
42 USC 498A(b)(1) and (2)
Approval of research involving prisoners as participants under the following regulations:
45 CFR 46.305 and 45 CFR 46.306

- Determination of the level of risk
- Determinations of serious or continuing non-compliance
- Unanticipated Problems and Unanticipated Adverse Device Effect

Other Issues
Other issues are documented in the minutes, including but not limited to:
- Other events and information that require prompt reporting to the IRB
- DSMB reports
- Approval of minutes of prior convened IRB meetings
- Presentation of information from an outside consultant or expert as previously requested by the IRB
- Special situations such as use of a test article and humanitarian use devices
- The names of IRB members who abstain for reasons other than conflict of interest
- Education items presented to the committee
- Other items as applicable.

Disposition of the IRB Minutes
The HSPPO staff writes minutes and makes them available for IRB review. Minutes may not be altered by anyone including a higher authority once approved by the members at a subsequent IRB meeting.

The minutes of convened IRB meetings are considered confidential, and access to them is restricted and secured.
In this chapter:

9.1 **Steps to Minimizing Risk**
- Identifying Potential Risks (PI Input)
- Minimal Risk
- Physical Risks
- Psychological Risks
- Social, Legal and Economic Risks
- Drug Risks
- Device Risks
- Ensuring Risks are Minimized (IRB Determination)
- Potential Risks v. Anticipated Benefits (PI Input)
- Potential Risks v. Anticipated Benefits (IRB Determination)

9.2 **Data Monitoring Plan**
- IRB Review of the Data Monitoring Plan
- Reporting Data Monitoring Findings to the IRB

9.3 **Risks to Vulnerable Populations**
- Considerations in Reviewing Research Involving Vulnerable Populations
  - Children
  - Prisoners
  - Decisionally Impaired Participants
  - Pregnant Women, Fetuses and Neonates
  - Students
  - Employees
  - Other Potentially Vulnerable Participants

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<tr>
<td>II.3.A</td>
<td>The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.</td>
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</table>

**Definitions**

**Risk:** The probability of harm (physical, psychological, social, legal, or economic) occurring as a result of participation in a research study. Both the probability and the magnitude of possible harm may vary from minimal to significant. The Federal regulations only define “minimal risk.”

**Minimal Risk:** A risk is considered to be minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

**Benefit:** A valued or desired outcome; although these terms may appear straightforward, evaluations of risk and benefit are made more complex both by the subtle distinctions between therapeutic and research activities, and by evaluations of actual risks in the lives of normal and vulnerable classes of subjects (i.e., prisoners, children, cognitively impaired individuals, etc.)
9.1 Steps to Minimizing Risk

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These policies and procedures are based on: Common Rule 45 CFR 46.111(a)(1),(2); FDA 21 CFR 56.111(a)(1),(2).

When reviewing the application submitted by the Principal Investigator (PI), the IRB analyzes levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, before approving the proposed research.

Investigators submitting research proposals for IRB review should understand that the IRB is responsible for assessing the possible risks vs. anticipated benefits, if any, of research as one of its primary functions. In addition, once risks and benefits have been assessed, the IRB is responsible for ensuring that the risks of study participation are minimized to the greatest extent possible, while the benefits of study participation are maximized.

**Identifying Potential Risks (PI Input)**

When considering risks, the IRB considers only those risks associated with the research, i.e., physical, psychological, social, legal, or emotional. Investigators should be aware that risks would include immediate risks of study participation, risks of randomization (especially to placebo groups in medical and pharmaceutical research), risks of breach of confidentiality, and risks of long term effects.

For biomedical research (primarily medical and pharmaceutical research) the IRB is required to determine and differentiate between the risks associated with the research and the risks associated with standard diagnostic or therapeutic interventions or therapies subjects would undergo regardless of participation in research. The IRB does not establish or determine what constitutes “standard of care.” It is important for investigators to clearly distinguish procedures which they consider are “standard of care” from those which are conducted solely for research purposes in the protocol and the informed consent form.

**Minimal Risk**

Much of the IRB review process is governed by the concept of “minimal risk.” Assignment of research for expedited review, approval of waiver of consent, and the conduct of research involving vulnerable research populations may be dependent upon whether the research places subjects at minimal risk or greater than minimal risk (significant risk).

**Physical Risks**

Some research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation (especially those which result from medical procedures, drug research or device research) may result in permanent injury to subjects. For all research with the potential to do physical harm investigators are encouraged to think through all risk possibilities, however rare they may seem, so that they can be resolved quickly and effectively to minimize harm to subjects. By clearly detailing procedures to address situations of physical harm, the IRB can be assured that the investigator has made efforts to minimize physical risks to the greatest extent possible.

**Psychological Risks**

Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, and hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem. As is the
case with physical risks, these effects are usually transient. For all research with the potential to cause psychological harm investigators are encouraged to think through all risk possibilities, however rare, so that a course of action can be planned to quickly and effectively minimize the distress to subjects. By clearly detailing procedures to address situations of psychological harm, the IRB can be assured that the investigator has made efforts to minimize psychological risks to the greatest extent possible.

Social, Legal and Economic Risks
Some research proposals involve the handling of sensitive information which may result in injury to subjects through a breach of confidentiality. These breaches may result in embarrassment within a subject’s business or social group, loss of employment, or criminal prosecution. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior, and illegal activities. For these situations investigators should clearly detail strong precautions to ensure that the research does not cause social, legal, or economic risks to the subjects.

Research may also pose direct economic risk to study subjects. Procedures billed to insurance companies may require a significant co-payment on behalf of subjects, insurance companies may refuse to pay for "investigational" therapies, subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize economic costs to subjects. If the research may involve additional actual costs to individuals, the anticipated costs should be described to subjects during the consent process.

Drugs Risks
The IRB is frequently called upon to consider protocols involving drugs that are in development and have yet to receive approval from the FDA, as well as those that have already been approved for specific indications by the FDA. Any research with a drug, whether approved or not, requires IRB approval. Drugs or drug combinations that have not been approved, will require a specific IND number from the FDA. The number must be clearly stated in the submission information.

Approved drugs being tested for unapproved indications may also require an IND or a specific waiver from the FDA of the requirement for an IND. An IND is required if the investigation involves a route of administration, a dosage level or use in a vulnerable patient population (e.g., children, prisoners, pregnant women and fetuses, etc.), or other factors that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.

In considering drug studies, it should be indicated that drug studies have traditionally been divided into Phase I, II, III and IV. Knowing the phase of the trial helps the reviewer determine the adequacy of the consent form and the appropriateness of the protocol. The four types are described as follows:

Phase I studies are the initial studies of a new drug and are designed for a small number of subjects to determine safety and toxicity. Risks are often considerable, direct benefits to subjects questionable, and studies are potentially non-therapeutic. In reviewing Phase I studies, therefore, it is important to consider both the underlying pharmacology of the drug as well as the compelling animal evidence and/or any human anecdotal evidence for utilizing a given drug in the treatment of a particular condition. In general, Phase I studies may involve studying dosage and convey the language of “dose-limiting toxicity.” Phase I studies are not intended to be therapeutic. Specific language regarding Phase I cancer studies has been compiled by a bioethics committee convened by the National Cancer Institute. Such studies, however, should not hold forth the expectation of cure and, when appropriate, should include the comfort care language as part of the options of therapy.

Phase II studies are often carried out to examine the dose and frequency of the drug and to begin to establish the treatment’s efficacy. They may be expected to have some benefit for the subjects but, subjects should be cautioned that there might be no direct benefit to them. These studies are often carried out as part of a larger, multi-center study. The
fact that a study may involve multiple centers does not negate the local IRB’s responsibility to exercise appropriate oversight based on institutional policies. The local IRB reserves the right to impose additional constraints.

**Phase III** studies typically involve large subsets of patients and describe the effect of a drug in treating a particular disease state. Phase III studies often compare the experimental treatment against the standard of care or placebo. In consideration of these studies, proper grounding of early Phase I and Phase II trials must be noted in the underlying rationale. To the extent that there is expectation of favorable outcome, it may be appropriate for the investigator to so indicate. If stated in the Informed Consent Document, the IRB must review the language closely to determine if this or similar statements will be allowed. Under no conditions, shall the investigator hold forth an expectation of treatment or cure if such appears unlikely from the preliminary data. Reviewers will examine both the consent form and the research protocol to ensure that the language involved is neither exculpatory nor coercive.

**Phase IV** studies are usually defined in terms of post-marketing surveillance and are mandated by the FDA. Such studies evaluate drugs that have already been approved. In Phase IV studies, the new research treatment becomes standard treatment in patient care and may be used in new combinations with other approved drugs or with other treatment modalities, such as surgery or radiation therapy.

An additional factor the reviewer must weigh is the role of placebo. The current custom at the University of Louisville IRB is to allow placebo studies, but to be certain that appropriate rescue procedures are in place if participants are endangered. Specific psychiatric protocols may also require inpatient hospitalization and supervision by a separate team of physicians responsible for the clinical care rather than study investigator if withdrawal from normal drugs is deemed to be a potential risk to the participant or to society.

**Device Risks**

Unless specifically exempt from FDA device regulations (e.g. low risk devices or new devices considered “substantially equivalent” to approved devices), all devices are categorized as either significant risk (SR) or non-significant risk (NSR). While SR studies must be submitted to the FDA for an Investigational Device Exemption (IDE) and to the IRB, NSR studies are conducted following the FDA’s “abbreviated requirements,” do not require an IDE, but require special oversight by the IRB of: record keeping, labeling, promotion, and study monitoring. As a result, a critical part of the review process for IRB submissions involving devices is the verification of if a device is considered significant risk or non-significant risk. Although the sponsor makes the initial determination regarding NSR versus SR, the IRB may differ in its assessment. The FDA has the authority to rule that a device is a SR device based on one IRB’s view, and the sponsor is then obligated to inform all the institutions using the device that a judgment about the device being a NSR was in error. Because all SR devices are required to secure an IDE number, a protocol cannot be approved if this is missing. If the IRB determines that a device proposed as NSR is more appropriately considered SR, the PI will notify the sponsor, who has the responsibility to contact the FDA to obtain an IDE.

In considering if a device is SR or NSR, a reviewer should 1) consult the FDA list of SR and NSR devices, 2) consider the proposed use of a given device in a study and risks that may be associated with it, and 3) consider the innate risks and benefits, and how they compare to those of alternate devices or procedures. A reviewer should present his/her rationale to the committee so that the minutes can document the decision.

Some NSR studies per federal regulations may be eligible for expedited review once they are reviewed by the full board.

**Ensuring Risks Are Minimized (IRB Determination)**

The IRB considers the overall level of risk to participants in evaluating the proposed research in accordance with the conditions outlined in 45 CFR 46.111(a)(1-7), 21 CFR 56.111(a)(1-7) and the ethical principles outlined in the Belmont
When assessing risks and benefits, the IRB is required to:

1. identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in the research;
2. determine that the risks will be minimized to the fullest extent possible;
3. identify the probable benefits to be derived from the research;
4. determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained;
5. assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits; and
6. determine intervals for periodic review (no greater than annually), and, where appropriate, determine that adequate provisions are in place for monitoring the data collected and, if the subjects are likely to be members of vulnerable populations, determine that appropriate additional safeguards are in place to protect the rights and welfare of these subjects.

The IRB examines the research plan, including research design and methodology, to determine that there are no inherent flaws that would place research participants at unnecessary risk. This includes the risk that research lacking in statistical power may not lead to meaningful results. Appropriate safeguards can also minimize risk to participants, for example: having an adequate data monitoring plan, or protecting confidentiality by using coded data. If risks are not adequately minimized, the protocol will not be approved as written.

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research team to protect participants and minimize potential harm. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.

Potential Risks v. Anticipated Benefits (PI Input)
The Protocol Application requires that the PI describe the potential benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants or society. The PI must explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

Potential Risks v. Anticipated Benefits (IRB Determination)
The IRB determines whether the risks of the research are reasonable in relation to the anticipated benefits (if any) to research participants and the importance of the knowledge that may reasonably be expected to result. [45 CFR 46.111(a)(2), 21 CFR 56.111(a)(2), 38 CFR 16.111(a)(2)]

The IRB bases its risk/benefit analysis on the information provided by the PI and by the expertise of its members and consultants who utilize the most current information about the risks and benefits of the interventions involved in the research.

The IRB considers only those risks that result from the research, and does not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research. The IRB does not consider those risks and benefits that participants would receive even if not participating the research. [45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2)]
9.2 Data Safety Monitoring Plan (DSMP)/Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

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<th>AAHRPP Std./Element</th>
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<td>II.3.B</td>
<td>The IRB has and follows written policies and procedures for reviewing the plans for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants.</td>
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To approve research, the IRB must determine that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants. (45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6), 38 CFR 16.111(a)(6))

Many studies (e.g., if more than minimal risk) need a DSMP:

- The DSMP must be commensurate with the level of risk, size and complexity of the study.
- The DSMP might need to include a DSMB or DMC (a data safety monitoring board, or committee – the terms are generally used interchangeably): for example, a DSMB or DMC may be required as part of the monitoring plan by NIH, FDA, other sponsors, or the IRB.

**Data and Safety Monitoring Board** – committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

PIs are required to describe a DSMP, if applicable, in the Protocol and IRB Application.

- Chapter 14 - discusses PI responsibilities
- Data Monitoring Committees - FDA March 2006 “Guidance for Clinical Trial Sponsors”

Data Monitoring Plans and Data Monitoring Committees – NIH and NCI policies:

- NIH: Policy for Data and Safety Monitoring
- NIH: Further Guidance On Data And Safety Monitoring For Phase I And Phase II Trials

**IRB Review of the Data Safety Monitoring Plan**

The IRB primary reviewer reviews the proposed DSMP, and the administration and composition of the monitoring entity, when applicable. If additional expertise is needed, the IRB will seek input from persons with appropriate knowledge.

**Reporting Data Safety Monitoring Findings to the IRB**

It is not the role of the IRB to perform data monitoring, but to ensure that appropriate monitoring is taking place, and to review reports from the monitoring entity.

The IRB must ensure that the conditions satisfied in order for initial IRB approval of the research are still satisfied at continuing review. These include, but are not limited to, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for participants. Thus, the PI must include in the continuing review application the outcomes of data and safety monitoring including, any unanticipated problems, and any new information pertaining to the research - either from the research itself or from other sources, which have occurred since the previous IRB review. The amount of detail required depends on the type of research being conducted. In many cases, an appropriate summary would be a simple brief statement that there have been no unanticipated problems and that adverse events...
have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

In addition, periodic (usually annual) reports from the monitoring entity are submitted by the PI to the IRB at continuing review. (When a monitoring entity is used, the IRB conducting continuing review of the research may choose to rely on a current statement from the monitoring entity indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research.)

Whether the method of monitoring is by PI oversight or from the establishment of a DSMB, the IRB can tailor a specific timeframe for future reporting of data monitoring findings to the IRB. The IRB can set the date of continuing review for the protocol as being less than the maximum of a year, if they determine that interim reporting of data monitoring information will serve to better protect participants. Alternatively, the IRB can request a report after a specific number of participants are enrolled or after a serious adverse event has been reported.

9.3 Risks to Vulnerable Populations

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<td>II.4.A</td>
<td>The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.</td>
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The IRB is cognizant of the vulnerable nature of many participants. Food and Drug Administration (FDA) regulations and the Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable participants. In order to approve research involving vulnerable populations, the IRB must determine, where appropriate, that additional safeguards have been included to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Children (45 CFR 46 Subpart D; 21 CFR 50 Subpart D),
- Prisoners (45 CFR 46 Subpart C),
- Decisionally impaired,
- Pregnant women, human fetuses, or neonates (45 CFR 46 Subpart B),
- Economically or educationally disadvantaged persons,
- Students,
- Employees.

The IRB includes among its members persons who are knowledgeable about and experienced in working with vulnerable participants. (45 CFR 46.107(a); 21 CFR 56.107(a)). When a research study involves a vulnerable population not otherwise covered by these policies, the IRB takes steps to evaluate whether additional safeguards have been included in the research to protect the rights and welfare of participants. See also Chapter 12.2 for consent procedures for vulnerable populations.

Considerations in Reviewing Research involving Vulnerable Participants

The IRB considers the following elements of the research plan when reviewing research involving vulnerable participants:

**Strategic issues** that involve inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
Group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants.

Participant selection to prevent over-selection or exclusion of certain participants based on perceived limitations or complexities associated with those participants. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available “captive” population.

Application of state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes (as discussed in Chapter 12) often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.

Procedures for assessing and ensuring participants’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable participants, the IRB verifies that such procedures are a part of the research plan. In certain instances, it may be possible for investigators to enhance understanding for potentially vulnerable participants. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing-impaired participants, translation of informed consent forms into languages the participants understand, and reading the consent form to participants slowly and ensuring their understanding paragraph by paragraph.

Need for additional safeguards to protect potentially vulnerable populations. For example, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

Children

Children: Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

- The IRB follows the requirements of the DHHS regulations at 45 CFR 46, Subpart D and FDA regulations at 21 CFR Part 50, Subpart D in reviewing protocols involving children. The IRB makes the findings and determinations required by the DHHS and FDA regulations related to the risks before allowing research involving children to proceed. See Chapter 12.2 for consent requirements for research involving children participants.

Children should be included in research, along with adults, unless there is a compelling rationale for their exclusion. Research that limits enrollment to children is generally not appropriate unless:

1. The condition or disease is limited to children, or
2. The research seeks to obtain information on a test article or procedure that previously had been studied only in adults.

The Chair/Vice Chairs may approve research involving children through the expedited review procedures as long as the study does not involve more than minimal risk to the participant. Specific determinations must be made concerning whether one or two parents must sign the informed consent, and whether assent of the child is required. See guidance:

- Additional Protections for Inclusion of Children in Research (OHRP)
- Additional Safeguards for Children in Clinical Investigations (FDA)
Prisoners

Prisoner: Any individual involuntarily confined or detained in a penal institution. This includes individuals:

- sentenced to such an institution under a criminal or civil statute,
- detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution,
- detained pending arraignment, trial, or sentencing.
- DHHS details special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as participants in research.
- [45 CFR 46, Subpart C]. The IRB will apply the standards of Subpart C to all prisoner research, whether or not DHHS-supported.

Once the determination for full-board review has been made, the study will be assigned to a primary reviewer. Specific additional protections are listed in Additional Protections for Prisoners involved in Research, 45 CFR 46 Subpart C. An IRB must have present at its meeting a designated prisoner advocate in order to review projects involving the use of prisoners in research.

For research involving interaction with prisoners reviewed by the expedited procedure:

1. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.
   a. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
2. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
3. Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative.

For research that does not involve interaction with prisoners (e.g. existing data, record review) reviewed by the expedited procedure:

1. It may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.
2. Review by a prisoner representative is not required.
3. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.
4. Review of modifications and continuing review must use the same procedures as initial review.

DHHS-supported research: The IRB must certify to the Secretary (of DHHS), via the Office for Human Research Protections (OHRP) that it has reviewed and approved the research under 45 CFR 46.305; additionally, the Secretary (through OHRP) must determine that the proposed research falls within permissible categories [45 CFR 46.306(a)(2)]. If biomedical or behavioral research is conducted or supported by DHHS, approval must be obtained from the Secretary of DHHS (through OHRP) before commencing research.

Note: OHRP discourages expedited review of any research involving prisoners as participants.

Non-DHHS-supported research: Certification to OHRP is not required; the IRB substitutes a comparable risk assessment measure in place of the review and approval by the Secretary of DHHS. Refer to guidance Additional Protections for Prisoners in Research for:

- Special requirements regarding IRB composition and additional duties
- Categories of permissible research
- Other requirements pertaining to DHHS-supported research
• IRB required findings.
• In order to consider research involving prisoners, the IRBs must:
  o Ensure a majority of its members are not otherwise associated with the prison(s) involved in the
    research, and Include a prisoner or a prisoner advocate, who can adequately represent the
    interests of the prisoners, unless the research has already been reviewed by an IRB that
    included a prisoner advocate.

When a previously enrolled research participant becomes a prisoner and the relevant research protocol was not
reviewed and approved by the IRB (under 45 CFR 46, Subpart C), the PI should promptly notify the IRB of this event
through the IRB Amendment Form. The PI should state that all research interactions and interventions with, and
obtaining identifiable private information about, the now-incarcerated prisoner-participant will cease until the
requirements of Subpart C have been satisfied with respect to the relevant protocol, unless the PI asserts that it is in
the best interests of the participant to remain in the research study while incarcerated, in which case the IRB Chair may
determine that the participant may continue to participate in the research until the requirements of Subpart C are
satisfied. Upon receipt of notification that a previously enrolled research participant has become a prisoner, the IRB
should promptly re-review the protocol in accordance with the requirements of Subpart C if the PI wishes to have the
prisoner participant continue to participate in the research.

DHHS Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects
Under certain conditions DHHS conducted or supported epidemiologic research may be approvable by the Secretary of
DHHS, as outlined in the Federal Register Vol 68 No.119, June 20, 2003.

For additional guidance on protections for prisoners see Guide 004 Additional Protections for Research
Involving Prisoners. For additional clarification on prisoners see Prisoner Research FAQs

Decisionally Impaired Participants
The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence, and must determine
whether such participants should be recruited and whether support mechanisms, such as surrogate consent, are
appropriate.

In order for the IRB to assess the decision-making capacity of the participant, the investigator shall include a protocol-
specific plan for assessment if the investigator determines that the participant lacks decision-making capacity: the
investigator will describe the research to the participant and the investigator’s intent to obtain LAR consent; and
document this communication in the research file confirming that the research protocol was described to the
participant. However, if the investigator determines that the participant is non-responsive, the investigator shall
document that observation in the research file. If the participant expresses resistance or dissent to participation or to
the use of LAR consent by word or gesture, the participant shall be excluded from the research study. Discussion of
who make act as an LAR is discussed in Chapter 12, Informed Consent and Assent.

Because no generally accepted criteria for determining competence to consent to research (for persons whose mental
status is uncertain or fluctuating) exist, the role of the IRB in assessing the criteria proposed by the investigator is of
major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for
themselves must be accomplished without clear guidance from statutes, case law, or regulations. Within the boundaries
of existing legal precedents, IRBs can be creative in helping investigators formulate appropriate procedures in these
uncertain areas.

The Chair/Vice Chairs may approve research involving vulnerable participant through the expedited review
procedures as long as the study does not involve more than minimal risk to the participant.
Cognitively Impaired: Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Incapacity: Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

Incompetence: Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

Institution: A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

See Chapter 12.2 for more information on the consent process, and criteria for including decisionally “cognitively” impaired participants in research.

Pregnant Women, Human Fetuses, and Neonates
Women should not be excluded from any phase of research unless the science of the project or the health of the participant will be compromised. Regarding clinical drug research, Phase I, II, and III trials should have the proportion of women in the study which at least reflects the proportion of women in the population which will receive the drug when it is marketed, and should enroll numbers adequate to detect clinically significant sex differences in drug metabolism and response.

In order to assure that adequate numbers of women are included, researchers are encouraged to actively recruit women into their trials. For specific outreach methodologies, researchers may obtain the "NIH Outreach Notebook of the Inclusion of Women and Minorities in Biomedical and Behavioral Research."

The Department of Health and Human Services (DHHS) details special protections for research involving pregnant women, human fetuses, and neonates. [45 CFR 46, Subpart B.]

Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent, in accordance with the guidance Additional Protections for Research Involving Pregnant Women, Fetuses, and Neonates.

In general, Subpart B requires that research involving pregnant women, human fetuses, and neonates should involve the least possible risk. Persons engaged in the research may have no part in the timing, method, or procedures used to terminate the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.

Three separate conditions, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses, and neonates:
Research Involving Pregnant Women. No pregnant women may be involved as a participant in research unless either of the following conditions applies: The purpose of the activity is to meet the health needs of the mother, and the fetus is placed at risk only to the minimum extent necessary to meet such needs; OR the risk to the fetus is minimal. The mother and the father must be legally competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

Research Directed at Human Fetuses. The IRB must find that: the purpose of the research is to meet the health needs of the individual fetus and shall be conducted in a way that will minimize risk; OR the research will pose no more than minimal risk to the fetus, and the purpose of the activity is to ascertain important biomedical knowledge that is unobtainable by other means. These activities are permitted only if the mother and father are legally competent and have given their informed consent, unless the father is not reasonably available or the pregnancy resulted from rape.

Research Involving Neonates. For research involving neonates, the IRB must distinguish between viable and non-viable neonates. Viable is defined in the regulations as being able to survive to the point of independently maintaining a heartbeat and respiration, given the benefit of available medical therapy. If the neonate is viable, it is considered a “child” and may be involved in research to the extent permissible under 45 CFR 46, Subpart D, which is discussed above.

- A non-viable neonate may not be involved in research unless all of the following conditions apply: The vital functions of the neonate are not artificially maintained; experimental activities that would of themselves terminate the heartbeat or respiration are not employed; AND the purpose of the research is development of important biomedical knowledge that cannot be obtained by other means. Research involving a non-viable neonate is permitted only when both parents have given their informed consent, unless one parent is not reasonably available or the pregnancy resulted from rape or incest. In the case of non-viable neonates consent by a parent’s legally authorized representative is not allowed.

- A neonate of uncertain viability may not be involved in research unless one of the following conditions applies: There is no added risk to the neonate and the purpose of the research is to obtain important biological knowledge that cannot be obtained by other means; OR the purpose of the activity is to enhance the probability of survival of the individual neonate. Research involving a neonate of uncertain viability is permitted only if either parent or the parent’s legally authorized representative gives their permission.

Specific additional protections are listed in Guide-003 - Additional Protections for Pregnant Women and Fetuses Involved in Research, 45CFR 46 Subpart B §46.204

Non-pregnant women of reproductive potential

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Students

It is not uncommon for research projects to involve students, either those enrolled in a specific course or those enrolled in university programs. For instance, it is common practice for medical students to serve as subjects in biomedical research or for psychology students to serve as subjects in behavioral research. The obvious concern is that their participation may not be truly voluntary, because of a desire to appear particularly cooperative or highly motivated, or because participation in research is a course requirement.

Various procedures have been suggested to reduce the possible unintended coercion, while still permitting students to participate as subjects in research. These include:
a. Posting IRB approved advertisements throughout the university to recruit subjects from a broad base of students.
b. Offering students the opportunity to participate in “mass screenings” with follow-up with those who meet research criteria. It should be clearly stated that participation in the screening, as well as participation in the research is voluntary.
c. Avoiding any personal solicitations by students, faculty, GTAs or RAs for fellow students or faculty.
d. Providing a number of research projects from which to choose, if participating as a research participant is a course requirement.
e. Providing alternative and equal methods for meeting course credit (or extra credit) requirements, such as attending a series of research presentations by faculty, writing a brief paper, or conducting one’s own research.

Researchers need to exercise special caution when they desire students in a class to participate in research. Unintended coercion must be avoided by ensuring that (1) participation is voluntary, (2) no one knows who is and is not participating, and (3) a time and effort equivalent alternative is provided for those who wish not to participate. Course grades should not be based on research participation. Basing grades on research participation is coercive and should be avoided.

A researcher should not have access to the data collected until after the class grades have been posted. Researchers often ask a colleague not affiliated with the research or class to administer the evaluation and hold the data until after the grades are posted.

**Employees**

University employees, such as faculty, office staff, lab technicians, and postdoctoral fellows, are similar to students in that they are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor’s work. Accordingly, many of the same procedures described above to reduce the likelihood of coercion in recruiting student volunteers apply equally to university employees.

**Other Potentially Vulnerable Participants**

The context of the research is an important consideration for the IRB when reviewing research that involves other potentially vulnerable participants such as research involving persons who are homeless, members of particular minority groups, or the economically or educationally disadvantaged. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of participants and the IRB takes such considerations into account. Nevertheless, research involving these participants is socially important for understanding and eventually improving adverse health and general well-being in these populations.
In this chapter:

10.1 Equitable Selection
10.2 Vulnerable Subjects
10.3 Non-English Speaking Participants
10.4 Review of Recruitment Methods, Advertising Materials and Payment
10.5 Addressing Concerns of Research Participants
10.6 Participant Education and Outreach
10.7 Involvement of Community Members in Community Based Participatory Research

10.1 Equitable Selection

PIs are directed to enter detailed information on how participants will be identified and recruited in response to questions in the study application.

PIs are required to identify the target populations (including age range, gender, and ethnic background), the inclusion and exclusion criteria and whether payments will be made for participation. In addition, PIs are required to justify the inclusion of targeted persons (e.g., healthy participants, employees, students or participants with certain medical conditions). In determining if the selection and recruitment of participants is equitable, the IRB takes into account the purpose of the research, the setting in which the research will be conducted, whether prospective participants will be vulnerable to coercion or undue influence, the selection (inclusion/exclusion) criteria, participant recruitment and enrollment procedures, and the influence of payments to participants. The IRB also evaluates whether the study imposes fair and equitable burdens and benefits - such that one group of persons does not disproportionately receive the benefits compared to another group assuming only the risks.

IRB staff and members review this information and confirm the recruitment and selection strategies are fair, equitable, and not misleading. If recruitment strategies fail to meet these requirements, the protocol will not be approved as written and the PI will be asked to modify the recruitment plan accordingly, as a condition of approval.

10.2 Vulnerable Subjects

Investigators must provide a rationale for involvement of vulnerable subjects, such as children, prisoners, pregnant women, economically and educationally disadvantaged, and the decisionally impaired. The PI must substantiate his/her decision to involve a vulnerable population and further provide a rationale why a less vulnerable population would not serve the purpose of the research. When vulnerable populations will be targeted for enrollment, the IRB assesses the additional safeguards proposed by the PI to minimize the possible risks and the chance of harm to these populations. While pregnant women are considered vulnerable participants, women of reproductive age should not be arbitrarily excluded from participation in research. If women are to be excluded, such exclusion must be fully justified by the PI based on scientific rationale.

10.3 Non-English Speaking Participants

Non-English speaking participants should not be systematically excluded because of language barriers. The IRB encourages the inclusion of non-English speaking participants and permits such persons to be enrolled via a translated consent or the short form consent process consistent with 45 CFR 46.117(b)(2) and 21 CFR 50.27(b)(2).
10.4 Review of Recruitment Methods, Advertising Materials and Payment

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<td>II.3.C.1</td>
<td>The IRB has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate.</td>
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Recruitment tools (advertisements, etc.) are required to have IRB review and approval prior to implementation. When reviewing recruitment tools the IRB must review the final mode of its communication, including the final copy of printed advertisements and the final audio or video advertisements.

Only IRB approved advertisements, considered fair, honest and appropriate by the IRB, may be used in the conduct of participant recruitment. Recruitment materials should be included with your initial application. If the material is not ready at the time of the initial application, investigators must submit the material as an amendment to an already approved project. Requests for approval of recruitment materials following initial IRB review of the protocol should allow sufficient time for any necessary revisions prior to publication. Advertisements, press releases, etc., may qualify for expedited review.

When recruiting subjects from another institution with an IRB, investigators are required to gain IRB approval from that institution. In institutions without an IRB, investigators are required to obtain a letter of agreement on the facility’s letterhead indicating the research can be conducted at the site and will comply with the procedures approved by the UofL IRB.

A recruitment tool informs potential subjects of a research activity and provides them with an opportunity to contact the researcher. A recruitment tool may include, but is not limited to, post-cards, flyers, advertisements, press releases, brochures, and postings on the internet and social media.

Use the following guidelines when developing recruitment tools:
1. name and address of the clinical investigator and research facility (letterhead is acceptable),
2. the condition under study and/or the purpose of the research,
3. in summary form, the criteria that will be used to determine eligibility for the study,
4. a brief list of the benefits of study participation, (if any),
5. time or other commitments required,
6. the location of the research and the person or office to contact for further information.

The recruitment tool should not:
1. state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
2. include exculpatory language.
3. emphasize the payment or the amount to be paid, by such means as larger or bold type.
4. provide excessive monetary or other incentives that could be interpreted as inappropriate or coercive.
5. promise “free treatment” when the intent is only to say subjects will not be charged for taking part in the investigation.
When following FDA regulations and guidance the recruitment tool should not:

1. make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling.
2. use terms, such as “new treatment,” “new medication,” or “new drug,” without explaining that the test article is investigational.
3. make claims to the superiority, safety or effectiveness of the drug or device.
4. allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Advertisements
The IRB considers that advertisements begin the informed consent process and thus, consistent with the consent process, coercion and undue influence are prohibited during recruitment. If recruitment will be by advertisement, the mode of advertisement (flyers, radio, newspaper, or internet) and information contained in the advertisement must be approved by the IRB.

- *Audio and video tape:* The IRB may review and approve the wording prior to taping in order to preclude re-taping due to inappropriate wording. The IRB reviews the final version of the advertisement.
- *Printed advertisement:* The IRB reviews the final copy.

Telephone Screening
For protocols involving telephone screening of participants in response to an advertisement, the IRB generally requires investigators to review all the required elements of informed consent orally with prospective participants. However, investigators may request a waiver of documentation of consent limited to the screening portion (only) of the protocol if they demonstrate that the screening procedure meets regulatory criteria in 45 CFR 46.117(c)(2) or 21 CFR 56.109(c)(1).

Cold Calling
The IRB discourages cold-calling of potential research subjects. “Cold-calling” is the practice of investigators or research staff, unknown to the potential research participant, initiating contact with the potential participant based on their prior knowledge of private information. To avoid a cold-calling scenario, the research study should be introduced to the potential research participant by an individual who, by virtue of their position, would normally have access to the potential subject’s confidential information (e.g., the personal physician of the potential participant or a member of the clinic or practice staff) through a phone call or a mailed letter. If the potential research participant indicates an interest in study participation, they should be instructed to either (a) contact the investigators directly or (b) permit the individual who initiated this contact to share with the research team the person’s interest in study participation so that the researchers can subsequently contact the potential participant and provide more information about the study.

The individual who initially introduced the study to the potential participant should document this permission in their records. As per the HIPAA privacy regulations, a health care provider may not share individually identifiable health information with research investigators without the written HIPAA authorization of the patient or waiver of HIPAA authorization.

Payment
PIs must disclose any proposed payments to participants in the protocol application form, including the method, type and timing of the payments. Payments to research participants may not be of such an amount as to result in coercion or undue influence on the research participant’s decision to participate. If a study has multiple paid visits, payment should
be prorated throughout the duration of the study to provide partial payment to persons who withdraw before completing the study. See Paying Human Subjects Policy and Guide-030 Paying Human Subjects Guidance.

Payment Arrangement among Sponsors/Organizations, Investigators and Others
Finder’s fees and other financial incentives paid by a sponsor or by an investigator to others related to the recruitment of research subjects are prohibited. No one may receive any incentive for the purpose of encouraging individuals to participate in research. All payment by sponsors for research conducted under the auspices of the University of Louisville must be made directly to the University of Louisville Research Foundation, Inc. (ULRF) or the University of Louisville and will be managed by the Foundation or University. Payments should never go directly to investigators, key personnel or participants without first going through the ULRF or the University.

10.5 Addressing Participants Concerns

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<th>AAHRPP Std./Element</th>
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<tr>
<td>I.4.A</td>
<td>University of Louisville has and follows written policies and procedures that establish a safe, confidential, and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan.</td>
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<tr>
<td>III.1.G</td>
<td>Researchers and Research Staff have a process to address participants’ concerns, complaints, or requests for information.</td>
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Consent Form Requirements
The IRB requires that all consent forms include information on how to contact the investigator(s) conducting the research study. Participants are instructed to call the investigators and/or the HSPPO if they have any questions about the research, about their rights as a research participant, or if they believe they have suffered a research-related injury. Each consent form must also include telephone numbers for the IRB (a local number and a toll free number). The IRB contact information affords current or past research participants or their designated representatives a means to contact an informed individual who is independent of the research team. The IRB also serves as a conduit for receiving information from any party who is not satisfied with the manner in which a study is (or was) being conducted, or if any party has any concerns, complaints or general questions about research or the rights of research participants.

Consent form templates, available on the Human Subjects Protection Program website, include instructional text and verbatim language for the inclusion of the investigator’s contact information and IRB telephone numbers under the consent form heading “Contact Information.”

Recruitment Tools, Advertisements and Telephone Screening
The IRB requires investigator and IRB contact information be included in recruitment tools, advertisements and telephone scripts. This contact information provides prospective participants with channels of communication to the investigators and the IRB for questions, concerns, input, information or complaints.
Responding to Contacts from Participants or Others

Concerns of research participants are investigated by the HSPPO Research Compliance Auditors. All reports of concerns received either directly by the Research Compliance Auditors or forwarded to the HSPPO by the Institutional Compliance Office or the Research Integrity Program, are shared with the HSPPO Director(s). Research Compliance Auditors prepare a summary which indicates the concerns expressed by participants or others and the actions to be taken to resolve any issues or problems. Minor concerns are generally resolved by a phone call. However, more complex concerns are followed up by the HSPPO Director with the relevant IRB Chair and others in the Human Subjects Protection Program Office. Participants and others may reach the HSPPO at (502) 852-5188 or by emailing the Human Subjects Protections Program Office at hsppofc@louisville.edu.

Website

The Human Subjects Protection Program website includes participant outreach information addressing the general rights of research participants and provides links to various research resources. Additionally, the website has a toll free Compliance Hotline where current, prospective or past research participants or their designated representatives may discuss concerns and questions or offer input to an individual who is unaffiliated with the specific research protocol or plan. The Compliance Hotline is a 24 hour hot line answered by people who do not work at the University of Louisville. Participants may address their concerns anonymously by calling toll free at 1-877-852-1167.

Information concerning the ways to contact the HSPPO with questions are contained in the following webpage: https://louisville.edu/research/humansubjects/about/questions-complaints-or-concerns-for-the-irb

10.6 Participant Education and Outreach

The University of Louisville and the Human Subjects Protection Program employ several mechanisms for communication and education to increase public awareness and educate potential research participants.

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<td>I.4.B</td>
<td>University of Louisville conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement.</td>
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Participant education materials and outreach activities are reviewed annually by the HSPPO Director(s) and the Chairs and Vice Chairs of the IRBs. Suggested revisions are discussed with the Executive Vice President for Research and Innovation and the individual research deans or program directors.

HSPPO activities include, but are not limited to, attending community fairs, health fairs, and campus events. In addition, other University of Louisville departments participate in research events, community events, and health fairs.

On-line Resources and Human Subjects Educational Materials

The Human Subjects Protections Program website contains information for research participants. The tab for “Participants” contains the following:

General Information about becoming a research volunteer;  
Information about informed consent for research volunteers;  
Information about voluntary participation in research;  
Questions participants are urged to ask prior to enrolling in a research study;  
Information concerning the rights of a research participant which includes a toll free number for the University of Louisville; Information concerning an anonymous Hotline to assist participants in asking questions or expressing concerns about on-going research at the University of Louisville;
A link to Clinicaltrials.gov to assist participants in finding open clinical trials; 
Links to OHRP brochures: Becoming a Research Volunteer: It's Your Decision; 
Links to entities and organizations where research information can be obtained (e.g. National Cancer Institute, FDA, OHRP, Cancer.net and the American Cancer Society;)
A link to NIH Clinical Research Trials and You.

Contact information for inquiries about current research at University of Louisville and their affiliated research partners:
Norton Healthcare Office of Research Administration (NHORA): This website has information regarding all the research and clinical trials for all the Norton Hospitals and physician offices in the Louisville and Southern Indiana area.
Brown Cancer Center Clinical Trials (JGBCC): Multidisciplinary cancer clinics with a listing of all their clinical trials according to the type of cancer.
University of Louisville Hospital: Listing of departments and contact phone numbers to call
University of Louisville Clinical Trials Unit: Multidisciplinary listing of clinical trials.
Just 4 Kids: Information pertaining to common types of heart defects in children and research being performed at Norton Children’s Hospital.
Kosair Charities Pediatric Clinical Research Unit (KCPCRU).

Other University of Louisville Research Resources
Colleges and Schools at the University of Louisville provide web-based information on current research or outreach opportunities.

College of Arts and Sciences
College of Business
School of Dentistry
College of Education and Human Development
School of Interdisciplinary and Graduate Studies
Kent School of Social Work
Brandeis School of Law
School of Medicine
- FOAMed – Free Open Access Medical Education
- Department of Surgery http://www.louisvillesurgery.com/downloads/ClinicalTrials_Q_A.pdf
- Kentucky Spinal Cord Injury Research Center

School of Music
School of Nursing
School of Public Health and Information Sciences
- Center for Environmental Genomics and Integrative Biology
Speed School of Engineering
KBRIN – Kentucky Biomedical Research Infrastructure Network

10.7 Involvement of Community Members in Community Based Participatory Research

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<td>I.4.C</td>
<td>University of Louisville promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results.</td>
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Both institutional IRBs have community members who support the roles of local community participants in human subjects research. Community members are encouraged to participate in annual continuing education workshops (through PRIM&R and AAHRPP) addressing community research needs. Both the Biomedical and Social Behavioral Education IRBs include members with expertise in community based research. If necessary to review specific IRB proposals, internal University of Louisville consultants would be invited to participate in the discussion of such research proposals.
In this chapter:

11.0 Privacy and Confidentiality
- Introduction
- Definitions

11.1 Protecting the Privacy of Participants

11.2 Protecting the Confidentiality of Participant Information
- Confidentiality
- Limits
- Confidentiality Requirements for approval
- Certificates of Confidentiality (CoC)
- Continuing Confidentiality

11.3 HIPAA - Health Insurance Portability and Accountability Act Regulations
- HIPAA Authorizations
- HIPAA Waivers or Alterations of Authorizations
- HIPAA Coordination
- HIPAA Data Sequestration, Determinations and Processes

11.4 Confidentiality Breach - Unauthorized Release of Information
- HIPAA Violations

11.0 Privacy and Confidentiality

Introduction: Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information of all human subjects participating in research, except as required by law or released with the written permission of the participant. Those who conduct research under the direction of the University of Louisville must develop a plan for each protocol submitted to protect the privacy and confidentiality of subjects. Participants have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and to expect that the confidentiality of private information will be preserved. The more sensitive the research, the greater the care is required in obtaining, handling, and storing the data. The conditions for maintaining confidentiality of the subjects and the research records are required for the life of the data. The University of Louisville IRBs serve as the Privacy Board for the institution, and in order to approve research, the IRB must be satisfied that, “when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data” [45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7)].

Definitions
Privacy means, in the context of a research protocol, respecting an individual’s right to be free from unauthorized or unreasonable intrusion, including control over the extent, timing and circumstances of obtaining personal information from or about them. For example, individuals may not want to be seen entering a place that might stigmatize them, such as a clearly-identified pregnancy counseling center. Privacy refers to persons and their interest in controlling the access of others to themselves.

Confidentiality means respecting a potential or current participant’s right to be free from unauthorized release of information that the individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. In the context of a research protocol, “confidentiality” refers to the understanding between the participant and investigator (e.g., as set forth in the consent and authorization documents) as to how participant information will be handled, managed, and disseminated (e.g., shared with others) as part of the research.
Covered Entity can be:
- A health plan,
- A health care clearinghouse,
- A healthcare provider who transmits any health information in electronic form in connection with a transaction covered by the HIPAA regulations.

Private information means individually identifiable information:
- About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place,
- Which has been provided for specific purposes by an individual and which the individual can reasonable expect will not be made public (for example, and medical record).

Sensitive Information is private information relating, but not limited to:
- Sexual attitudes, preferences or practices,
- Use or treatment for alcohol, drugs or other addictive products,
- Illegal conduct,
- Information which if released could reasonably cause stigmatization or discrimination, or result in damage to areas such as financial well-being, employability, or reputation,
- Certain health information, including psychological or mental health.

Protected Health Information (PHI) is individually identifiable health information that is:
- Transmitted by electronic media;
- Maintained in electronic media; or
- Transmitted or maintained in any other form or medium.

Protected health information excludes individually identifiable health information:
- In education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g;
- In records described at 20 U.S.C. 1232g(a)(4)(B)(iv); and
- In employment records held by a covered entity in its role as employer; and
- Regarding a person who has been deceased for more than 50 years.

Hybrid Covered Entity is an entity in which some, but not all, portions of the institution must comply with HIPAA regulations. The University of Louisville is a hybrid covered entity as defined by the HIPAA Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164)

11.1 Protecting the Privacy of Participants

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<td>II.3.D</td>
<td>The University of Louisville IRB has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.</td>
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Researchers have a duty to respect the privacy of prospective subjects. That is, the researcher allows the research participant to determine when, how, and to what extent information about him or her is communicated to others. Researchers usually protect an individual’s right to privacy by obtaining free and informed consent before collecting personal information about him or her. The act of contacting potential subjects to seek free and informed consent to
access private information may constitute a breach of privacy if the investigator does not have access to such individuals in the course of his or her usual professional activities.

The PI must describe provisions he or she will take in order to protect the privacy of the research subjects during each phase of the study. The IRB may ask for additional details regarding plans to protect participant privacy. If the planned provisions are not adequate, the IRB may not approve the study.

The PI must ensure conditions in which research procedures are performed, or research information is collected, occur in a manner which prevents their sensitive data inadvertently being viewed or overheard. In addition, the PI must also ensure the data collected is the minimum necessary to perform the research.

11.2 Protecting the Confidentiality of Participant Information

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<tr>
<td>II.3.E</td>
<td>The IRB has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research.</td>
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<tr>
<td>III.2.C</td>
<td>Researchers and research staff follow the requirements of the research protocol or plan and adhere to University of Louisville policies and procedures and to the requirements or determinations of the IRB.</td>
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Researchers have a duty to respect the confidentiality of personal information collected during research. Research projects vary substantially in the sensitivity of the information involved, the possibility of identifying particular individuals, and the magnitude and probability of harms that may result from identification of research subjects. Breaches in confidentiality may also have a negative impact on family and friends or the group to which the research participant belongs.

The researcher has a duty to protect research subjects from harm through unauthorized release of identifiable personal information.

Confidentiality

When information collected through research is disseminated, the information is de-identified, unless identification has been agreed to or requested by the research participant. Often, data are presented in aggregate form which also reduces the potential to link specific responses to individuals.

Limits

In some instances, research results may be disclosed to the government, government agencies, the research sponsor, the IRB or its designees, a regulatory agency, or those individuals who may be responsible for financial oversight at the institution where the research is conducted. State statutes may require reporting of child abuse, sexually transmitted diseases, intent to murder, or suicidal thoughts. Additionally, in the cases of well-known individuals, those with very rare conditions, or research that requires presentation of photographs or videotapes, it may be impossible to present the data without identifying the research participant. Research participant need to be aware of any limitations to anonymity in these situations.

In other cases, research records may be liable to subpoena in judicial and administrative proceedings, and data may be vulnerable to search warrants. Because researchers have a duty to protect the confidentiality undertaken in the free and informed process to the extent possible within the law, it is legitimate for the researcher and the institution to argue the
issue in court. In fact, this may be the only legal option open to a researcher to protect the confidentiality of research data.

Confidentiality Requirements for approval
In order to approve the research, the IRB will determine if there are adequate provisions in the research which protect the confidentiality of participants which include the following:

- Limiting the recording of personal information to that which is absolutely essential to the research;
- Storing personally identifiable data securely and limit access to the principal investigator or authorized research assistants/associates;
- Code data as early in the research as possible, and plan for the ultimate disposition of the code linking the data to individual subjects;
- Apply for Federal Certificates of Confidentiality (see below) for all situations for which certificates are reasonable and available;
- Do not disclose personally identifiable information to anyone other than the research team without the written consent and authorization of the subjects or their legally authorized representatives. (Exceptions may be made in case of an emergency or as required by regulatory agencies).

Certificates of Confidentiality (CoC)
Data collection about sensitive issues (such as illegal behavior, alcohol or drug use, or sexual practices or preferences) requires the protection of confidentiality beyond preventing accidental disclosures. Under Federal law, researchers can obtain an advance grant of confidentiality, known as a Certificate of Confidentiality that will provide protection against compulsory disclosure, such as subpoena, for research data.

The investigator should delineate in the IRB application any conditions under which confidential information might be disclosed and create an informed consent document that accurately reflects those conditions, including any voluntary disclosure by the researcher. The IRB is required to determine whether the risks to subjects are minimized, informed consent is appropriate, and privacy and confidentiality protections are adequate.

The CoCs were developed to encourage participation in research by granting certain protections to a participant divulging possible compromising information. The COCs, however, do not exempt investigators from performing ethical research nor do they allow investigators to abdicate the responsibility to act in the public good. The IRB expects investigators to act in an ethical manner and therefore comply with state law by informing subjects in the consent form of the obligation of a researcher to obey state law. Therefore, investigators are required to include a statement in the consent form that alerts potential subjects of the legal and ethical mandate compelling researchers to report known or suspected child/elder abuse/neglect. Investigators should contact the IRB staff for more information on obtaining a CoC. Additional information may also be obtained from the NIH Certificate of Confidentiality.

Continuing Confidentiality
Once the active research has been completed, investigators should consider taking additional precautions in maintaining confidentiality that were not feasible while the research was active, including de-identifying data, archiving data in a University approved secure long-term storage service, and limiting access to the data. The University policy states that records should be kept a minimum of five (5) years after submission or publication of the final project report for which the data were collected, whichever is longer. If retention requirements specified in a funding agency's regulations are longer, the agency requirements will apply. In addition, at the discretion of the university, some data may be retained longer for use in subsequent projects under a separate IRB submission Therefore, study record retention above the minimum time requirement and final disposition is at the discretion of the principal investigator.
11.3 HIPAA - Health Insurance Portability and Accountability Act Regulations

In addition to the privacy and confidentiality requirements under the Common Rule and FDA regulations, The University of Louisville IRB oversees compliance with HIPAA privacy regulations. The Health Insurance Portability and Accountability act of 1996 (HIPAA) aims to protect health insurance coverage for workers and their families during a job change (portability) and to protect health data integrity, confidentiality, and availability (accountability). HIPAA also requires standards for the secure storage and transmission of health data under the Privacy Rule of 2003. If research conducted within a covered entity portion of the University of Louisville will involve protected health information (PHI), the research must be conducted in accordance with the HIPAA Privacy Rule. The University of Louisville HIPAA privacy policy and the guidelines below will determine a researcher’s need for a valid HIPAA Authorization.

HIPAA Authorization

A HIPAA Authorization is an individual’s signed permission to allow the covered entity to use the individual’s protected health information (PHI) as described in the Authorization. This is different from the research informed consent form (ICF) in that the Authorization allows the use of the PHI, whereas the ICF is the individual’s agreement to participate in the research.

The Privacy Rule specifies core elements and required statements that must be included in an Authorization. An Authorization is not valid unless it contains all of the required elements and statements. An Authorization form may include optional elements so long as they are not inconsistent with the required elements and statements and are not otherwise contrary to the Authorization requirements of the Privacy Rule. The University of Louisville Biomedical IRB includes all the requirements of the authorization in the combined biomedical informed consent and research authorization template form. The Social, Behavioral, and Educational (SBE) IRB also includes all required language in the SBE combined informed consent and research authorization form.

Authorization Core Elements (45 CFR §164.508(c)(1))

- Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner).
- The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure.
- The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure.
- Description of each purpose of the requested use or disclosure. Researchers should note that this element must be research study specific, not for future unspecified research.
- Authorization expiration date or event that relates to the individual or to the purpose of the use or disclosure (the terms "end of the research study" or "none" may be used for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the Authorization is signed by an individual’s personal representative, a description of the representative’s authority to act for the individual.

Authorization Required Statements (see Privacy Rule, 45 CFR § 164.508(c)(2))

- The individual’s right to revoke his/her Authorization in writing and either (1) the exceptions to the right to revoke and a description of how the individual may revoke Authorization or (2) reference to the corresponding section(s) of the covered entity’s Notice of Privacy Practices.
- Notice of the covered entity’s ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the Authorization, including research-related treatment, and, if applicable, consequences of refusing to sign the Authorization.
• The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information.

Waivers or Alterations of the Authorization Requirements
The Privacy Rule contains criteria for a waiver or alteration of the Authorization requirement under certain conditions in which it may not be practical to obtain written authorization from all research participants. Either an IRB or a Privacy Board must determine if these criteria are met. The University of Louisville IRB serves as the institution’s Privacy Board.

Criteria for the Authorization waiver or alteration (45 CFR 164.512(i)(2)(ii))
1. An adequate plan to destroy identifiers at the earliest opportunity absent a health or research justification or legal requirement to retain them, and
   a. An adequate plan to protect health information identifiers from improper use or disclosure,
   b. An adequate plan to destroy identifiers at the earliest opportunity absent a health or research justification or legal requirement to retain them, and
   c. Adequate written assurances that the PHI will not be used or disclosed to a third party except as required by law, for authorized oversight of the research study, or for other research uses and disclosures permitted by the Privacy Rule;
2. Research could not practicably be conducted without the waiver or alteration; and
3. Research could not practicably be conducted without access to and use of PHI.

HIPAA Coordination
The University of Louisville has a Privacy Office responsible for the development and the implementation of HIPAA policies and procedures and overseeing compliance with HIPAA. The University of Louisville IRBs serve as the Privacy Board(s) for the institution, and in order to approve research, the IRB must be satisfied that, “when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data” [45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7)].

HIPAA Data Sequestration, Determinations and Processes
When a HIPAA authorization for PHI use human subjects research is not obtained, University of Louisville Policy, “Action When a Required HIPAA Authorization in Human Subjects Research is not Obtained,” # HPR-2.01 may apply.

When compliance monitoring or a self-report from an investigator reveals that HIPAA authorization has not been properly obtained, the IRB/Privacy Board may determine that the information/research record/data/samples may need to be sequestered from the active study research records. If such determination is made, the PI will lose access to the collected information/research record/data/samples and sequestration may occur. If the IRB/Privacy Board determines loss of research data, and the following steps should be taken.

The IRB/Privacy Board will convey the determination to the investigator through correspondence from the electronic submission system. The investigator or key study personnel will place the information/research record/data in a separate envelope which will be sealed with tamper resistant tape. The envelope will clearly be labeled with the assigned participant ID number and identified as Sequestered Data. If your study includes specimens, you will be required to notify the IRB/Privacy Board of how they will be destroyed. If your study involves electronic data sent outside of the University of Louisville, you will be required to notify the sponsor of the IRB/Privacy Boards determination. When the study is completed, the sealed and labeled envelope will be put in storage with the other study documents.

The investigator will promptly submit a letter (sequestering plan) to the IRB/Privacy Board (and sponsor, if applicable) that will include the following information:
• Identification of the PI for the research study;
• IRB# and Study Title;
• Assigned participant ID number;
• Date the Sequestration Took Place;
• Date the sponsor (if applicable) was notified;
• A description of the process that was followed that discusses how the research record has been sequestered (e.g. electronic data being stored on a thumb drive/CD/Spreadsheet in a sealed envelope);
• Where the sequestered information will be kept;
• What security measures will be taken to keep the sequestered information secure.

The letter must include the investigator’s printed name, signature and date of sequestration.

If applicable, the study sponsor must be notified of the IRB/Privacy Boards determination along with a copy of the letter. When the sponsor responds, a copy of the response should be kept with the sequestered information/research record/data/samples.

In certain cases, the IRB/Privacy Board may determine that the investigator can obtain retrospective HIPAA Authorization from subjects when a valid HIPAA Authorization was not initially obtained. This would allow the investigator to use the data/specimens. Those determinations and instructions for the investigator will be relayed to the investigator through the ESS.

11.4 Confidentiality Breach - Unauthorized Release of Information
The IRB requires that investigators report any possible or actual unauthorized release of information. It is important to immediately contact the IRB if a breach is suspected related to a research study. There is a limited time frame for responding to breach incidents. The IRB/HSPPO will work with the UofL Privacy Officer to investigate the potential breach. The UofL Privacy Office can be reached at 502-852-3803 or via email at privacy@louisville.edu. The IRB treats such a problem as non-compliance, and follows the process set forth in Chapter 3, in order to review and respond to the situation.

HIPAA Violations
If a potential violation involves PHI, the University of Louisville also treats it as a potential violation of HIPAA policies and the HIPAA privacy and security regulations. The IRB will communicate and coordinate its review and response with that required under the applicable HIPAA policies in collaboration with the UofL Privacy Office.
In this chapter:

12.1 Requirements for Informed Consent
   12.1.1 Elements of Informed Consent
   12.1.2 Additional Consent Requirements
   12.1.3 Re-consenting study participants

12.2 Consent Procedures for Vulnerable and Other Special Populations Including Consent by a Legally Authorized Representative
   12.2.1 Adults with Impaired Decision-Making Capacity – “cognitively impaired”
   12.2.2 Pregnant Women, Fetuses and Neonates
   12.2.3 Children and Consenting Minors
   12.2.4 Illiterate Participants
   12.2.5 Non-English Speaking Participants
   12.2.6 Prisoners

12.3 IRB Review of the Consent Process, including Consent Documents

12.4 Documentation of Informed Consent – Signature Requirements

12.5 Waiver or Alteration of Informed Consent Requirements
   12.5.1 Waiver or Alteration of the Consent Process
   12.5.2 Waiver of Documentation of Consent – (“waiver of signature”)

12.6 Exceptions to Informed Consent in Planned Emergency Research

The HSPPO has developed Informed Consent Document templates that provide investigators with guidance in developing this form. The template prompts the investigator to add details about the study, levels of risk, and other issues as indicated. The format and language in the template have been approved by the IRB. For research involving children, an assent template is also provided.

Informed consent is a continuing process whereby the investigator and research participant have an on-going dialogue about all aspects of a research study that might inform a participant’s decision to take part in the study and their decision to continue their involvement as a participant. The purpose of the consent process is to assure knowledgeable decision-making and voluntary participation.

This process generally includes:
   1. Bringing the research study to the notice of potential participants;
   2. Presentation and explanation of the study activities to the participant or their legally authorized representative (LAR);
   3. Documentation of the informed consent via a signed and dated written consent document;
   4. Ongoing discussions between the investigator and the participant regarding continued participation in the study.

The consent process must:
   1. Provide sufficient opportunity for the participant, or the participant’s legally authorized representative (LAR), to consider whether to participate;

AAHRPP Std./Element | Description
--- | ---
II.3.F | The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process.
2. Minimize the possibility of coercion or undue influence;
3. Be free of exculpatory language; and
4. Be in language understandable to the participant or their representative.

The IRB also requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants. The IRB recommends the consent form includes lay language comprehensible to those with an 8th grade reading level.

Refer also to Chapter 14.3 for more information on the consent document and Principal Investigator responsibilities in the informed consent process.

### 12.1 Requirements for Informed Consent

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<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
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<td>II.3.F</td>
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</table>

Unless waived by the IRB, legally effective informed consent must be obtained from participants or their LARs as a condition for protocol approval. All relevant requirements in OHRP in 45 CFR 46.111 and 46.116, and in the FDA regulations in 21 CFR 50.20, 50.25, 50.27 and 56.111 that are applicable to the consent process and the consent document must be satisfied.

### IRB Evaluation of Compliance with Informed Consent Requirements

The evaluation of compliance is achieved by:

1. IRB review of the informed consent process information and document(s) provided by the PI.
2. Consent form reviews at the time of continuation comparing signed and dated consent forms with the IRB approved versions.
3. Observation of the consent process, performed either as a periodic review function of the HSPPO Compliance Auditors, or as requested by the convened IRB. See Chapter 3.7.

### 12.1.1. Elements of Informed Consent

Legally effective informed consent includes the basic required elements and the additional elements specified in 45 CFR 46.116 and 21 CFR 50.25. Informed consent requirements for vulnerable and other special populations are addressed in Chapter 12.2.

Guide 019 Informed Consent-Required Criteria
12.1.2. Additional Consent Requirements

<table>
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<tr>
<th>AAHRPP Std./Element</th>
<th>Description</th>
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<tbody>
<tr>
<td>I.1.G</td>
<td>The University of Louisville has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.</td>
</tr>
</tbody>
</table>

University legal counsel can provide assistance to investigators and the IRB in resolving any conflicts among applicable laws.

1. HIPAA
2. HIV Testing or Research on AIDS
3. Genetic Testing
4. Data and Tissue Repositories
5. International research
6. Other Federal Agencies

1. Health Insurance Portability and Accountability Act (HIPAA)
If the study application involves protected health information (PHI) as defined by HIPAA, then HIPAA authorization may be included in the consent process. HIPAA authorization is an authorization to use or disclose PHI, and must be executed by signature, date, and relationship of LAR (if applicable). Consent templates incorporating HIPAA authorization language are provided on the Human Subjects Protection Program Office website.

2. HIV Testing; Research on AIDS

Public Health System (PHS) Funded Research
If the protocol is supported by funding from the Department of Health and Human Services and includes testing for HIV, the consent documentation must state that identifiable participants will be informed of their results and provided with the opportunity for counseling. The IRB requires this except in cases where it is not required by PHS policy.

HIV testing and disclosure:
Individually identifiable research records of AIDS-related research and/or HIV testing are confidential and may only be disclosed with the prior written consent of the participant and may be subject to Kentucky Legislature 214.181.

Additionally, the following language must be inserted into the informed consent document:
“This study involves testing for ______. If you have a positive test, we are required by Kentucky law to report the results to the local Health Department nearest where you live or to the Kentucky Department for Public Health.”

3. Genetic Testing
If a protocol includes genetic testing, the IRB requires that the informed consent information disclose the risks specific to this type of testing. Genetic testing includes research that studies the characteristics, genes, and gene versions that are transmitted by parents to offspring. This may include many types of information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual or family medical histories, reactions to medication, and responses to treatment. The IRB includes detailed provisions and issues in its informed consent template that should be considered by the Principal Investigator when the research includes genetic testing. The template is also used by IRB staff and members as a guide for their review of such a consent document.
As required by federal regulations, any study that involves genetic information must include the following statement as written within the informed consent:

“Research Involving Genetic Information
A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research or use your genetic information when making decisions regarding your eligibility or premiums.
2. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Employers with 15 or more employees, health insurance companies, and group health plans must follow this law. This new law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.”

4. Data and Tissue Repositories
The NIH guidance on Data and Tissue Repositories is of interest to investigators who collect data or tissues of participants for repositories, and IRB staff and members who review such protocols.

Researchers who wish to develop or maintain a repository for current or future research, must submit an application for IRB review. IRB approval, or determination of exemption, is required before initiating the repository. Operators of the repository must implement physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens. These procedures must be reviewed by the IRB and must be sufficient to ensure the protection of subjects’ privacy and the confidentiality of subjects' information. When such repositories collect individually identifiable health information of participants, the HIPAA privacy regulations in 45 CFR Parts 160 and 164 must also be satisfied. This may require either a written HIPAA authorization from the participants or a waiver of authorization by the IRB. These requirements are discussed in Chapter 11.

Researchers who wish to use data and/or specimen from a repository should consult with the IRB. IRB oversight is required for each research protocol that uses identifiable or re-identifiable information contained in the database. Each research protocol requires its own separate submission to the IRB and may not proceed until IRB approval is obtained. The HIPAA Privacy Rule also requires a separate HIPAA Research Authorization for each use or disclosure from the data repository for a specific research activity.

Separate IRB review may not be required if the use is considered “Not Human Subjects Research” or NHSR. NHSR activity involves data/specimens in which the investigators cannot readily ascertain the identities of the data/specimens. IRB oversight of NHSR activity is not required, however, the IRB encourages investigators to submit the Non-Human Subjects Research determination form in iRIS to receive an official determination from the IRB. For additional details see Guide 008- Research with Databases, Registries, and Specimen Repositories
5. International Research

When conducting research in certain communities or social contexts, whether in the U.S. or abroad, it may be inappropriate to document consent by using the standard written and signed consent document. Other consent procedures may be more culturally or socially sensitive and may afford better protection to participants.

Investigators may ask the IRB to consider a waiver or alteration of some of the mandatory elements of consent [45 CFR 46.116(d)], or a waiver of documentation of consent [45 CFR 46.117(c); 21 CFR 56.109(c)]. See Chapter 12.5.

6. Requirements - Other Federal Agencies

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, Department of Justice): see Guide-014 - Other Federal Agencies - Additional Requirements

Consult Legal Counsel If Necessary: PIs should contact the legal advisor to the IRBs in the Office of University Counsel to assist in determining who under local law may serve as a legally authorized representative, if children or adults who are unable to consent may be enrolled as participants.

12.1.3 Re-consenting Study Participants

Consenting is an ongoing process. When changes to the informed consent are made, it may be necessary to re-consent subjects. All applicable criteria below would trigger re-consenting a participant:

1. The investigator of the study changes.
2. The contact information in the Informed Consent for the participant to reach a member of the study team changes.
3. Any change to the informed consent that would affect the subject’s willingness to continue participation (e.g. changes to risks, procedures, new findings, etc...).
4. Research related injury payment changes.
5. Participant previously signed an assent and turns 18 years old while participating in the study. They must be re-consented to the most current informed consent and research authorization (if applicable).
6. Compensation to the participant is changed.
7. A participant who regains the cognitive ability to consent as determined by the PI, must be re-consented using standard consenting procedures.
8. In the event a participant has been initially consented by a LAR, and a LAR of higher priority subsequently notifies the investigator of that relationship to the participant, the investigator must defer to the higher priority LAR’s decision regarding whether the participant will continue to participate or to withdraw from the study.
9. Investigators shall describe to potential LARs the nature of ongoing decisions during the study regarding the subject’s participation, decision to participate in certain procedures, changes to the study, etc., in order to ensure that the LAR will be willing to undertake these ongoing responsibilities.
10. In the event that the LAR dies, the participant must be re-consented prior to any event that would require re-consenting.

Additional criteria not mentioned above may also require re-consent. How participants will be notified of the changes above, will depend on the nature of the study and where subjects fall within the protocol schedule of events. The IRB will notify the researcher on the approval letter if re-consenting is necessary. If no changes are made to the consent at time of continuing review, active participants do not need to be re-consented.
12.2 Consent Procedures for Vulnerable and Other Special Populations Including Consent by a Legally Authorized Representative

“Surrogate” and “legally authorized representative” have the same meaning when used in this Chapter 12 and the HSPP.

<table>
<thead>
<tr>
<th>AAHRPP Std./Element</th>
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<tbody>
<tr>
<td>II.4.A</td>
<td>The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.</td>
</tr>
<tr>
<td>II.4.B</td>
<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
</tr>
</tbody>
</table>

Determining the decision-making capacity of the participant

Whenever possible, investigators will attempt to obtain informed consent directly from the participant.

The application reviewed by the IRB must detail a protocol-specific plan for the assessment of the decision-making capacity of the participant that will be conducted by the investigator for any participant who may qualify for LAR consent. While there are no standardized measures for determining capacity to consent, subjects may be assessed on their ability to understand and to express a reasoned choice concerning the:

1. Nature of the research and the information relevant to his/her participation;
2. Consequences of participation for the subject’s own situation, especially concerning the subject’s health condition; and
3. Consequences of the alternatives to participation.

The capacity to understand all of these concepts may not be necessary in order to consent to participate in a particular research protocol -- greater capacity is required for higher-risk protocols. This standard should be used for determining the capacity of the LAR as well, if necessary.

In protocols in which a LAR’s consent has been approved by the IRB, assessment of the decision-making capacity of the LAR should be implemented only when the investigator has reason to believe that the LAR’s decision-making capacity may be impaired.

If the investigator determines that the participant lacks decision-making capacity, the investigator shall inform the participant of the investigator’s intent to seek LAR consent and shall document this discussion in the research file. If the participant is unconscious due to trauma or due to medication administered to treat that trauma, the investigator shall document that condition in the research file and the above described required discussion regarding intent to seek LAR consent shall be waived. If the participant expresses resistance or dissent to participation or to the use of LAR consent, the participant shall be excluded from the research study.

LAR consent for participation in a research study should be employed only to the extent that it is consistent with the intent of 45 CFR 46, 45 CFR 46 and 21 CFR 50 and all other federal and state laws and regulations pertaining to protecting human subjects participating in research.
IRB Review Criteria for use of LAR

While no specific set of criteria can encompass all conceivable situations in which the use of LAR consent complies with the intent of 45 CFR 46 and 21 CFR 50, the following criteria should be viewed as fundamental guidelines to be used by the UofL IRBs when determining whether to permit the use of LAR consent for participation in a research study.

1. LAR consent should be considered only in research studies relating to the cognitive impairment, lack of capacity, serious or life-threatening diseases and conditions of research participant, or as determined by the IRB.
2. LAR consent is a protocol-specific request of the investigator, and must be reviewed and approved accordingly by the IRB.
3. LAR consent is requested through the application process for new research studies or through the modification process for an existing protocol.
4. The IRB may consider whether the frequency of a specific protocol’s review cycle should be reasonably modified when LAR consent is implemented.

The IRB may consider additional safeguards to protect participants, such as:

- Requiring the involvement of participant advocates,
- Requiring independent monitoring,
- Requiring waiting periods,
- Appointing a monitor to supervise the informed consent process.

Such decisions may be based on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation.

Determination of who may act as a LAR

In a non-emergency room environment, LAR consent may be obtained from any of the following potential LARs who have reasonable knowledge of the participant, in the following order of priority:

1. The judicially-appointed guardian of the person, if the guardian has been appointed and if medical decisions are within the scope of the guardianship;
2. The attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for health care decisions;
3. The spouse of the person;
4. If the person is incompetent, an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation;
5. The parent(s) of the person;
6. The nearest living relative of the person, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives.

In non-emergency room research settings, no consent by LAR may be used if there is a disagreement between two members of the same category above (e.g. two cousins disagree and no one is available from categories 1-5, participation is not possible.

In non-emergency room research settings only, the investigator is responsible for ensuring that the LAR:
1. Has reasonable knowledge of the participant;
2. Is familiar with the subject’s degree of impairment;
3. Is willing to serve as the legally authorized representative;
4. Understands the risks, potential benefits, procedures and available alternatives to research participation;
5. Makes decisions based on the subject’s known preferences, and where the subject’s preferences are unknown, makes decisions based upon the LAR’s judgment of what the subject’s preferences would be.

In an emergency room setting, the order of priority does not apply. LAR consent may be obtained from a LAR decision maker who is any of the following:

1. The judicially-appointed guardian of the person, if the guardian has been appointed and (for biomedical research) if medical decisions are within the scope of the guardianship;
2. The attorney-in-fact named in a durable power of attorney, if the durable power of attorney (for biomedical research) specifically includes authority for health care decisions;
3. The parent or spouse of the person;
4. If the person is incompetent, an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation;
5. The nearest living relative of the person, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives.

In emergency room research settings, no LAR consent may be utilized if there is a disagreement whether to consent among any available LARs.

In both a non-emergency room and an emergency-room setting:

1. LARs are prohibited from receiving any financial compensation for providing consent. This does not prohibit the LAR from being reimbursed for expenses the LAR may incur related to the LAR’s participation in the research.
2. In protocols in which a LAR’s consent has been approved by the IRB, assessment of the decision-making capacity of the LAR should be implemented when the investigator has reason to believe that the LAR’s decision-making capacity may be impaired.

12.2.1 Adults with Impaired Decision-Making Capacity - “Cognitively Impaired”

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</tr>
<tr>
<td>II.4.B</td>
<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
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</table>

Special consideration is given to protecting the welfare of vulnerable participants, such as children, prisoners, pregnant women, fetuses, and mentally disabled persons, handicapped persons, or economically or educationally disadvantaged persons (45 CFR 46.111(b) and 21 CFR 56.111(b)). There are specific regulatory provisions for research involving pregnant women, fetuses, and neonates (45 CFR 46, Subpart B), prisoners (45 CFR 46, Subpart C), and children (45 CFR 46, Subpart D and 21 CFR 50 Subpart D). Special considerations for providing legally effective informed consent for these participants are discussed in the following sections.
Also see Chapter 9.3 concerning determination of the risks to vulnerable populations as defined in applicable federal regulations, and specifically for determining the required risk categories in protocols involving children and prisoners.

Cognitively Impaired Participants
The IRB will determine that adequate provisions are made for seeking the assent of the cognitively impaired person, as well as the informed consent of the person’s LAR when in the judgment of the IRB the person is capable of providing assent. In determining whether the cognitively impaired person is capable of assenting, the IRB will take into account the age, maturity, and psychological state of the person involved. This judgment may be made for all cognitively impaired persons to be involved in research under a particular protocol, or for each individual, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the cognitively impaired persons is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the individuals and is available only in the context of the research, the assent of the persons is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

Assessment and Determination of Incompetence
If it is believed that the prospective participant is not competent to consent for him or herself, competency must be determined by a physician (generally an investigator on the protocol). A determination of incompetence shall be made after an appropriate medical evaluation that concludes there is little or no likelihood that the participant will regain competence in a reasonable period of time, or as established by legal determination. This definition of incompetence is not limited to the legal definition but also may be a clinical judgment that a person lacks the capacity to understand the circumstances of participating in research and to make an autonomous decision to take part.

Competency should be evaluated on an individual basis to avoid incorrect assumptions as to an individual’s ability to make decisions. Criteria for determining competence might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated.

Some approaches to this assessment include:

- A post-consent quiz documenting the participants’ knowledge of critical elements in the informed consent document - i.e., nature of the illness being studied, voluntary nature of participation, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality, and whom to call with any questions.
- The study investigators may ask a physician/psychologist outside the research team to evaluate the potential participant’s decisional capacity.

Protocols submitted to the IRB should describe how capacity to consent will be determined, by whom it will be done, and what procedures will be in place to assure that legally effective informed consent is provided for all individuals found to lack decision-making capacity.
12.2.2. Pregnant Women, Fetuses and Neonates

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<tbody>
<tr>
<td>II.4.B</td>
<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
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</table>

In accordance with OHRP, the IRB requires that additional protections be provided to pregnant women, fetuses and neonates involved in research. General considerations related to research involving pregnant women, fetuses and neonates are set out in Chapter 9. The special informed consent requirements are specified in 45 CFR 46, Subpart B (OHRP).

**Pregnant Children**

If the pregnant person is under the age of 18 and is not emancipated, the IRB generally requires, consistent with OHRP, that parental permission and child assent be obtained. If the research is therapeutic, and the PI believes that the child’s participation in the research falls into one of the categories under Kentucky law where an un-emancipated minor is permitted to consent to her own medical care, the PI should confirm this with IRB staff or the IRB legal advisor in the Office of Legal Counsel.

**Nonviable Neonates**

Consent may not be obtained from a legally authorized representative of either or both of the parents of a nonviable neonate. The IRB will not permit elements of the informed consent process to be altered or waived in research involving nonviable neonates, even if the general requirements for waiver are satisfied. When it has been determined that the neonate is viable, the neonate is considered a child and the consent requirements laid out below apply. See Guide 003-Research Involving: Pregnant Women, Fetuses, Neonates

12.2.3. Children and Consenting Minors

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<tr>
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</table>

The IRB imposes additional protections on research involving children, in accordance with 45 CFR 46, Subpart D and 21 CFR 50, Subpart D.

Children in Kentucky under age 18 (unless emancipated) must have consent given by a LAR. The LAR may be determined by the following:

1. The judicially-appointed guardian of the child, if the guardian has been appointed and if medical decisions are within the scope of the guardianship;
2. The attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for health care decisions;
3. The parent or parents of the child;
4. An adult sibling of the child, or if the child has more than one (1) sibling, the majority of the adult siblings who are reasonably available for consultation;
3. The nearest living relative of the child, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives

Eligibility for Emancipation
Although there’s no law specifying an emancipation procedure in Kentucky, it’s still possible to become emancipated before 18. This can happen in any of the following ways:

- **Marriage**: A child can marry before 18 and be considered a legal adult. This requires parental consent or a court order granting the marriage license.
- **Self-Support**: Moving out of a parent’s home and becoming self-supporting will by implication emancipate the child, if the parent doesn’t try to get the child back to the home
- **Court Order**: A minor can petition the court for emancipation and, possibly, be granted it by court order.

Assent
When, in the judgment of the IRB, the children are capable of providing assent the IRB may determine that assent is required, that adequate provisions are made for soliciting the assent of the children, and whether and how assent must be documented. Generally, children aged 7 and above may be asked to give their assent to participation. The IRB has developed assent templates for PI use when developing these documents.

The assent form does not replace a thoughtful discussion with the child regarding participation in the research. Investigators should remember that the assent process should take into account, in oral and written communication, the child’s experience and level of understanding. Ultimately, the assent process should illustrate respect for the child and convey the essential information the child requires, in a manner the child can understand, in order to make a decision about participating in the research.

Parental Permission
Parents or legal guardians grant “permission” for children to participate in research. The “permission” form is in essence a consent document and should follow all applicable requirements for informed consent as outlined in this guide. This document should be written to the parent(s) who will give permission for the child.

Whenever possible, the permission of both parents should be obtained; however, current Federal regulations do not require permission from both parents in all research situations. In general, the risk to the child and the prospect of direct benefit for the child as a research participant determine whether single parent/guardian permission may be permitted. If the research involves no greater than minimal risk, permission of one parent is sufficient. If the research involves greater than minimal risk, consent of both parents must be obtained, unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Investigators must have signed permission from parents before contacting children for participation in research.
Parental Permission for Participation

<table>
<thead>
<tr>
<th>§46.404</th>
<th>Minimal Risk</th>
<th>One or both parents’ permission, as determined by the IRB</th>
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<tbody>
<tr>
<td>§46.405</td>
<td>Greater than minimal risk with prospect of direct benefit</td>
<td>One or both parents’ permission, as determined by the IRB</td>
</tr>
<tr>
<td>§46.406</td>
<td>Greater than minimal risk, without prospect of direct benefit, likely to yield general knowledge about the subject’s disease or condition</td>
<td>Both parents’ permission required by regulation, when reasonably available</td>
</tr>
<tr>
<td>§46.407</td>
<td>Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children</td>
<td>Both parents’ permission required by regulation, when reasonably available</td>
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<tr>
<th>Parent</th>
<th>Legal Guardian</th>
<th>Foster Parents</th>
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<tbody>
<tr>
<td>Biological Adoptive</td>
<td>Legal Guardianship established by state law with written provision documenting the guardian’s ability to consent for the child’s medical care and any other activities contemplated by the research.</td>
<td>Generally do not have authority to consent to non-routine medical care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consent may be given by the case worker if the research meets the requirements of 45 CFR 46.409</td>
</tr>
<tr>
<td>Can provide consent</td>
<td>Can provide consent with a copy of the appropriate court order filed with the consent form</td>
<td>Cannot provide consent</td>
</tr>
</tbody>
</table>

A child under the age of 18 is not required to sign the parental permission form, however, they must sign the assent form if seven years of age or older.

**Conditions of Confidentiality for Parental Permission**
The Commonwealth of Kentucky mandates that investigators and their staff report a reasonable suspicion of known abuse or neglect of a child. When research is likely to reveal possible child abuse, such as interviews about personal behavior, child-rearing practices, discipline or when talking to others about the child or specific familial relationships, or
when the research is conducted in the subject’s home, a medical facility, or a doctor’s office, the parental permission from should clearly state that the investigator is required to report a reasonable suspicion or known abuse or neglect of a child. The following statement is required for parental permission forms when investigators conduct research with children that requests information regarding sensitive personal or family behavior or is conducted in the subject’s home:

Under Kentucky statute the privilege of confidentiality does not include information about sexual or physical abuse of a child. If a member of the research team has or is given information, she or he is required by law to report it to the authorities. The obligation to report includes alleged or probable abuse as well as known abuse.

### 12.2.4. Illiterate Participants

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<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
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</table>

A person who can read and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. For example, subjects who are not able to write can enroll in a study by “making their mark” (e.g., signing or marking an “X”) on the consent document, after going through the informed consent process.

The IRB allows individuals who speak and understand English, but who cannot read the consent materials due to illiteracy or a visual impairment, to enroll in a study if (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study.

The following guidelines on communicating informed consent for individuals who are deaf or hard of hearing should be used to develop a consent process for these participants. Information can be found at [https://www.nih.gov/health-information/nih-clinical-research-trials-you/guidelines-communicating-informed-consent-individuals-who-are-deaf-or-hard-hearing-scientists](https://www.nih.gov/health-information/nih-clinical-research-trials-you/guidelines-communicating-informed-consent-individuals-who-are-deaf-or-hard-hearing-scientists).

In all cases described above, the research record should document the method used for communication with the prospective participant and the specific means by which the prospective participant communicated agreement to participate in the study.

For cases related to illiteracy, hearing or vision impairment, an impartial third party must witness the entire consent process and sign the consent document. A video tape or audio tape recording of the consent interview is recommended. Witness signature can be documented using the supplemental signature page located at [http://louisville.edu/research/humansubjects/templates/links-to-forms](http://louisville.edu/research/humansubjects/templates/links-to-forms).
12.2.5. Non-English Speaking Participants

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<tr>
<td>II.4.B</td>
<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
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Investigators are encouraged to recruit and include all segments of the community in research, including individuals whose primary language is not English. Participants who do not speak English should be presented with a consent document written in a language understandable to them, and which embody all the elements necessary for legally effective informed consent.

The University of Louisville HSPP and OHRP strongly encourage the use of a combined informed consent and research authorization form translated into the participant’s language whenever possible. When all of the participants in a study (i.e., the target population) are anticipated to be non-English speaking, a full translated consent is required. In addition, a person fluent in both the participant’s language and English needs to available for research visits.

When a full-length form embodying all elements of consent is required by the IRB to document consent, the IRB requires that appropriately translated consent documents be submitted to the IRB for review and approval prior to their use in enrolling participants.

Investigators may use language translators or interpreter services to obtain consent in a language understandable to the participant or the participant's legally authorized representative. The researcher must document the consent process including who served as a translator. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved.

In addition, plans for ensuring ongoing communication with the participant in a language understandable to the participant must be provided to the IRB. Any additional study documents such as surveys/questions that the participant will be required to complete should also be translated.

Development of non-English language consent forms will typically necessitate translation of the original consent from English to the second language. A certificate of accuracy from the qualified translator should be submitted.

A certificate of accuracy is a document signed by a qualified translator who performed or verified the translation affirming that the entire document has been translated, that nothing has been omitted or added, and that the translation is true and correct.

**Short Form Consent Process**

Federal regulations permit the use of a short form consent process (45 CFR 46.117(b)(2) and 21 CFR 50.27(b)(2)) with the prior approval of the IRB.

The short form consent process may be approved by the IRB, on a protocol-specific basis, for use with participants who are non-English speaking. The IRB considers the study complexity and the amount and duration of participant involvement when determining if using the short form consent process is appropriate and can be approved.

If a non-English speaking participant is encountered unexpectedly, investigators may rely on an oral translation of the English language consent form but should take extra care in the informed consent process to ensure that the participant has understood the study procedures, risks, benefits, etc.

The research participant should be provided with a short form consent document, written in the participant’s native language that summarizes the basic elements of the informed consent.

Consent procedures:

a. The standard (i.e. IRB approved, full description) informed consent document should be presented verbally to the participant in his/her native language and all questions must be answered.

b. With the agreement to participate in the research study, the participant should sign and date the translated “short form” consent document and the witness to the informed consent process should sign and date the “short form” consent document and the standard consent document. The investigator or person obtaining informed consent should sign and date the standard informed consent document.

c. Copies of the signed “short form” consent document and the standard informed consent should be given to the participant with the originals of both documents retained in the investigator’s research records.

d. A statement in the research records should indicate that the translation took place; the name of the translator; and the translator’s belief that the participant understands the study and the consent process.

e. Investigators should consider that in obtaining clinical consent, family members most often shield their loved ones from bad news (i.e. risks of study). A proper medical translator is an important safeguard that should not be set aside lightly.

f. Subsequent modifications of the informed consent document should be fully translated to a language understood by the participant. This could be as an addendum to the consent form.

When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

Who can serve as a translator/interpreter?

- an officer or employee of an official translation bureau or agency
- professor or instructor who is teaching the translated language in an accredited college or university in the United States
- interpreter services provided by the medical facility
- a family member of the participant, only if the participant has declined the use of the above mentioned interpreter.
- If a member of the study staff speaks the participant’s language, the staff member can act as the interpreter and Person Obtaining Consent (POC), but cannot also act as a witness.

Who can be the witness?

- A person who attests to the oral presentation and is conversant in both English and the participant’s language.
- The witness may be the interpreter

To request the use of a Short Form, submit an amendment in the ESS with the following:

- Explain the intention to use the short form consent process and how the consent will take place.
• Provide the IRB with the plan for ensuring ongoing communication with the participant in a language understandable to the participant.
• Provide certified translations of all documents the participant will be required to complete (surveys/questionnaires).
• Attach the translated Short Form in the participant’s native language.
• Attach the English version of the Short Form.
• Attach the revised English consent form adding witness signature lines as indicated below.

Note: If the English version of the Short Form has not been approved previously by the convened IRB, the amendment will be assigned to a full board meeting per §46.117(b)(2).

“The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.”

_____________________________  ______________________ __________
Signature of Witness     Printed Name of Witness Date

Stand-alone Research Authorization
In cases where there is a stand-alone research authorization and the research authorization is NOT available in the subject’s language, verbally translate the English-language approved research authorization. The participant, the interpreter, and a separate witness must sign the form. The witness can be a member of the research team.

12.2.6. Prisoners

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<td>The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.</td>
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The IRB considers prisoners to be a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether to participate in research. The IRB imposes additional protections pertaining to biomedical and behavioral research involving prisoners, limits the types of research that can be approved, and requires special consent information as specified in OHRP in 45 CRF 46 (Subpart C). See Chapter 9 and Guide-004-Additional Protections for Research Involving Prisoners. If the Principal Investigator (PI) is not familiar with these legal requirements, the PI who proposes to involve prisoners in research (or who has a participant become incarcerated after enrollment) should contact IRB staff for additional guidance.

12.3 IRB Review of the Consent Process, including Consent Documents

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<td>II.3.F</td>
<td>The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process.</td>
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Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.

PIs must submit for IRB review any consent document(s) and explanation of the circumstances under which informed consent will be sought for new protocols, at continuing review, and whenever a modification to the consent process or documents is requested.

The Protocol Application solicits the information necessary for the IRB to evaluate whether the informed consent process will be appropriately conducted given the protocol-specific circumstances (e.g., level of risk, inclusion of special participant populations) and adequately protects participants, considering issues such as whether:

1. Participants have sufficient time to discuss concerns and decide whether to participate in the research;
2. The possibility of coercion and undue influence is minimized;
3. Communications to the participant or their LAR are in a language understandable to them; and
4. Consent process communications do not include any exculpatory language through which the participant or their LAR is made to waive, or appear to waive, any of the participant’s legal rights, or which releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence.

The same evaluation criteria apply to review and approval of the consent process and consent document(s) when reviewed by the expedited process, as by regular review.

The IRB staff review the consent document(s) and consent process information. For continuing review or modifications, any new information that could impact participants’ risks (e.g., adverse events) or procedure changes are also examined to ensure the consent document is appropriately updated. Consent process requirements are discussed in Chapter 12.1 above.

The IRB considers the relationship between the person(s) who will solicit, obtain consent, and explain the consent document and the potential participant. The person obtaining consent must be approved personnel on the study and have the required Human Subjects Protections training. The IRB requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants, and protects participants by minimizing the possibility of coercion and undue influence and allowing adequate time for them to discuss and decide whether to participate in the research.

The IRB also reviews any direct advertising (e.g., newspaper, TV or radio ads, posters, flyers, letters or postcards, emails, postings on bulletin boards/ internet/ web), since it is considered by the FDA “to be the start of the informed consent and participant selection process.” In order to approve advertisements, the IRB must determine that the direct advertising is not unduly coercive and does not promise a certainty of cure or favorable outcome or other benefits beyond what is outlined in the consent and the protocol. (See Chapter 10.4)

Consideration at an IRB Convened Meeting
The IRB determines that all basic, and all additional elements appropriate to the research, are included in the consent process. All the relevant requirements in OHRP in 45 CFR 46.109(b) and 46.116, and in the FDA regulations in 21 CFR 56.109(b), 50.20 and 50.25, that are applicable to the consent process and the consent document, must be satisfied for IRB approval. See Guide-022-IRB Research Approval Criteria.
The IRB may require revisions to the consent document as a condition for approval. If the revisions are minor and can be dictated verbatim at the meeting, the protocol may be approved contingent upon the revisions being made. An IRB member must confirm that the revisions have been implemented as specified before the contingency can be removed. If revisions are greater than minor or cannot be dictated verbatim at the convened meeting, the protocol is deferred, and the consent document is referred back to the PI for the drafting of the revisions and submission at a future convened meeting. If the PI objects to the revisions specified by the IRB, the PI must submit a new consent document for future consideration.

12.4 Documentation of Informed Consent – Signature Requirements

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<td>The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process.</td>
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**Documentation of informed consent** refers to a participant, or their legally authorized representative (LAR), signing and dating an IRB stamped approved consent document, which includes the basic elements of informed consent and the additional elements of informed consent, when appropriate (45 CFR 46.116; 21 CFR 50.25(a),(b)). When a person agrees to be a participant in a research study, signing the IRB stamped approved consent document indicates that they have participated in the consent process, and understand the information provided to them. Documentation requirements for informed consent are specified in OHRP in 45 CFR 46.117(a),(b) and FDA 21 CFR 50.27(a),(b).

In order to approve research, the IRB must determine that informed consent will be appropriately documented, unless the IRB waives documentation under OHRP or FDA regulations (see Chapter 12.5.2.). If a participant lacks the capacity to consent, then consent for research must be obtained from their LAR. See Chapter 12.2 above.

Consent is documented through use of an IRB stamped approved written consent document signed and dated by the participant or their legally authorized representative that embodies all of the required elements of informed consent (see Chapter 12.1). Only the IRB stamped approved informed consent document may be used, and unless the requirement is waived by the IRB, the document must be signed and dated by the participant (or the participant’s LAR). FDA regulations require that the signature be dated by the participant/LAR.

A copy must be given to the person signing the form. HIPAA regulations require that participants receive a signed copy of the HIPAA research authorization. If the HIPAA research authorization is combined with the informed consent document, a signed copy of the consent/HIPAA research authorization must be given to the participant.

As a local requirement, the “person obtaining consent” and the “investigator” must also sign the consent document. The Principal Investigator or Sub-Investigator(s), if not the person obtaining consent, must sign and date the consent within 14 days of participant signature. If the investigator conducts the consent process, they do not sign the “person obtaining consent” line on the consent document. They will only sign and date the investigator signature line. The person who conducts the consent process, whether it is an investigator or study team member, signs and dates the consent on the same date as the participant.

In certain cases, it may be necessary for the participants or parent(s) of children who are participants to mail/emailfax a signed copy of the consent or parental permission form to the investigator. The participants or parents need not provide the investigator with the original signed consent. The participants cannot participate in the research until the signed and
dated consent document is in the possession of the investigator. The person obtaining consent and/or the investigator will sign and date the consent document once received by the study team following the guidelines in the paragraph above.

When consenting by mail/email/fax, the IRB recommends keeping any documentation showing the date of receipt/postmark. In addition, a written description of the consent process that took place should be filed in the research record for documentation.

**Short Form Consent Process – Additional Signature Requirements**

Subject to prior approval of the IRB, consent may be documented through use of a short form written consent document with the requirements and process specified in OHRP 45 CFR 46.117(b)(2) and the FDA regulations in 21 CFR 50.27(b)(2). The short form consent process is generally applicable to situations involving non-English participants. If the participant agrees to take part in the study, the following signatures are required:

**On the short form consent document (translated):**

i. Participant or the participant's legally authorized representative [LAR]  
ii. Witness (the interpreter may act as the witness)

**On the summary form (English Consent Form):**

i. Person obtaining consent  
ii. Witness (the interpreter may act as the witness)

For information on using the short form consent process see Chapter 12.2.5

**Children Participants, Documentation of Informed Consent, and Assent**

Since children cannot legally give consent, informed consent must be obtained from parents (“parental permission”), or the legally appointed guardian. When, in the judgment of the IRB, the children are capable of providing assent, the IRB may determine whether and how assent must be documented. See the Assent Template and Chapter 12.2.3. For additional information on the requirements for documentation of consent for children participants, see Guide-018-Informed Consent of Minors.

**12.5 Waiver or Alteration of Informed Consent Requirements**

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<td>II.3.G</td>
<td>The IRB has and follows written policies and procedures for approving waivers oralterations of the consent process and waivers of consent documentation.</td>
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- Waiver or alteration of the consent process  
- Waiver of documentation of informed consent – (“waiver of signature”)

**12.5.1. Waiver or Alteration of the Consent Process**

Under OHRP 45 CFR 46.116(c) (d), and (e), IRBs have authority to alter or waive the requirement to obtain informed consent.
FDA regulations do not provide for a waiver or alteration of the informed consent process. The only exceptions to the informed consent requirements are for clearly defined circumstances of emergency use of a test article (see Chapter 5.9), and waivers granted for planned emergency research (see Chapter 12.6). Thus, the information below in this Chapter 12.5.1 applies only to non-FDA-regulated research.

The IRB may approve an investigator’s request to waive or alter the requirement to obtain informed consent if the investigator demonstrates with specificity that the criteria under 45 CFR 46.116(c) or 46.116(d) are met. To approve such a request under 46.116(d), the IRB must find and document the following:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration;
4. If the research involves using identifiable private information or biospecimens, the research could not practicably be carried out without using such information in an identifiable format (applicable to research approved by the IRB on or after January 21, 2019); and
5. Whenever appropriate, subjects will be provided with additional pertinent information after participation.

Also, under 45 CFR 46.116(c) the IRB may waive or alter the consent process. To request a waiver or alteration of the informed consent process the investigator must demonstrate that each of the criteria under Section 46.116(c) or (d) is met for the given protocol.

To approve a waiver or alteration of the informed consent process the IRB must find and document that all regulatory criteria under 45 CFR 46.116(d) (OHRP) are met and that the research is not subject to FDA regulations.

**Special Considerations for Research Involving Deception**

In research involving deception, the investigator may, with protocol-specific justification, request an alteration of the consent process. The IRB may approve the research, including the request to alter the requirement for informed consent if the investigator demonstrates that deception or incomplete disclosure is necessary and addresses concerns relating to participant protection; e.g., debriefing.

In order for the IRB to adequately review the research, investigators should justify, in detail, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of: (a) the necessity for deceiving subjects; (b) how potential benefits of the research justify the use of deception; and (c) how the investigators will conduct the debriefing. In addition, investigators should include a debriefing script or statement that indicates the information subjects will receive regarding their participation in the research.

**Research Involving Children: Waiver of Parental Permission/Guardian Consent**

Research regulated by the FDA is not eligible for waiver of parental permission, except for the use of an FDA test article meeting the emergency exception (see Chapter 12.6).

The IRB will often consider a request for a waiver or partial waiver of parental permission for minimal risk research to be conducted in a classroom.

The IRB may waive parental permission by determining that the criteria for waivers or alterations are met. However, research is ordinarily not suitable for a waiver of parental permission if it involves any of the following issues:

1. Parental political affiliations or beliefs,
2. Mental or psychological problems,
3. Sexual behavior or attitudes,
4. Illegal, antisocial, or self-incriminating behavior,
5. Appraisals of other individuals with whom the minor has a familial relationship,
6. Relationships legally recognized as privileged (lawyers, doctors, clergy), and
7. Religious affiliations or beliefs.

If the IRB waives the requirement for parental permission, it may require an alternative mechanism to protect the child participants (e.g., appoint a qualified child advocate).

**12.5.2. Waiver of Documentation of Consent – (“waiver of signature”)**

As allowed by OHRP (45 CFR 46.117 (c)) and FDA regulations (21 CFR 56.109(c)), the IRB may waive the requirement to obtain written documentation of informed consent. This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of the consent process itself. A waiver of documentation of consent does not mean that requirements of the consent process are removed.

Even if a waiver of documentation is granted by the IRB, permitting the investigator to forego obtaining the participant’s signature on a written consent document, the investigator still must provide the participant with all of the information described in Chapter 12.1 required to constitute a complete and appropriate consent process, through an information sheet, or through an oral script in a language understandable to the participants. In all cases in which the requirement for documentation of consent is waived, the IRB may require the PI to provide participants with the written consent document with an option to sign the consent document, or with a written statement regarding the research.

To approve a waiver of documentation, the IRB must find that the protocol-specific justification for waiving documentation satisfies regulatory criteria. Specifically, the IRB must determine the regulatory basis for the waiver as one of the following (note that (a) does not apply for FDA-regulated research):

(a) Under OHRP (45 CFR 46.117(c)(1)) the IRB must find and document either:
   i. the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant’s wishes will govern; or
   ii. the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context;

or

(b) For research subject to OHRP and FDA regulations, the IRB must find and document that the research involves no more than minimal risk to participants and involves no procedures for which written consent is normally required outside of the research context. (45 CFR 46.117(c)(2), 21 CFR 56.109(c)(1)).

**12.6 Exceptions to Informed Consent in Planned Emergency Research**

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<td>II.4.C</td>
<td>The IRB has and follows written policies and procedures for making exceptions to consent requirements for planned emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance.</td>
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**Note:** “Planned emergency research” *is not synonymous with* emergency use of a test article”, which is addressed in Chapter 5.9.

**Planned emergency research** refers to research planned for emergency settings, including the planned use of a test article.

Planned emergency research involves an extensive approval process, including FDA approval, prospective IRB review, and approval and consultation with representatives of the communities where the research will be conducted and from where participants will be drawn. Investigators must submit a protocol application including a description of the informed consent process or a request to waive informed consent; often in emergency settings it is not possible to obtain informed consent from a potential participant when there is insufficient time and a legally authorized representative (LAR) is not available.

The IRB may waive the requirement for informed consent in accordance with an exception under 21 CFR 50.24 (FDA) or 45 CFR 46.101(i) or 45 CFR 46.116(f) (OHRP), depending on whether or not the research is subject to FDA regulation, given that all required IRB determinations under these provisions can be made. Under these regulations, the IRB may permit planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives in a limited class of emergent situations where the participant is in need of an emergency experimental intervention, but cannot give informed consent due to a life-threatening medical condition and there is not sufficient time to obtain consent from the participant’s legally authorized representative.

Prior to scheduling a study which qualifies as Emergency Research for initial IRB review, the IRB Analyst will discuss the study with the Director/Associate Director, HSPPO. The IRB Chair/Vice Chair and the assigned primary reviewer will be notified by the Director/Associate Director that such a study has been received.

The IRB with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation finds and documents each of the following:

- The application clearly identifies the protocols that will include participants who are unable to consent.
- The research participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which might include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining consent is not feasible because:
  - The participants will not be able to give their consent as a result of their medical condition.
  - The intervention under investigation must be administered before consent from the participants’ legally authorized representatives is feasible.
  - There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- Participation in the research holds out the prospect of direct benefit to the participants because:
  - Participants are facing a life-threatening situation that necessitates intervention.
• Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the individual participants.

• Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

• The clinical investigation could not practicably be carried out without the waiver.

• The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each participant within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.

• The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

• The IRB has reviewed and approved consent procedures and a consent document consistent with 50.25. These procedures and the consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documented is feasible.

• The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant’s participation in the clinical investigation consistent with the paragraph below.

• Additional protections of the rights and welfare of the participants will be provided, including, at least:

  • Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the participants will be drawn.

  • Public disclosure to the communities in which the clinical investigation will be conducted and from which the participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

  • Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

  • Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.

  • If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the participant’s family member who is not a legally authorized representative, and asking whether he or she objects to the participant’s participation in the clinical investigation.

  • The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

• Procedures are in place to inform, at the earliest feasible opportunity, each participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not
reasonably available, a family member, of the participant’s inclusion in the clinical investigation, the details of the investigation and other information contained in the consent document.

- There is a procedure to inform the participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, that he or she might discontinue the participant’s participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

- If a legally authorized representative or family member is told about the clinical investigation and the participant’s condition improves, the participant is also to be informed as soon as feasible.

- If a participant is entered into a clinical investigation with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the participant’s legally authorized representative or family member, if feasible.

- The protocol is performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identified such protocols as protocols that might include participants who are unable to consent.

- The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

- If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (within 30 days) in writing to the clinical investigator and to the sponsor of the clinical investigation.

For the purposes of this waiver “family member” means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship. In addition, advance notice of such planned emergency research protocols will be provided to the Office for Human Research Protections pursuant to 45 CFR 46.101(i).

See also:
- Informed Consent Requirements in Emergency Research [OHRP]
- Exception from Informed Consent for Studies Conducted in Emergency Settings [FDA]
In this chapter:

13.1 Definitions
13.2 Information Management in Multi-Site Research
   - Reporting to the IRBs in Multi-Site Research
   - Identifying Material Changes in Multi-Site Protocols
13.3 Communication among IRBs in Multi-Site Research
   - University of Louisville Serving as Participating Institution
13.4 Transnational Research
   - HIPAA Considerations in Transnational Research

13.1 Definitions

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

Transnational Research: research extending or going beyond national boundaries.

13.2 Information Management in Multi-Site Research

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<tr>
<td>II.2.1</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 and IRB application, including communications of adverse outcomes, UPIRTSOs, protocol modifications, enrollment numbers, 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 and 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 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. Continuing review information, including enrollment numbers, for all relying sites must be submitted at the time of continuing review to the University of Louisville IRB. 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 7.10, Review of Reportable Events.

**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.

**13.3 Communication among IRBs in Multi-Site Research**

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<th>AAHRPP Std./Element</th>
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<tr>
<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>
</tr>
</tbody>
</table>
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.

The Code of Federal Regulations, 45 CFR 56.114, provides that institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort. An external IRB review process involves an agreement under which multiple study sites in a multicenter trial may rely in whole or in part on the review of an IRB other than the IRB affiliated with the research site. To promote efficiency and consistency across multiple research sites, alternative models of IRB review are available to University of Louisville investigators. University of Louisville IRBs may rely on the IRBs of other sites or agree to have other sites rely on University of Louisville IRBs.

**University of Louisville serving as the IRB of Record**

If University of Louisville agrees to serve as the IRB of Record for an external site, that site obtains an FWA through OHRP. Once an FWA is in place, an IRB Authorization Agreement (IAA) or a Reliance Agreement is signed by the institutional officials, or delegates, of University of Louisville and the external site. This agreement authorizes University of Louisville to serve as IRB of Record for that site.

When submitting a request for the University of Louisville IRB to serve as the IRB for an external site, the UofL investigator must have sufficient resources for ensuring appropriate communication with the external institution takes place. This includes, but is not limited to, communicating approval correspondence, approved documents, obtaining enrollment numbers, and other applicable information. The investigator must also ensure the external site reports events to the UofL investigator as required by UofL policy. See chapter 7.10 for event reporting.

**University of Louisville relying on an external IRB**

All submissions to request an external IRB of record must be made to the HSPPO by submitting an application in the electronic submission system (ESS). Steps for this submission are outlines in Guide 035 Utilizing an external IRB of record for sponsored multi-center clinical trials.

When the external IRB does not serve as the Privacy Board, for example NCI CIRB, the University of Louisville IRBs serve as the Privacy Board for UofL. The University of Louisville IRB chair/vice chair or designee reviews and approves the HIPAA documents required for the research study.

The University of Louisville works with other external academic IRBs utilizing IRB Authorization Agreements to work cooperatively, and with central IRBs such as NCI CIRB, Western IRB, Advarra, and Quorum Institutional Review Board. For projects where the University of Louisville cedes review/approval authority to an external IRB, the following applies:

**Investigator Responsibilities**

1. Initiate research only after receiving approval from the external IRB of record and notification from University Louisville IRB acknowledging the study review is ceded to the external IRB of record.
2. Initiate amendments or changes to an approved protocol only after review and approval from the IRB of record, except where necessary to eliminate apparent immediate hazard to the participant.
3. Conduct the project in accordance with University of Louisville policies, the applicable external IRB policies and federal and state regulations.
4. Notify external IRB of reportable events per their policies.
5. Notify the University of Louisville IRB office of reportable events & updates as described in this policy.
University of Louisville Responsibilities:
The University of Louisville, having responsibility for the local conduct of the trial, will follow its regular processes for review of HIPAA documents (if serving as the privacy board), human subjects and HIPAA training verification, conflicts of interest, and reporting applicable events to the Office for Human Research Protections (OHRP).

Auditing for Compliance
The University of Louisville Human Subjects Protection Program Compliance Program team will include these studies in the routine review program.
Per the IRB Authorization Agreement/Division of Responsibilities, the external IRBs may request to conduct audits or consent observations of studies deferred by the University of Louisville to the external IRB.

Determinations Resulting from Review
UofL retains the authority to:
- Accept the external IRB approval;
- Accept the external IRB approval with minor modifications; or
- Not accept the external IRB approval in which case the investigator may either withdraw the study or have it referred to a convened UofL IRB for review.

External IRB Responsibilities
1. Conduct review of research according to all applicable regulations and laws, including initial review, continuing review, unanticipated problems involving risks to participant and others, incidents of serious or continuing non-compliance, and review of modifications to previously approved research.
2. Make available to UofL relevant minutes of its meetings and any other documents related to the review, approval and continuing oversight of the research study.
3. Provide prompt notification of all actions, requirements and determinations it makes related to the participation of UofL in the research study.

13.4 Transnational Research

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<td>1.3</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.

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 sufficient justification. 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 participant 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.

For research greater than minimal risk, the UofL IRB will not 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 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.

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. The IRB will consider each individual case based on its potential to identify subjects and the sensitive nature of the data being transmitted (see Chapter 11).

Resources:
OHRP Guidance: International Compilation of Human Research Standards
In this chapter:

14.1 **Principal Investigator Qualifications**
- Human Subjects Protection Resources
- Investigator Attestations

14.2 **Knowledge of Applicable Federal, State and Local Laws**
- Knowledge of the Definition of Human Subject Research

14.3 **Research Oversight**
- Sound Study Design
- Minimization of Risks through Study Design and During the Course of the Research
- Oversight of Research Staff during Recruitment
- Selection of Study Participants
- Informed Consent
- Obtaining Informed Consent in the Clinical Research Context - Special Considerations
- Study Conduct
- Compliance with the IRB
- Continuing Review Application
- Closure Report (amendment)
- Confidentiality of Records and Personal Data
- Privacy Rule (HIPAA)
- Delegation of Research Responsibilities
- Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies

14.5 **Data Monitoring Plan (DMP)**
- Sponsor Responsibilities

14.6 **Response to Participants’ Requests for Information and Complaints**

### 14.1 Principal Investigator Qualifications

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<td>III.2.A</td>
<td>Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization’s policies and procedures regarding the protection of research participants.</td>
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</table>

University of Louisville policies, procedures, and education programs help Principal Investigators (PIs) and all University of Louisville investigators carry out research studies in an ethical manner. In addition to following applicable federal, state, and local regulations, investigators follow ethical principles and standards appropriate for their discipline. In designing and conducting clinical trials, PIs follow Good Clinical Practice (GCP) guidelines defined by the Food and Drug Administration, and have the protection of participants’ rights and welfare as their primary concern.

The University of Louisville will allow faculty and staff of the University to act as a Principal Investigator (PI)/Program Director (PD) on funded or unfunded research.
Individuals who are enrolled in either undergraduate or graduate educational programs may not serve as the principal investigator on a research study. A faculty member must be named as the PI and the student may be named as a co-investigator. Individuals who are in advanced training programs (such as residencies or fellowships) must have a faculty member serve as the PI. Some departments designate individuals in fellowship programs as lecturers or instructors. If the individual holds such an appointment, they may serve as a PI. The PI must provide proof of the lecturer or instructor status along with their IRB application.

If an individual is not a permanent employee of the University of Louisville, the term of appointment must be sufficient in length to complete the proposed project. Such individuals must obtain formal approval by the appropriate chair and/or dean to submit the application in the name of the University with assurances that adequate resources and supervision will be available for the project to be successful should it be funded. Gratis Faculty with research appointments who wish to conduct Human Subjects Research and act as a PI on a study may also require EVPRI approval. This is determined on a case by case basis and the final decision is made by the EVPRI.

In most circumstances, all paid faculty and gratis faculty with research appointment, who conduct human subjects research associated with their appointment, must utilize the University's IRBs for review, approval and continued oversight of the research. In certain circumstances, individual or institutional conflicts of interest may require the utilization of an independent IRB. Requests for use of an independent IRB must be made to the EVPRI or the University IRB and approved by the EVPRI. The IRB considers the professional qualifications and resources (including time, equipment, support services) of the PI and research team to protect participants and minimize potential harm. The PI and all research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.

For additional information, OHRP has a list of frequently asked questions (FAQs) about investigator responsibilities.

**Human Subjects Protection Resources**

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<td>III.1.D</td>
<td>Researchers determine that the resources necessary to protect participants are present before conducting each research study.</td>
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Principal Investigators (PIs) are required to indicate in the Protocol Application whether they will have access to adequate resources to carry out the research. Resources, including space, personnel, services and equipment required for conducting the proposed research properly and safely, must remain available as needed throughout the research. The PI must provide information about the qualifications and number of study staff, personnel training, available facilities, and the time available to conduct and complete the research, and must demonstrate sufficient access to a population allowing recruitment of the required number of participants.

PIs should continually monitor the resources allocated for their research and notify the IRB if any change in the availability of resources may adversely impact the rights and welfare of participants.

In addition to IRB approval of the protocol, human participant research (including recruitment and enrollment) which is sponsored cannot begin until a contract has been finalized, or a grant award activated.
The principal investigator is also responsible for obtaining all additional approval(s) required, such as facility approval, before beginning their research.

A Review of Scientific and Scholarly Merit and a review by the PIs Department Chair are also required at the time of initial submission. This “sign off” is completed through the electronic submission system.

**Investigator Attestations**

The protection of human participants in research is the shared responsibility of PIs, sponsors, and the IRBs; and the PIs are ultimately responsible for the safety and welfare of participants. When conducting research with human participants, the PI attests that the following statements are true, as part of the electronic submission of the IRB application:

1. The information provided in this application is correct.
2. If relevant, the grant document that I have forwarded to my funding agency is attached to this IRB submission and it accurately and completely reflects what is contained in the submission.
3. I will not begin my research until I have received written or electronic notification of final IRB approval.
4. I will not begin my research until I have received any other written or electronic notification of additional compliance approvals I may need (e.g., administrative approvals from sites or facilities, Industry Contracts, Institutional Biosafety Committee, Radiation Safety Committee, Jefferson County Public Schools, etc.)
5. I will maintain records of this research according to Federal and institutional requirements.
6. I will seek and obtain prior written or electronic approval from the IRB for any modifications in the proposal, including any changes in procedures, any changes in study personnel, and changes in informed consent language, applicable HIPAA documents, funding agencies, etc.
7. I will utilize the most recently approved (and stamped when required) IRB/Privacy Board document(s) for this study.
8. I will promptly report to the IRB any unexpected or otherwise significant adverse events or unanticipated problems or incidents that may occur in the course of this study.
9. I will report in writing to the IRB any significant new findings which develop during the course of this study which may affect the risks and benefits to participation.
10. I will comply with all IRB requests to report on the status of the study. This includes filing Continuing Review 8 weeks in advance of the study approval expiration.
11. If appropriate, I certify to the Privacy Board that I will not reuse/disclose PHI, to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which use/disclosure would be permitted by the HIPAA privacy regulations.
12. If appropriate, I certify to the IRB/Privacy Board that I will maintain, store, and/or transmit any sensitive information, including PHI, obtained during this study, on any electronic media (server, desktop computer, laptop, PDA/Smart phone, USB drive, DVD/CD or any other electronic storage media) in a manner consistent with the University of Louisville Information Security Policies and Standards.
13. If this is an industry sponsored study, I certify to the IRB that the research related injury language in the contract and the language included in the informed consent are consistent.
14. If this is an industry sponsored study, I agree to pay, or ask the sponsor to pay the initial and continuing review fees in a timely manner. I accept that my final approval letter will not be provided until the required fees are paid.
15. If these conditions are not met, I understand that the IRB can rescind its approval of this research and the research could be suspended or terminated.
Failure to follow this policy could result in disciplinary action. Disciplinary recommendations, if any, will be based on penalties similar to those outlined in the University’s Administrative Sanctions for Violations of University of Louisville Research Policies. Violations of this policy will be reported following the procedures in Chapter 3.6, Internal and External Report of Findings.

14.2 Knowledge of Applicable Federal, State and Local Laws
The HSPPO disseminates and makes available to the University of Louisville research community, via the Human Subjects Website and education programs, the following resources to promote knowledge about applicable Federal, State and organization policies for human subjects research:

- Guidance on topics affecting the conduct of research, such as informed consent, vulnerable populations, conflict of interest, reporting requirements, etc.
- Template consent forms and instructions that include federal, state and local requirements
- Electronic protocol submission system - with application questions intended to address required considerations
- Information and instructions on submitting protocols to the IRB
- References and links to federal, state and organizational requirements
- Contact information for IRB staff for assistance
- The University of Louisville Research Policy Handbook (RPH) is also available online

Where applicable, Kentucky State laws have been included in the HSPP Policy Manual and document templates. When University of Louisville investigators conduct research in states other than Kentucky, they are expected to be knowledgeable of and adhere to the laws of the state in which research is being conducted, as well as those of Kentucky. Investigators are advised to seek guidance from the IRB staff or Legal Counsel if they have questions as to the applicable laws.

Knowledge of the Definition of Human Subject Research

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<tr>
<td>III.1.A</td>
<td>Researchers and Research Staff know which of the activities they conduct are overseen by the Human Research Protection Program, and they seek guidance when appropriate.</td>
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Prior to submitting a protocol for IRB review investigators are instructed to consider whether their project meets the statutory definition of human subject research or clinical investigation contained in Guide-025-Is my Project Research? This provides guidance based on DHHS- (OHRP) and FDA specific requirements.

IRB staff is also available to assist investigators in determining if a project needs to be submitted for IRB review. If the proposed activity does not involve “research” or “clinical investigation” and “human subjects”, it does not require submission to the IRB. For an official determination by the IRB, the investigator must submit a Non-Human Subjects Application to the IRB through the Electronic Submission System (ESS). See Chapter 6.1 for additional information on the definition of human subject research.
14.3 Research Oversight

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<td>III.2.B</td>
<td>Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions.</td>
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<tr>
<td>III.1.E</td>
<td>Researchers and Research Staff recruit participants in a fair and equitable manner.</td>
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<tr>
<td>III.1.C</td>
<td>Researchers employ sound study design in accordance with the standards of the discipline.</td>
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The general principles stated here apply to all research, including behavioral/social/educational research.

**Sound Study Design**

The significance of the research depends upon the validity of the results. It is unethical to put subjects at risk or to inconvenience them through participation in a study that may produce little or no reliable information. Regardless of the source of funding, it is the PI’s responsibility to judge the research design to be sound enough to meet its objectives before submitting the protocol for IRB review. The Protocol Application provides questions addressing the various considerations for sound study design. The Protocol Application also includes a description of the provisions for monitoring the data and reporting to the IRB and other entities (see Chapter 14.4 below).

In developing, or in evaluating the adequacy of, a research design involving investigational drugs or biological products, the PI should refer to the FDA Guidance Documents representing the Agency's current thinking on good clinical practice (GCP) and the conduct of clinical trials, and including selected guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”), as published in the Federal Register on May 9, 1997.

The PI should also be familiar with the various types of control groups, their relative advantages and disadvantages, and the ethical issues associated with each control type, as outlined in the FDA guidance Choice of Control Group and Related Issues, published May 2001. Although directly applicable to FDA-regulated trials involving investigational drugs or biological products, many of the principles can be applied to clinical trials in general.

**Minimization of Risks through Study Design and During the Course of the Research**

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<tr>
<td>III.1.C</td>
<td>Researchers design studies in a manner that minimizes risks to participants.</td>
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The PI must minimize risks at all times by using procedures that are consistent with sound research design and that do not expose participants to unnecessary risks, and whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

When submitting a Protocol Application to the IRB, the PI must:

- Describe the potential risks.
- Include, where possible, a scientific estimate of their frequency, severity, and reversibility. If statistical incidence of complication and the mortality rate of proposed procedures are known, this data should be included.
- Explain how risks will be minimized.
- Justify the level of risk.
• Describe adequate provisions for monitoring the data during the conduct of the research to minimize risk to participants (see Chapter 9.2).

For proposed changes to the research, including any change to mitigate potential harm to participants, the PI must submit a protocol amendment to the IRB describing any resulting changes in the level of risk to participants, and explaining the risk level and potential benefits.

At Continuing Review, the PI must indicate whether there has been an increase, no change, or a decrease in the level of risk of the study. If the risk assessment has changed the PI must update the information in the Risks section of the protocol (if applicable) and informed consent document(s).

All studies considered more than minimal risk must include a data and safety monitoring plan which describes how the PI will oversee the participants’ safety and welfare and how unanticipated problems involving risks to participants or others, and adverse events will be characterized and reported.

**Oversight of Research Staff during Recruitment**
The PI is responsible for ensuring recruitment activities, whether undertaken by research staff or the PI, are via methods set forth in the protocol application and approved by the IRB. The PI must ensure that informed consent is obtained from each research participant before that individual participates in the research study. The PI may delegate the task of obtaining informed consent to another individual knowledgeable about the research, while retaining ultimate responsibility over the conduct of the study.

**Selection of Study Participants**
In selecting a population from which to draw participants for a particular research protocol, the PI must consider whether the choice of population results in an equitable distribution of the burdens and benefits of research. The PI must provide appropriate justification in the protocol application when recruiting participants among vulnerable populations such as prisoners, pregnant women, economically and educationally disadvantaged, decisionally impaired, and people who are homeless. (45 CFR 46.111(a)(3); 21 CFR 56.111(a)(3)). In addition, the PI must ensure selection of study participants is equitable and appropriate to the goals of the study. Adequate safeguards for the protection of participants during the recruitment and conduct of research must be set forth in the protocol application. See:

- Chapter 10.1 (Equitable Selection)
- Chapter 7.2 (Equitable Selection)
- Chapter 10.4 (Recruitment)

**Informed Consent**

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<td>III.1.F</td>
<td>Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.</td>
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In the Protocol Application, the PI must:

- Describe the consent process in enough detail to allow for meaningful review by the IRB,
• Include the proposed written informed consent document(s) that address each of the elements of informed consent in the context of the research (unless the IRB waives the documentation requirement – see below), and
• Include any written material to be given to prospective participants to explain the nature of the research.

The PI is responsible for making all revisions to the proposed consent document as requested by the IRB. Any other change to the consent document must be submitted to the IRB for prior review and approval.

PIs are responsible for assuring the quality of the informed consent process and for making sure that consent is obtained and documented before participant participation, unless waivers are granted by the IRB. No research procedures, including screening procedures to determine if an individual is eligible to enroll in the research, may begin until after the participant has signed the consent form, unless the IRB has approved a waiver or alteration of consent. Retroactive consent – i.e., consent obtained or documented after the participant has undergone one or more research procedures – is not acceptable.

The PI may delegate all or a portion of the informed consent process to others on the research team, such as sub-investigators or research coordinators. However, it is ultimately the responsibility of the PI to ensure that those individuals carry out their tasks properly and in accordance with regulatory and IRB requirements.

The PI must use the consent document currently approved by the IRB. The IRB approval stamp must appear on the consent document.

No participants should be involved in research prior to the IRB approval date, and no participants should be involved in research using a consent document whose approval period has expired.

The PI or their delegate should plan to discuss research with potential participants at a time when they are not under duress, and to allow sufficient time and opportunity to ask questions and to consider whether or not to participate in the research before agreeing to participate.

In discussing research with potential participants, the PI or their delegate:

• May not describe items or procedures under investigation as if they were known to be safe and effective as a treatment for the potential participant’s disease or condition, or as if they present a known advantage,
• May not understate the risks of the research, as there may be no countervailing benefits to participants.

The PI or their delegate is responsible for giving the participant a copy of the signed informed consent document, and for maintaining the original form.

**Obtaining Informed Consent in the Clinical Research Context - Special Considerations**

The distinction between treatment and research is especially important if the PI is also the potential participant’s attending physician, a situation that increases the risk of confusion. Thus, it must be clearly stated to the participant that they will be involved in research and that if randomization is involved, that this is also described.

The purpose of medical or behavioral treatment is to provide interventions designed solely to enhance the well-being of the patient or client. By contrast, research is designed primarily to develop generalized knowledge rather than to benefit
each participant in the research. Research involves activities to test a hypothesis and draw conclusions, and any therapeutic benefit to the participants is secondary to the objectives of the research.

Research involving randomization of participants, whether to proven or experimental procedures, raises further issues. In these circumstances, the PI should ensure that each participant understands that the assignment will not be based upon the attending physician's clinical judgment as to which treatment may prove more beneficial to that participant, and may involve additional testing that would not be performed as clinical care.

For a detailed discussion of the informed consent process requirements and description of available templates and guidance, see Chapter 12-Informed Consent and Assent.

### Study Conduct

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<th>AAHRPP Std./Element</th>
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<tr>
<td>III.2.C</td>
<td>Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to University of Louisville policies and procedures and to the requirements or determinations of the IRB.</td>
</tr>
</tbody>
</table>

The PI is responsible for conducting the study in a manner that is scientifically and ethically sound and for ensuring the use of appropriate methods and correct procedures, according to the approved protocol.

The PI is also responsible for the timely and proper administration of the research project. Beyond the scientific and clinical conduct of the study, responsibilities include:

- Compliance with federal, state, and local laws and University of Louisville policies, including disclosure of any potential conflict of interest
- Fiscal management of the project
- Training and supervision of postdoctoral candidates, students, and residents
- Compliance with the sponsor’s terms and conditions (e.g., non-disclosure of sponsor confidential information)
- Submission of modification and continuing review applications in a timely manner
- Obtaining approval for changes prior to implementation.

### Compliance with the IRB

Federal regulations require that any research study involving human subjects be reviewed and approved by an IRB. IRB approval must be obtained before any recruitment or screening can take place.

It is the PI’s responsibility to submit a written protocol to the IRB for review. At submission, the obligations of the PI with respect to oversight of their research protocols and research staff during recruitment, selection of study participants, and conduct of the study according to the protocol as approved by the IRB are stated in the protocol application and must be agreed to by the PI for the submission to be accepted. The PI is responsible for ongoing adherence to the determinations and requirements of the IRB for the duration of the research.

The documents required for protocol submission are listed in Chapter 7. A detailed discussion of the roles and responsibilities of IRBs is presented in Chapter 6.
Continuing Review Application
PIs must submit protocols (other than those subject to 45 CFR 46.101(b) - Exempt research) for continuing review by the IRB before the expiration date of the protocols, and in sufficient time to ensure the non-interruption of studies.

Closure Report (amendment)
At the conclusion of the study, PIs involved in research approved under regular review (including student research with a faculty advisor) must submit a closure amendment to the IRB. This should submitted to the IRB within 30 days of closure.

When a Principal Investigator terminates employment or association with UofL, he or she is obligated to submit a closure amendment to the IRB or transfer the protocol to another Principal Investigator via amendment.

Confidentiality of Records and Personal Data
PIs working with human subjects must safeguard the privacy of participants and protect the confidentiality of personal information:

- Safeguard mechanisms must be established, maintained, and documented throughout the research process.
- Sustained attention must be paid to maintaining confidentiality of research data in the design, implementation, conduct, and reporting of research.
- Full information about the privacy and confidentiality of data must be provided to prospective participants through the informed consent process.
- Unintentional breaches must be avoided by taking additional precautions in communication, administration and storage of information.

Privacy and confidentiality are addressed in Chapter 11.

Privacy Rule (HIPAA)
When conducting research that involves the use and disclosure of protected health information (PHI), the PI must abide by the applicable HIPAA policy of the University of Louisville and facilities where the research is being conducted in order to account for disclosures of PHI when an individual requests such accounting. See Chapter 11.3.

Delegation of Research Responsibilities
PIs may delegate research responsibility. However, PIs maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. The conduct of a study usually requires the involvement and contribution of other individuals under the direction of the PI, based on their qualifications and capabilities. In delegating study-specific tasks and responsibilities to other members of the research team, the PI must ensure that those assuming a duty are well trained and competent.

Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies
FDA regulations and guidance specify the responsibilities of sponsors (and their investigators) using FDA test articles. [21 CFR 31 Subpart D; 21 CFR 812 Subparts C,E].

In sponsor-investigator research, the PI assumes all of the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects.
14.4 Data Safety Monitoring Plan (DSMP)/Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

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<th>AAHRPP Std./Element</th>
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<tr>
<td>III.2.D</td>
<td>Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; University of Louisville policies and procedures; and the IRB's requirements.</td>
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</table>

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6)).

See also Chapter 9.2.

The extent of monitoring varies by the risk/benefit ratio of the study and by the size, complexity and nature of the study. The IRB requires a data safety monitoring plan (DSMP) for all studies greater than minimal risk. For externally sponsored studies, the DSMP is normally incorporated into the protocol. For an investigator-sponsored study greater than minimal risk, the principal investigator is responsible for creating and implementing a data and safety monitoring plan. The IRB will review the proposed level of risk and monitoring plan and will accept or amend the DSMP. Any proposed change to the IRB approved DSMP must be reviewed and approved by the IRB. The responsibility for human participant protection in human subject research is shared among the IRB, PI, trial sponsors and oversight boards or committees. The safety of participants must be considered in study design.

**Studies that are greater than minimal risk** to participants must include a data safety monitoring plan (DSMP) to evaluate whether the character, incidence, and severity of expected harms match those expected, and to evaluate the causality of unexpected harms. Additionally, a description of the DSMP is required in the Application submitted to the IRB. In order to approve research, the IRB determines that when appropriate, there will be adequate monitoring of data to protect the safety and well-being of participants.

Monitoring may be conducted by the PI, or a Monitoring Entity (ME). In all studies, the PI has ultimate responsibility for identifying potential risks and identifying adverse events occurring in the study population and reporting the events to the sponsor and to the IRB as required in Chapter 3.6.

**Sponsor Responsibilities**

Sponsor responsibilities may include (but are not limited to), as appropriate to the scope and complexity of the research:

- Establishing procedures to assure that interim data remains confidential
- Notifying all participating IRBs of unanticipated problems involving risks to participants or others
- Notifying FDA and the responsible IRBs of any recommendations or requests made by a Monitoring Entity to the sponsor that address safety of participants.

If there is a Data Safety Monitoring Committee or Board, sponsor responsibilities may include:

- Appointing a Chair
- Establishing procedures to assess potential conflicts of interest of proposed members
- Establishing Standard Operating Procedures (SOPs) for statistical analyses, report format, and meeting schedules
- Submitting SOPs to the FDA prior to interim data analyses, optimally before the initiation of the trial.
In sponsor-investigator research, the PI assumes all of the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects. This includes the responsibility of registering all “applicable clinical trials” on the clinicaltrials.gov registry.

14.5 Response to Participants’ Requests for Information and Complaints

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<tr>
<td>III.1.G</td>
<td>Researchers and Research Staff have a process to address participants’ concerns, complaints, or requests for information.</td>
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</table>

**Requests for information**

The PI and members of the research staff are required to respond promptly and adequately to all requests for information received from participants, prospective participants and their family members or designated representatives. In addition to providing information and answering questions that arise as part of the informed consent process, the PI must inform the participant that he/she is available to answer any questions that arise about the research in the future. The consent form must list the full name and contact information for the PI, sub-investigators, and other research study staff as appropriate. The consent form must also inform participants how to reach the IRB if they have any questions about their rights as research participants. See University of Louisville consent form template for contact information language.

**Complaints**

The PI is expected to investigate and respond promptly to complaints, and to follow the proper procedure for addressing and reporting complaints to the IRB. A complaint is a formal or informal, written or oral, expression of dissatisfaction by the participant or the participant’s representative. Complaints that are not resolved promptly by the PI or member of the research staff must be reported to the IRB as follows:

- Complete and submit a Deviation/Violation/Misc Form to the IRB
- Include with the Form a brief description of the complaint and the circumstances in which the complaint was made and any action taken to date in addressing the complaint. Complaints are handled in accordance with the policies described in Chapter 3.7.

If the complaint is not directly related to the conduct or design of the research, the IRB staff may refer the complaint to the appropriate University of Louisville institutional official or committee. In circumstances in which the complaint is referred, the IRB staff should provide the participant with the name and contact information for the referral. On Continuing Review, investigators are required to list all complaints received about the research in the past year, whether or not they were previously reported to the IRB.

**Privacy issues**

If the complaint involves University of Louisville privacy practices, the University of Louisville Privacy Officer should be notified. All documentation relating to the complaint must be retained for at least six years from the date of creation.
In this chapter:

15.1 Agreement Includes Protections for Research Participants
15.2 Provision Addressing Medical Care for Participants
15.3 Communications from Sponsors Affecting IRB Oversight
15.4 Publication of Research Results

Definitions

**Sponsored research:** Research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices or biologics.

### 15.1 Agreement Includes Protection for Research Participants

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<tr>
<td>I.1.D</td>
<td>University of Louisville has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, Research Participants, and the Institutional Review Board, as appropriate.</td>
</tr>
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</table>

In sponsored research conducted at the University of Louisville, the University of Louisville addresses the protection of research participants by:

- Including in their standard contract template a provision that the sponsor acknowledges and understands that the University of Louisville HSPP is applies to all human participant research. See: University of Louisville University Clinical Trials/Study Agreement template
- Asking for the inclusion of such a provision in any proposed contract that does not use their standard templates

Additionally, the IRB will review the proposed consent form and delete any provision that requires a participant to waive or appear to waive any legal rights (i.e., exculpatory provisions).

### 15.2 Provision Addressing Medical Care for Participants

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<tr>
<td>I.8.A</td>
<td>The University of Louisville has a written agreement with the sponsor that addresses medical care for research participants with a research-related injury, when appropriate.</td>
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</table>

For sponsored research and as appropriate, University of Louisville study agreements will include provisions that specify the sponsor will pay or make arrangements for the medical care for study participants who suffer research-related injuries.

If it is not appropriate for a sponsor to pay or make arrangements for the medical care study participants who suffer research-related injuries, University of Louisville study agreements will not include provisions regarding payment or arrangement for medical care.
15.3 Communications from Sponsors Affecting IRB Oversight

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<td>I.8.B</td>
<td>In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, University of Louisville has a written agreement with the Sponsor that the Sponsor promptly reports to University of Louisville findings that could affect the safety of participants or influence the conduct of the study.</td>
</tr>
<tr>
<td>I.8.C</td>
<td>When the Sponsor has the responsibility to conduct data and safety monitoring, University of Louisville has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to University of Louisville.</td>
</tr>
<tr>
<td>I.8.E</td>
<td>When participant safety could be directly affected by study results after the study has ended, the University of Louisville has a written agreement with the sponsor that the researcher or organization will be notified of the results in order to consider informing participants.</td>
</tr>
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</table>

For sponsored research, University of Louisville agreements include provisions that specify that the sponsor will notify the Principal Investigator or the IRB of:

i. Non-compliance with the protocol or applicable laws, particularly those laws related to participants, that could impact the safety or welfare of the participants,

ii. Data or safety concerns that have been reported to the FDA or other governmental agency in relation to the protocol at University of Louisville or any other site,

iii. Unanticipated outcomes to the protocol detailed in the data at University of Louisville or any other site that could relate to risks to participating participants, and

iv. Circumstances that could affect participants’ willingness to continue to participate in the protocol or the IRB’s continuing approval of the protocol.

When non-standard contract templates are used, the sponsor is asked to include equivalent statements.

When the IRB learns of events that could affect participant welfare after a study has closed (e.g., a drug studied at University of Louisville is withdrawn by the FDA), the IRB seeks information, deliberates, and considers whether (and how) to contact participants who might be affected. When necessary, even when the study is not yet closed, but participants have completed participation, the IRB may require investigators to notify former participants when information is learned that could affect their welfare.

15.4 Publication of Research Results

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<tr>
<td>I.8.D</td>
<td>Before initiating research, the University of Louisville has a written agreement with the sponsor about plans for disseminating findings from the research and the roles that researchers and sponsor will play in the publication or disclosure of results.</td>
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</table>

For sponsored research, University of Louisville agreements generally include provisions detailing the role of its researchers in the dissemination of findings from the research. University of Louisville agreements specify:

i. which persons or entities involved in the research are allowed to publish or republish results of such research,

ii. how the sponsor may be involved in the review and editing of such results in order to protect confidential information or intellectual property, and

iii. as appropriate, how research results are to be disseminated in studies conducted at multiple research locations.