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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>
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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**

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 strong application will contain good ideas, address important issues, and generate confidence that the investigator(s) will make a significant impact.

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 and Department Chair 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 approval process takes place within the IRB ESS. Once the approval has been submitted, the system allows the submission to route to the IRB for review and approval.

Responsibility for conducting such a review may be delegated to other agencies provided that the circumstances and the identity of the agency are specified.

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

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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 and 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:

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). 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\(^1\) as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

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 subject 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)).

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 decide whether their research can be expedited, exempted, or will require full Board Review.

Federal Guidance: OHRP Decision Tree for Use in Defining Whether a Project Requires IRB Review
Chart 1: Is an Activity Research Involving Human Subjects?
Chart 2: Is the Human Subjects Research Eligible for Exemption?
Chart 3: Does Exemption 45 CFR 46.101(b)(1) (for Educational Settings) Apply?
Chart 4: Does exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?
Chart 5: Does Exemption 45 CFR 46.101(b)(4) (for Existing Data, Documents, Records and Specimens) Apply?
Chart 6: Does Exemption 45 CFR 46.101(b)(5) (for Public Benefit or Service Programs) Apply?
Chart 7: Does Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies) Apply?
Chart 8: May the IRB Review Be Done by Expedited Procedures?
Chart 9: May the IRB Continuing Review Be Done by Expedited Procedures?
Chart 10: May Informed Consent Be Waived or Consent Elements Be Altered under 45 CFR 46.116(d)?
Chart 11: May Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?
7.2 Protocol Review

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<tr>
<td>II.2.D</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.D.1.</td>
<td>Initial review</td>
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<tr>
<td>II.2.D.2.</td>
<td>Continuing review</td>
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<td>II.2.D.3.</td>
<td>Review of proposed modifications to previously approved research</td>
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<tr>
<td>II.2.E</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used.</td>
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<tr>
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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 subjects stop, unless the IRB finds an over-riding safety concern or ethical issue involved so that it is in the best interests of individual subjects 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 subjects 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 subjects 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 the purview of its responsibility.

3. Selection of subjects 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 subject or the subject’s legally authorized representative, in accordance with, and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by §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 approval. 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 the grant proposal insofar as it impacts the rights and welfare of the human subjects. The Office for Protection from Research Risks (now 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 subject 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 study2.

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 maintained.

2 Payment for participation in research is not considered a benefit.
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protected and, to the extent possible, risks are reduced to a minimum. This plan does not need to be complicated but should be appropriate for the risks associated with the study.

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 subject;
b. The research is likely to benefit the subject 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 subject. 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.

Considering Risk: Minimal Risk
An especially prominent concept is that of minimal risk. By statute and custom, the IRB may consider studies, deemed to be 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.

Considering 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 that 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.

Considering Risk: 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.

Considering Risk: Social, Legal and Economic Risks
Some research proposals involve the handling of sensitive information that 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.

**Considering Risk: Drugs**

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 are on 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.

It is important also for the reviewer to note that all advertisements pertaining to drug studies must be included. Thorough review of all written or visual advertisements as well as those anticipated to be placed on electronic media is important in the consideration of all protocols. Any statement of compensation (e.g. for emergency treatment) other than that which is normally contained within the consent form is prohibited.

In addition to drug studies utilized for the development of new therapies, many volunteer studies may include drugs that are either waiting for approval or have been approved. The same rule concerning advertisements applies to these except an extra level of scrutiny should be applied to be certain that volunteers are drawn from an appropriate population.

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 patients are endangered. Specific psychiatric protocols may also require inpatient hospitalization and supervision by a separate team of physicians responsible for the clinical care rather the study investigator if withdrawal from normal drugs is deemed to be a potential risk to the patient or to society.

Considering Risk: Devices
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. When a research project is posed as a NSR research, reviewers should consider three questions: 1) does the device, 2) the research design itself, or 3) the failure of the device poses a significant risk to the subject. 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 may be eligible under the federal regulations for expedited review.
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 subjects by ameliorating their condition or provide 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 subject 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 subject populations, such as children, prisoners, subjects with cognitive disorders, or economically or educationally disadvantaged subjects. Primary reviewers and who have expertise in representing vulnerable subject 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 subject 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 subject 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 subject signs serves as documentation that a dialogue has taken place and as a record that the subject has agreed to participate in the research. In addition to providing the subject 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 subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's LAR. The FDA (drug or device studies) explicitly requires that consent forms be dated as well as signed by the subject or the subject'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.

For additional information, 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**

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 Subjects**

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 “subject pool,” the IRB should ensure that consent for participation is sought only under circumstances, which minimize the possibility of coercion or undue influence, and that genuinely equivalent alternatives to participation are available.

**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:

- Posting IRB approved advertisements throughout the university to recruit subjects from a broad base of students.
- 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.
- Avoiding any personal solicitations by students, faculty, GTAs or RAs for fellow students or faculty.
- Providing a number of research projects from which to choose, if participating as a research subject is a course requirement.

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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.
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 at the same time. Unintended coercion must be avoided by (1) ensuring that participation is voluntary, (2) that 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.

**Fetuses, Pregnant Women, and Human In Vitro Fertilization**

Women should not be excluded from any phase of research unless the science of the project or the health of the subject 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."

Specific additional protections are listed in Guide-003 - Additional Protections for Pregnant Women and Fetuses Involved in Research, 45CFR 46 Subpart B §46.204.

**Prisoners**

An IRB must have present at its meeting a designated prisoner advocate in order to review projects involving the use of prisoners in research. The chair may approve new studies limited to retrospective review of prisoner records and minor modifications using expedited review procedures after review and comment by the prisoner advocate.

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.

**Children**

An IRB must have present at its meeting a designated advocate for children in order to review projects involving the use of children in research. 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 subject. 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 HSPP Guide-002 - Guidance on Additional Protections for Children in Research (OHRP) and/or Guide-001 - Guidance on Additional Protections for Children in Research (FDA).

Persons with Impaired Decision making Capacity

Special protections are essential to guide research involving vulnerable persons. An IRB must have present at its meeting an advocate for the vulnerable and cognitively impaired in order to review projects involving the use of these populations in research. The mere presence of the appearance of vulnerability should not lead to a presumption that a person is incapable of making a decision regarding participation in research and of giving valid informed consent. Yet sometimes these conditions do impair the decision-making capacity required to give a valid informed consent, raising ethical concerns about the vulnerability of persons in such conditions in research. The Chair/Vice Chairs may approve research involving vulnerable subjects through the expedited review procedures as long as the study does not involve more than minimal risk to the subject.

In order for the IRB to assess the decision-making capacity of the subject, the investigator shall include a protocol-specific plan for assessment if the investigator determines that the subject lacks decision-making capacity, the investigator will describe the research to the subject 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 subject. However, if the investigator determines that the subject is non-responsive, the investigator shall document that observation in the research file. If the subject expresses resistance or dissent to participation or to the use of LAR consent by word or gesture, the subject shall be excluded from the research study. Discussion of who makes 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 University of Louisville Biomedical IRB contains representation from the School of Medicine, Department of Psychiatry and Behavioral Sciences representing persons of impaired decision making capacity.

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.
### 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.

| Exempt Review | 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 designee (such as a senior IRB member). These studies are exempted from IRB continuing review - not from initial review. |
| Expedited Review | Minimal risk studies meeting specific criteria (pdf). Protocols are generally reviewed by one primary IRB reviewer. Protocols approved under Expedited review are subject to IRB continuing review. 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). |
| Regular “convened” review | 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. |
| Determination of Not Human Subjects Research (NHSR) | This application allows a PI to receive an official institutional 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 Analyst or IRB member, 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. The determination of NHSR would normally be made by an IRB Analyst, the HSPPO Director*, or HSPPO Assistant Director*. If the IRB Analyst is uncomfortable making the determination, the application may be routed to an IRB Chair/Vice, or to the Director or Assistant Director, HSPPO. *HSPPO Director and Assistant Director are alternate members of both the Biomedical and SBE IRBs and may make this determination as Senior IRB Members. |
| Determination of Not Engaged In Research (NEIR) | This application is submitted by an IRB Analyst when materials are received from an individual who has no association or affiliation with the University of Louisville or one of its affiliated research partners. 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 home institution, any questionnaires, surveys, or other materials that will be used in the research). The determination of NEIR would normally be made by an IRB Analyst, the Director*, HSPPO or Assistant Director*, HSPPO. *HSPPO Director and Assistant Director are alternate members of both the Biomedical and SBE IRBs and may make this determination as Senior IRB Members. |
### AAHRPP Std./Element | Description
---|---
II.2.A | 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.

II.2.B | 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.

## 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 will make a determination of exemption from IRB review. The IRB chair 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.

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.

### Exempt research fulfills the institution’s ethical standards, such as:
- The research holds out 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.
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.

1. The chair/designee will not consider any research exempt that involves prisoners (Except certain epidemiological research under category 4 that may qualify for exemption), sensitive aspects of subject’s behavior, sensitive surveys, or that takes place in settings where subjects have a reasonable expectation of privacy.

2. The chair/designee will not consider any research exempt that involves survey or interview procedures or observation of public behavior of children except for research involving observation of public behavior when the investigator(s) does not participate in the activities being observed.

3. The chair/designee will not consider any research exempt that involves a test article regulated by the FDA unless the research meets the criteria for exemption described in 45 CFR 46.101(b)(6).

4. 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 46.101(b)(1-6) or 21 CFR 56.104(a-d) justifying the classification of exempt.

5. 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 minor contingencies identified by the IRB reviewer.

6. 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.

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

8. 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 Criteria

Unless otherwise required by the IRB, research activities designated in 45 CFR 46 or 21 CFR 56.104(a-d), in which the only involvement of human subjects will be in one or more of the following categories, are exempt from this policy:

- That participation is voluntary.
- Name and contact information for the researcher.

There are adequate provisions to maintain the privacy interests of participants.
1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. Educational research proposals are exempt providing all of the following are met:

   a) All of the research is conducted in a commonly accepted educational setting (e.g., a private or public school).
   b) The research involves normal educational practices (e.g., comparison of instructional techniques).
   c) The study procedures do not entail a significant deviation in time or effort from those educational practices already existent in the study site.
   d) The study procedures do not involve an increase in the level of risk or discomfort beyond normal, routine educational practices, including physical education.
   e) The study procedures do not involve deception or withholding of information.
   f) The study procedures do not involve sensitive topics, such as sexual behavior of individual subjects. A sensitive survey is one which deals with socially questionable or highly personal issues or alcohol and/or drug abuse.
   g) Provisions are made to ensure the existence of a non-coercive environment for all students, including those who choose not to participate.
   h) The school or other agency grants written approval for the research to be conducted.
   i) Educational tests of (i) knowledge, (ii) mastery, or (iii) skills.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation.

**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 subject. 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

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5The No Child Left Behind Act of 2001 (Public Law 107-110) identified 8 categories of protected information for survey responses: political affiliations of student or student’s parent; mental or psychological problems of student or student’s family; sex behavior or attitudes; illegal, anti-social, self-incriminating or demeaning behavior; critical appraisals of others with whom students have close family relationships; legally recognized privileged or analogous relationships; religious practices, affiliations or beliefs of student or student’s parent; and income. Research involving any of the eight identified categories requires written parental informed consent prior to participation of a child.

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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 subject 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 subject 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

d. children are not involved as subjects.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) (b) of this section, if:

   (a) the human subjects are elected or appointed public officials or candidates for public office or (b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information be maintained throughout the research and thereafter. Copies of the informed consent form and questionnaire or survey instrument(s) to be used must be forwarded to the IRB for review.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

**Anonymous Data**

Investigators should note that a survey is anonymous (if containing PHI, meets the HIPAA de-identified definition) 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 subject. 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.

**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.

Research involving existing data, documents and/or specimens is typically exempt under Exempt Category 4 as long the following conditions pertain:

a. The data, documents and/or specimens exist prior to the conceptualization of the research project. This is what was earlier referred to as “archived” or “on-the shelf” data and/or documents.
b. The data, documents and/or specimens are publicly available. Data, documents and/or specimens whose access is restricted to select groups are not publicly available.
c. The information from the data, documents and/or specimens must be recorded in such a manner that subjects cannot be identified directly, or through identifiers linked to the subjects.
d. The researcher must provide written confirmation to the IRB that permission for the use of data, documents and/or specimens has been granted by the gatekeeper and that the information is publicly available.

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 subject 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 subject 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.

Material or tissue that has not been archived prior to the submission of the research protocol to the IRB does not qualify for a request for exemption. The IRB is also required to review research with residual material where the investigator intends to identify the patient/subject 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 subject 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 subject and review by the IRB. If 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.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.

OHRP has determined that the following criteria must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs" as specified under Department of Health and Human Services (DHHS) regulations at 45 CFR 46.101(b)(5):

a. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

b. The research or demonstration project must be conducted pursuant to specific federal statutory authority.

c. There must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB).

d. The project must not involve significant physical invasions or intrusions upon the privacy of participants.

Institutions should consult with the DHHS funding agency regarding the above conditions before invoking this exemption. In addition, it is extremely important that staff in all DHHS agencies understand and respect the following principles, which are critical to the successful implementation of human subject protections under DHHS regulations:

a. Institutions conducting (nonexempt) DHHS-supported human subjects research must provide OHRP with an acceptable Assurance of Compliance with the human subjects regulations [45 CFR 46.103(a)]. Under the terms of such Assurances, it is typically the responsibility of the Institutional Review Board (IRB) or other designated
institutional official(s), not the investigator, to determine whether research activities qualify for exemption. Institutions holding OHRP-approved Assurances generally require that all research involving human intervention/interaction or identifiable private information [45 CFR 46.102(f)(2)] be subjected to independent verification of exempt status.

b. Institutions may elect under their Assurance not to claim the exemptions provided in the regulations, choosing instead to require IRB review of all research involving human intervention/interaction or identifiable private information.

c. While DHHS requires neither an Assurance nor a Certification of IRB Review [45 CFR 46.103(f)] for exempt research, institutional requirements regarding review of such research are, nevertheless, binding on investigators. It would be inappropriate for staff of any DHHS agency to discourage potential awardees from submitting their activities for institutionally required IRB review.

6. 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.

7. The following categories of clinical investigations regulated by the FDA (21 CFR 56) are exempt from the requirements of this part for IRB review:

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 subject 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 subject 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, Executive 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 subject 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\(^6\) 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 subject risks. The exemption granted is only for the protocol as written at the time of the initial review when the decision to exempt was determined.

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 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.

**Exemption of Research Involving Children**
Research that involves children and falls into categories 1 - 6 described below may be found to be exempt by the IRB. However, the exemption category 2 at 45 CFR 46.101(b)(2) above, pertaining to survey or interview procedures or observations of public behavior, does not apply to research involving children, except for research involving public behavior when the Investigator does not participate in the activities being observed.

**Exemption of Research Involving Prisoners**
Research under categories 1-6 is not exempt if it involves prisoners. These applications must be submitted for convened IRB review. Because of the vulnerability of prisoners, OHRP recommends that all research involving prisoners be

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\(^6\) Institutional Official (EVPRI), or designee
reviewed by the convened IRB. If the research is reviewed under the expedited review procedure, OHRP recommends that the IRB member(s) reviewing the research include a prisoner or prisoner representative.

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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 by the IRB chair 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 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 46.100 and 21 CFR 56.110 are:

1. Clinical studies of drugs and medical devices only when conditions (a) or (b) is met:
(a) Research on drugs for which an investigational new drug application\(^7\) is not required. (Note: Research on marketed drugs that significantly increases the risks associated with the use of the drug is not eligible for expedited review.)

(b) Research on medical devices for which an investigational device exemption (IDE) application\(^8\) is not required; or the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:

   (a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period, and collection may not occur more frequently than 2 times per week; or

   (b) From other adults considering the age, weight, and health of the subjects, the collection procedure, the amount of blood collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

   (a) hair and nail clippings in a non-disfiguring manner;
   (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction;
   (c) permanent teeth if routine patient care indicates a need for extraction;
   (d) excreta and external secretions (including sweat);
   (e) uncannulated salvia collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a diluted citric solution to the tongue;
   (f) placenta removed at delivery;
   (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during delivery;
   (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
   (i) mucosal and skin cells collected by buccal swab, skin swab, or mouth washings;
   (j) sputum collected after saline mist nebulization.

4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples of non-invasive procedures that may qualify for expedited review are

a) physical sensors that are applied either to the surface of the body or at a distance and do not involve the input of significant amounts of energy into the subject or an invasion of the subject’s privacy;

b) weighing or testing sensory acuity;

c) magnetic resonance imaging;
d) electrocardiograph, ultrasound, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, diagnostic infrared imaging, doppler blood flow, and echocardiography; e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records or specimens) that have been collected solely for non-research purposes (such as medical treatment and/or diagnosis). (Note: Some research in this category may be exempt from IRB regulations for the protection of human subjects (45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

6. Collection of data from voice, video, digital or image recordings for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from IRB regulations for the protection of human subjects 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8. Continuing review of research previously approved by the IRB as follows:
   a. where
      I. the research is permanently closed to the enrollment of new subjects;
      II. all subjects have completed all research-related interventions; and
      III. the research remains active only for long-term follow-up of subjects; or
   b. where no subjects have been enrolled and no additional risks have been identified; or
   c. where the remaining research activities are limited to data analysis.

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

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 subject 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 subject 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.

Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.
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 rebut the decision as provided.

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 and found to meet one of the regulatory categories for Expedited Review are subject to at least annual review and this information is communicated electronically to the principal investigator in the approval letter sent through the IRB ESS. Studies submitted and determined to be Exempt are not subject to annual review.

**IRB Full Board Review**

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 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)**

Some specific types of studies have triggered questions with respect to investigators' responsibilities and the need to obtain prospective review and approval of the IRB. The following list notes 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. Experience has taught us that time spent with students discussing matters such as courtesy, and avoidance of unnecessary discomfort or invasion of privacy, will be time well spent. 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.

If you have questions regarding the distinction between these categories, please do not hesitate to contact the IRB for assistance.

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. Even though this may be the case, 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 following the instructions in the software.

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. In rare cases, the author(s) may apply for a waiver of authorization to the privacy board, but it is generally felt that an “n” of up to five allows authorization to be obtained.

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.

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.
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 a narrators’ informed consent do not meet this federal definition of “research.” Nor do they contribute to “generalizable knowledge within the context of the federal definition,” even if conducted with people identified with a common group, theme or event, and whether or not the interviewer or other researchers might draw some historical generalizations from multiple interviews.

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, 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. For additional information, see Guide-027-Quality Assurance-Quality Improvement.

Program Evaluation – An essential organizational practice in public health using a systematic approach to improve and account for public health actions.

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.

Research Involving Coded private information or Specimens
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, for example:
   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
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.

**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, does not require IRB review. Secondary analysis of public use survey data is one of the most common forms of research conducted by social scientists. The IRB maintains a list of public use data sources for the research community and will add to the list as appropriate additional sources are identified. If a data set is not available to the general public, then it is not a public use dataset and a full IRB application must be completed for review. The proposed dataset must be on the list of public use data sets listed below.

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. Once it has been determined that the de-identified datasets is appropriate, the link to the dataset will be posted on the IRB website.

Investigators are encouraged to help the IRB expand the list of public use data files that do not require IRB review for the purpose of conducting research utilizing human subjects.

**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. No University of Louisville faculty, staff or students are considered to be “engaged in the research” as defined by OHRP 10-16-2008 [Guidance on Engagement of Institutions in Human Subjects Research](http://www.hhs.gov/ohrp/policy/cdebiol.html). If the University of Louisville receives such a request, the Director or Assistant
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.
- Proof of current Human Subjects Protection training
- Proof of current HIPAA and Research training (if applicable)

Once these items are received, the IRB Analyst enters the information into the IRB ESS system using a Not Engaged in Research Form available only to IRB members through the IRB ESS. Once all documents are attached to the IRB submission form, the application may be reviewed and processed by the Director, Assistant Director or IRB Analyst. If the IRB Analyst is uncomfortable making this determination, the application is routed to either an IRB Chair/Vice Chair or to the Director or Assistant Director, HSPPO.

Correspondence is prepared to the requestor from within the IRB ESS that indicates:

- Title;
- Project Status at UofL;
- Name of the Requesting investigator;
- The name of the IRB of Record for the study;
- The status of the study at the reviewing IRB;
- 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;
- 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 six types of applications within the IRB ESS. Examples of these applications may be seen in 7.12 – IRB ESS examples.

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

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. subject 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 (required only for chart review studies)
- 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/collection/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 informed consent, 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 document 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. Chapter 5.8 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.

The University of Louisville has signed a master reliance agreement with the NCI CIRB to allow UofL investigators to participate in NCI cooperative group studies. The master reliance agreement allows the NCI CIRB to be the IRB of Record for these cooperative group studies. The UofL Biomedical IRB/Privacy Board reviews and approves any local HIPAA documents required for the study.

**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), 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. An IRB Assistant (Intake) in the HSPP Office opens the submission and enters basic information into the HSPPO accession database. Utilization of an Access database by the HSPPO allows for establishment of queries, tables, etc., for administrative purposes, such as calculating review times, responding to requests for information from colleges, schools, divisions or departments, etc. The new submission remains in the unassigned area until the IRB Analyst assigns the protocol to herself for administrative review of the submission.

There are five IRB Analysts in the HSPP Office. Four of the IRB Analysts work with the Biomedical IRB and one with the SBE IRB. The IRB Analysts 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 auto-generated email that comments have been sent on the protocol. 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 review the responses and changes for completion then forward responses to the reviewers. Comments and changes are reviewed by 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.

IRB Analysts make the preliminary assignment to the primary reviewer. That assignment is reviewed by the IRB administrator and may remain or may be changed due to the number of studies assigned to IRB reviewers or whether the IRB reviewer will be in attendance.

**Assignment of Primary Reviewer**

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<th>AAHRPP Std./Element</th>
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<td>II.1.E</td>
<td>The IRB has and follows written policies and procedures requiring research protocols or plans to be</td>
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reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.

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 auditor and IRB Chair/Vice chair or designated IRB 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 to the protocols have been made and questions answered when the protocol is presented and considered by the convened board for approval.

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 immediate 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 (partial waiver for recruitment or complete waiver is requesting a waiver of informed consent, e.g., for a chart or data review study).

A primary reviewer for an Initial Submission is assigned well 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.

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9 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
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.

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 (See Appendix 1).

7.7 Review of Initial Submissions by the convened IRB

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<th>AAHRPP Std./Element</th>
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<td>II.2.C</td>
<td>The IRB has and follows written policies and procedures for conducting meetings by the convened IRB.</td>
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<tr>
<td>II.2.D</td>
<td>The IRB has and follows written policies and procedures to conduct reviews by the convened IRB.</td>
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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 of 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 investigators 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. Color-coded laminated guidance documents (e.g., laminated sheet Additional Protections for the Inclusion of Children in Research (OHRP) for 45 CFR 46.404, 405, 406, 407 and 408; laminated sheet Regulations for Waiver or Alteration of
Consent Requirements for 45 CFR 46.116, 117 will be available during the convened meeting so that appropriate determinations can be documented in the minutes. See Human Subjects Research website Guidance page.

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 the form of color-coded laminated guidance documents, including:

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<th>Frequently referenced guidances (laminates)</th>
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Frequently referenced guidances (laminates)

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<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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<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>Waiver of HIPAA Authorization: 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(i)(2)(ii)(A), (B), and (C) are met, and if so, makes the required finding.</td>
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<td>(1) Clinical Trials Terms (2) Commonly Used Acronyms</td>
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Additionally, for protocols involving **fetal tissue transplantation**, the IRB considers the investigator’s rationale and the risks involved in order to make any finding required by 42 USC §498A (b)(1) and (2).

**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. If the protocol has been changed to an extent that it now qualifies for expedited review pursuant to expedited review category 9, the IRB will change the protocol review designation from regular to expedited.

**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 January 1, 2019).

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 have 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 Approvals**

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 15, Investigator Compliance);
- 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 dates 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.

**7.7.1 - Review of Initial Submissions by Expedited Review**

Expedited reviews are assigned by the IRB analyst either to the Chair/Vice Chair of the IRB or to a senior IRB member designated by the Chair as qualified to conduct expedited review. See Chapter 6 for reviewer qualifications, and the Evaluation of IRB Members which is completed annually.

**Range of Actions for Decisions on Protocols Subject to Expedited Review**

The reviewer(s) of protocols subject to expedited review act on behalf of the IRB and have the authority to approve, require modifications (to secure approval) or request full committee review of the protocols. The reviewers consider the approval criteria set forth in 45 CFR 46.111 and 21 CFR 56.111 in reviewing a protocol. The IRB reviewer confirms that proposed Application Form, informed consent documents and recruitment documents are accurate and complete. The possible decisions are:

**Approved with Modifications:** The IRB Analysts inform the PI in writing of any reviewer modifications, comments, questions, or concerns about the protocol and requests a reply within a specified time. The research may not proceed until the assigned reviewer has reviewed and approved the answers. Once returned through the IRB ESS, revisions are reviewed by the IRB Chair/Vice Chair or designee to ensure that the appropriate changes have been made.

**Approved with no changes:** (or no additional changes). After the reviewer(s) approve, the protocol is entered on a list that is circulated to all IRB members before the next meeting for the IRB and again at the convened meeting. (Note IRBs 6 and 8 only review protocols subject to expedited and exempt review and do not have regularly scheduled meetings. The list of protocols is circulated to all members of the IRB.)
**Moved to Regular (Convened) Review:** The protocol raises questions that warrant review at a convened meeting, PI does not agree to the modifications required for approval or if for research involving children, the children’s finding is that the research presents greater than minimal risk (greater than 45 CFR §46.404 (OHRP) or 21 CFR §50.51 (FDA)), the reviewer will request that the protocol be presented for regular review at the next convened IRB meeting.

**Decision to not approve:** A single IRB reviewer cannot reject or not approve a protocol; thus a reviewer using the expedited procedure may not disapprove research. If the expedited reviewer indicates non-approval, the protocol will be scheduled for review at the next available convened IRB meeting. A protocol can only be not approved (rejected) by a vote at a convened IRB meeting. Protocols subject to a move to regular review are presented and voted on at a convened IRB meeting with a quorum of reviewers present.

For studies approved through the Expedited Review procedures, continuing review will normally be conducted through the Expedited Review procedures as well. For projects approved via the expedited process, the chair or his/her experienced designee conducts the review and determines the length of approval but the approval time is still no greater than annual.

**7.7.2 – Review of Initial Submissions Deferred to the NCI CIRB**

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

Currently, the University of Louisville provides information about local context to the CIRBs. The CIRBs assume responsibility for initial review, continuing review, modifications to approved research, reporting of unanticipated problems and reports of non-compliance. The University of Louisville’s role in this process is to oversee the local conduct of the research. This responsibility is shared with the J. G. Brown Cancer Center Clinical Trials Office (CTO). The local IRB maintains a current list of protocols reviewed and approved by the CIRB.

Requests to utilize CIRB are submitted on an IAA application in the IRB ESS. Prior to submission to the local IRB, a request to participate in an approved NCI cooperative group study is submitted by the Brown Cancer Center staff to the NCI through the NCI ESS called IRB Manager.

The NCI CIRB does not serve as a privacy board and does not review and approve HIPAA authorizations or waivers. These documents are reviewed and approved by the local IRB.

**7.8 - Continuing Review Submissions by the Convened IRB**

Except for studies determined to be exempt from IRB oversight, all human subjects’ studies are required to undergo continuing review based on the level of risk as assessed by the board. This review takes place no less than annually, and may require more frequent review or reports as determined by the IRB.

Submission of an application for continuing review is required on all non-exempt 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.
In addition, for continuing review applications, the primary reviewer reviews the complete project file, that includes all modifications and reports of unanticipated problems involving risks to subjects or others.

Continuing review may stop only when:
- The research is permanently closed to the enrollment of new participants,
- All participants have completed all research-related interventions, and
- Collection and analysis of private identifiable information has been completed.

**Continuing Review Procedures**

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. Ordinarily, the continuing review will not be reviewed more than 30 days prior to expiration. If review occurs prior to this 30 day window, the next review date will be changed to reflect the review outside the 30 day window.

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 number of subjects enrolled, adverse reactions, and any protocol violations, proposed changes, confirmation on informed consent process, subjects not completing the study, description of preliminary results, 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 progress report and supporting documents, including the revised protocol and informed consent document, 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 subject 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 regular review, the continuing review application undergoes regular review, unless it meets the criteria for expedited review (see below). Those which will undergo regular review are assigned to one reviewer who reviews and 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 subjects 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 regular review, the continuing review application undergoes expedited review it meets the criteria 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.

**Lapse in IRB Approval**

If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported to OHRP as a suspension or termination of IRB approval under HHS regulations. However, the University of Louisville views the lapse in approval as significant non-compliance. See Chapter 3.5, Non-compliance Finding for Lapse in IRB Approval.

**Review of Continuing Review of Submissions by Expedited Review**

Submissions subject to expedited continuing review are assigned to one reviewer and are not presented at a convened meeting but are reported on an expedited review listing that is circulated to all board members as part of the meeting agenda.

**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 subject, 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 subject 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.

If the modification changes the review type from Expedited Review to regular or convened review, the IRB staff will convert the protocol to the appropriate review type within the IRB ESS. The modification approval correspondence will explain the change to the investigator.

### 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>

The investigator bears the responsibility of reporting events to the IRB for review. Following is a list of the timeframes for investigator reporting to the IRB.
### Reporting Timeframes

<table>
<thead>
<tr>
<th>Local Adverse Events</th>
<th>When to Report</th>
<th>iRIS Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Adverse Event PI determines to be:</td>
<td>Report within 5 working days of UofL site awareness</td>
<td>Complete the Serious Adverse Event (SAE) Reporting Form within the iRIS system</td>
</tr>
<tr>
<td>• Definitely, Probably, or Possibly related to the research intervention,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unexpected</td>
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</tr>
</tbody>
</table>

### Unanticipated Problems (UPIRTSOs)

<table>
<thead>
<tr>
<th>Unanticipated Problems (UPIRTSOs)</th>
<th>When to Report</th>
<th>iRIS Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Event PI determines to be:</td>
<td>Report within 5 working days of UofL site awareness</td>
<td>Complete the UPIRTSO Reporting Form within the iRIS system</td>
</tr>
<tr>
<td>• unexpected (in terms of nature, severity, or frequency), and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• related or possibly related to a subject’s participation in the research, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Deviations/Violations/Misc.

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

| Minor Deviations/Violations/Misc.                                                    | Report with the next continuation review application | Attach documentation with the continuation review application: |
| • The PI and/or study sponsor is responsible for determining if a deviation is major or minor |                                                      | These can be combined on one document (e.g. an excel file) |

### External Safety Reports

<table>
<thead>
<tr>
<th>External Safety Reports</th>
<th>When to Report</th>
<th>iRIS Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>The majority of IND Safety Reports, 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.</td>
<td>Not Required</td>
<td>Other-Amendment</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 enrolment 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 Monitor 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>
<tr>
<td>Minor Deviations/Violations/Misc. reported within 5 working days</td>
<td>IRB Analyst includes information at continuing review for Chair review.</td>
<td>IRB may require PI to submit a corrective action plan to ensure that such events do not occur in the future.</td>
</tr>
</tbody>
</table>
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, and/or the Clinical Contracts Division (when the study is externally funded). 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 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.

Study Closure Due to Lapse in IRB Approval

If an investigator has failed to provide continuing review information to the IRB by the required date, and the research approval has expired before the continuing review approval has been issued by the IRB, all research must stop. The investigator 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 10 working days from the date of the expiration notice to obtain continuing review approval for the research, or it will be administratively closed by the IRB and the Dean/department chair will be notified of the non-compliance.
If the study is closed by the IRB, the investigator must submit a new project application via the electronic submission system for IRB review and approval if s/he would like to re-open the project. A memo to the IRB must be included with the new submission with 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.

A lapse in approval represents significant non-compliance and is referred to the IRB for determination of serious or continuing non-compliance. Such a determination may be reported to federal regulatory agencies such as the OHRP and FDA, sponsors, and institutional officials. The HSPPO Research Compliance Monitors may also conduct audits on lapsed research to determine if there was any study activity conducted within the lapsed period.

In cases of on-going externally funded projects, the Office of Sponsored Programs Administration or the Clinical Contracts Division also receives a copy of the closure notice and makes an independent determination regarding the need to notify the sponsor. Notification of the sponsor by Office of Sponsored Programs Administration or the Clinical Contracts Division will be reported back to the HSPPO. Copies of the closure notice will also be sent to the Office of Research at any affiliated institution. Once a study has been closed due to lapsed approval, it must be resubmitted as a new submission.

If an investigator allows approval for a re-opened study to lapse a second time, the IRB will be notified an action may be taken to determine whether the lapse is serious and continuing noncompliance. If it is so determined the IRB, in conjunction with the IO, will notify appropriate regulatory offices. See Chapter 3, Noncompliance Finding for Lapse in IRB Approval.

**Safety of Subjects During Lapse in Approval**

During a lapse in approval, research activity may continue for currently enrolled subjects only if the IRB finds that it is in the best interest of individual subjects to continue participating in the research. In order for the IRB to make this determination, the principal investigator must submit to the IRB a written list of research subjects for whom stopping the research would cause harm, and the reason. An IRB Chair will review and determine who may continue in the research, and which procedures will be allowed to continue.

**7.12 Applications and Checklists**

Copies of Applications and Checklists are located in Appendix 1.