

IRB Standard Operating Procedures

**A GUIDE FOR IRB MEMBERS AT THE UNIVERSITY OF
LOUISVILLE**

November 2011

Prologue

This Guide is based on applicable federal regulations, Kentucky state statutes, and University of Louisville policy as they pertain to the conduct of human research at the University of Louisville.

This Standard Operating Procedure is intended to be a dynamic and useful document. We welcome your comments about the contents and structure. If you have suggestions on how to improve the document, please send your suggestions to the Human Subjects Protection Program Office using the comments section of our [HSPP Survey](#) or [e-mail](#) us your comments.

AUTHORITY OF THE INSTITUTIONAL REVIEW BOARDS

PURPOSE / BACKGROUND

This policy establishes the authority of the University of Louisville Institutional Review Boards (IRB).

POLICY

It is the policy of the University of Louisville that human research activities conducted under the oversight of the organization will be conducted in accordance with applicable federal law and regulations that include but are not limited to Federal Regulations 45 CFR 46, 21 CFR 50, 21 CFR 56, and 45 CFR 160.162. and 164, applicable Kentucky state statutes and regulations, the principles of *The Belmont Report* and local University Institutional Review Board (IRBs) requirements.

The University of Louisville authorizes the IRBs of the organization to review and have authority to:

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

Research covered by this policy that has been approved by a University IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, as per 45 CFR 46.112 and 21 CFR 56.112, those officials may not approve the research if a University of Louisville IRB has disapproved it.

Any IRB member or staff who believes that they have been subject to inappropriate influence should report this immediately to the IRB chair or the Director, Human Subjects Protection Program, who will report the attempt to influence to the Executive Vice President for Research (EVPR). The EVPR will investigate, or have investigated, the attempt to influence and determine an appropriate response to the attempt based on penalties similar to those outlined in the University's [Administrative Sanctions for Violations of University of Louisville Research Policies](#). This policy may be found on the [Research Integrity Program](#) Home Page under research policies.

PROCEDURE FOR POLICY

Procedures for conducting the business of the University of Louisville IRBs may be found in the [IRB](#), the [Investigator's Guide](#), the [IRB](#), the *Privacy Board SOP* and the *Human Subjects Protection Program Office (HSPPO) SOP*.

Policy approved by the University of Louisville Board of Trustees on September 23, 2004, Item 6, Tab 10.

TABLE OF CONTENTS

A GUIDE FOR IRB MEMBERS AT THE UNIVERSITY OF LOUISVILLE	i
November 2011	i
<i>AUTHORITY OF THE INSTITUTIONAL REVIEW BOARDS</i>	<i>i</i>
<i>I. INSTITUTIONAL AUTHORITY</i>	<i>9</i>
<i>II. PURPOSE</i>	<i>10</i>
<i>III. PRINCIPLES</i>	<i>10</i>
<i>IV. THE AUTHORITY OF THE IRB</i>	<i>10</i>
Scope	10
Biomedical IRB	11
SBE IRB	11
Referral to Other IRB	12
Referral to an External IRB	12
Communication with Other IRBs	12
Authority of the IRB	12
Authority of Institutional Officials	13
<i>V. RELATIONSHIP OF UNIVERSITY OF LOUISVILLE IRBS TO OTHER AGENCIES, INSTITUTIONS, OFFICES AND COMMITTEES</i>	<i>13</i>
Compliance with Federal Regulations	13
Relationship with Other Affiliated Institutions	14
Review of Human Subjects Research Activities by Other University Committees	14
Review of Human Subjects Research Activities by Other University Offices	16
<i>VI. THE MEMBERSHIP OF THE IRB</i>	<i>17</i>
Appointment and Service of Members	17
<i>VII. MANAGEMENT OF THE IRB</i>	<i>19</i>
IRB Members	19
IRB chair	19
IRB Designee	20
Administrative Designee	20
Consultants/Ad hoc Reviewers	20
IRB Member and IRB Consultant Conflicting Interests	20
Duties of IRB Members	22
Attendance at Committee Meetings	26
Removal of Member	27
IRB Chair and Member Training and Continuing Education Requirement	27
Compensation of IRB Members	28

IRB Member Liability	28
Administrative Support - The Human Subjects Protection Program Office (HSPPO)	28
Study File Documentation	29
Resources	29
<i>VIII. FUNCTIONS OF THE IRB</i>	<i>29</i>
DETERMINATION OF TYPE OF REVIEW	29
Levels of Review	29
Information Provide to Primary Reviewers and Board Members	29
Conducting Initial Review	30
Equitable Selection of Subjects	35
Special Consideration for Projects Involving Vulnerable Populations	35
Determining the decision-making capacity of the subject	37
Determination of who may act as a LAR	37
Students and Employees as Research Subjects	38
Identification of Subjects and Confidentiality	39
The Informed Consent Process	39
Primary Reviewer	44
Consultants	45
Expedited Review	45
Expedited Review Process	46
Exempt Human Subjects Research	49
Establishing Continuing Review Parameters for Approved Protocols	57
Continuing Review Procedures	58
Urgent Review of Applications	60
Revisions Prior to Final Approval	60
Rebuttal or Appeal of IRB Decisions	60
Suspension or Termination of IRB Approval	61
Submission of a Protocol to a Second IRB after Disapproval from another IRB	61
Reporting to Federal Oversight Agencies	62
<i>IX. OPERATIONS OF THE IRB</i>	<i>62</i>
Notification of Meetings and Distribution of Materials	62
Meeting Procedures	63
Auditing Activities	63

Auditing of Research Projects	64
Auditing for Cause	65
X. IRB RECORD REQUIREMENTS	67
IRB Membership Roster	67
Committee Members Coming and Going	67
Meeting Minutes	67
Study File and Minutes Maintenance	68
Record Retention by the IRB	69
Data Retention when Subjects Withdraw/are Withdrawn from Human Subjects Research	69
Data Retention when Subjects Withdraw/are Withdrawn from Human Subjects Research Regulated by the FDA	70
XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB	71
Qualifications for Principal Investigator/Project Director Status	71
The Basic Application	71
Additional Items that may need to be Addressed at Application Submission	77
Investigator as a Sponsor	77
Informed Consent Document	78
Initials and Date On Informed Consent Document	78
Content of the Informed Consent Document	79
Research Related Injury	82
Studies Requiring Cabinet for Health And Family Services (CHFS) IRB Approval	83
Short Form Consent	87
Non-English Consent Forms	87
Non-English Speaking Subjects	87
English Speaking Subjects Unable To Sign Consent Form	88
Process of Obtaining Informed Consent	89
Informed Consent (Assent) with Children	91
Guidance for Investigators for the Use of LAR Consent for Children	91
Waiver of Parental or Guardian Permission	91
Informed Consent with Cognitively Impaired Persons	92
Signing the Informed Consent Document	92
Modifying the Consent Process	93
Waiver of Consent or Elements of Consent	93

Waiver of Documentation of Consent	94
Protocol Changes (Amendments/Modifications), Deviations, Exceptions and Violations	94
Reporting Requirements	96
Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)	97
Additional Investigator Reporting Responsibilities	97
Study Closure	98
XII. EMERGENCY RESEARCH CONSENT EXEMPTION	99
Research subject to FDA regulations	99
Research not Subject to FDA regulations	99
XIII. RESEARCH USING FDA REGULATED PRODUCTS	101
Research involving an Investigational Drug or Device	101
Determination of Need for an IND	102
Determination of Significant Risk (SR) vs. Non-significant Risk (NSR) for Non-Exempt Medical Devices	103
Abbreviated IDE Requirements	104
Responsibilities of an Investigator as a Sponsor for Significant Risk Device Investigations	105
Device Studies in Pediatric Populations	108
Emergency Use Of an Investigation Drug or Biologic	108
Obtaining an Emergency IND	109
FDA Contacts for Obtaining an Emergency IND	109
Emergency Exemption from Prospective IRB Approval	109
Exception from Informed Consent Requirement	110
Emergency Use of Unapproved Medical Devices	110
Requirements for Emergency Use	111
After-Use Procedures	111
Exception from Informed Consent Requirement	112
Reporting the Use of a Test Article (Drug, Biologic or Device) to the IRB	112
Treatment Use of an Investigational Drug or Device	113
XIV. EDUCATION AND TRAINING	116
Educational Activities Aimed at the Community at Large	116
Educational Activities Aimed at the Research Community at Large	116
Educational Activities Aimed at Members of the IRB	116

Educational Activities Aimed at Members of the University Administration	117
DEFINITIONS	118
APPENDIX A: REPORTING SUSPECTED CHILD ABUSE, SPOUSE ABUSE, AND/OR ELDER ABUSE	133
Child Abuse	133
Spouse Abuse	133
Elder Abuse	134
Definitions for this Chapter	134
APPENDIX B: FETAL TISSUE RESEARCH	137
Fetuses and Human In Vitro Fertilization	137
Research Directed Toward the Fetus In Utero	137
Research Involving the Fetus Ex Utero	137
Consent for Research Involving In Utero and In Vitro Fertilization	138
Research Involving Human In Vitro Fertilization	138
Research with Dead Fetuses, Fetal Material, and the Placenta	138
Separating Abortion from Research	138
Prohibiting Payments and Other Inducements	139
Informed Consent	139
Prohibiting Direct Donations	139
Compliance with State and Local Laws	139
Research in Anticipation Of Abortion	139
APPENDIX C: PRISONERS IN RESEARCH	141
Definition of a Prisoner	141
Categories of Research in Which Prisoners May Participate	143
Additional Duties of the IRB	144
Requirements for Studies Funded or Supported by the Department of Justice (DoJ)	145
APPENDIX D: CHILDREN IN RESEARCH	148
Parental Permission and Research of Minimal Risk	148
Parental Permission and Research of More Than Minimal Risk	148
APPENDIX E: MONITORS FOR FDA CLINICAL STUDIES	151
Selection and Qualifications of Monitors	151
Extent and Nature of Monitoring	151
Monitor's Responsibilities	151

Monitoring Procedures	152
Monitoring Report	152
Audit	152
Selection and Qualification of Auditors	153
Auditing Procedures	153
Noncompliance	153
APPENDIX F: INTERNATIONAL RESEARCH	154
HIPAA Considerations in International Research	155
Additional Guidance	155
APPENDIX G: GUIDANCE FOR ADDITIONAL COMPLIANCE REQUIREMENTS FOR FEDERAL AGENCIES OTHER THAN OHRP OR FDA WHO MAY SPONSOR, FUND, OR OVERSEE HUMAN SUBJECTS RESEARCH	156
Department of Defense (DoD)	156
Department of Education (DE)	158
Department of Energy (DoE)	162
Department of Justice (DoJ)	165
APPENDIX H: HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 (HIPAA)	166
HIPAA Authorization for Research Overview	167
Authorization Core Elements (see Privacy Rule, 45 C.F.R. §164.508(c)(1))	168
Authorization Required Statements (see Privacy Rule, 45 C.F.R. § 164.508(c)(2))	168
Waiver or Alteration of Authorization (Complete Waiver or Partial Waiver)	169
Research Uses and Disclosures Under Permissions Obtained Prior to The Privacy Rule's Compliance Date	170
Discussion of Enrollment in Research without an Authorization	170
Call Centers	171
Research Databases	171
De-Identification of Data	172
Permitted Disclosures of Phi	173
Business Associate Agreement	173
APPENDIX I: REGULATIONS AND REGULATORY GUIDANCE	174

I. INSTITUTIONAL AUTHORITY

The University of Louisville (UofL) has demonstrated a commitment to human subject protections by establishing a human subjects protection program lead by a University of Louisville official, the Executive Vice President for Research (EVPR), with sufficient standing, authority and independence to ensure implementation and maintenance of the program.

The University utilizes a centralized program to review all human subjects research. The University of Louisville, at present, operates two Institutional Review Boards (IRBs), Biomedical IRB and Social/Behavioral/Educational (SBE) IRB¹, that review projects in a wide range of medical, biomedical, social, education and behavioral fields. As a part of the University of Louisville's continued commitment to human subjects protections, the resources allocated to the IRB are constantly monitored to ensure the existence of adequate support of IRB functions.²

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:

1. Represents "research," involves "humans" as participants, and "engages" the University of Louisville (as defined in 45 CFR 46.102(d), 45 CFR 46.102(f), and the OHRP guidance document "[Engagement of Institutions in Research](#)" respectively).
2. represents a clinical investigation of a test article involving one or more humans as participants (as defined in 21 CFR 50.3(c), 21 CFR 50.5(j), and 21 CFR 50.5(f) respectively) or individuals (humans) on whose specimens an investigational device is used (21 CFR 812.3(p)) .

[Research](#) is defined in federal regulations³ 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

¹ In the University of Louisville FWA, the Biomedical IRB is named IRB-01-NR (indicating no restriction) and the SBE IRBSBE IRBSBE IRB is named IRB-02-NR (indicating no restriction).

² 45CFR46.103(b)(2)

³ 45 CFR 46

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.

II. PURPOSE

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

The purpose of the UofL IRBs is to:

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

The Human Subjects Protection Program serves its purpose by:

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

III. PRINCIPLES

All human subjects research conducted at the University of Louisville is guided by the ethical principles set forth in *The Belmont Report* and as stated in the University's Federal-wide Assurance document.

IV. THE AUTHORITY OF THE IRB

Scope

All human subjects research carried out at the University or under its auspices must be reviewed and approved by an IRB prior to the start of the research. The IRBs are guided by the principles of *The Belmont Report* and the regulations and policies set forth by the DHHS and its subordinate agencies and offices in reviewing all human subjects protocols.

University of Louisville IRBs review human subjects research projects when:

1. the research is sponsored by the institution or one of its affiliated⁴ institutions,

⁴ The University of Louisville IRBs provide IRB review for Norton Healthcare, Inc., Jewish Health Care System Inc., University Medical Center, Inc., and the Louisville Metro Health Department. See [Relationship with Other Affiliated Institutions](#) on page 5.

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

The IRB chair, vice-chairs or Executive HSPPO management (Director, Assistant Director, or Executive IRB Coordinator), handle requests for confirmation that activities do not constitute human subject research. They use the criteria listed in the [guidance](#) and [charts](#) from OHRP to make this determination.

HSPPO management will only confirm situations that do not constitute human research as described by an investigator if the inquiry is made by phone or e-mail. HSPPO management will not determine activities that constitute human research.

For example, if an investigator describes a study involving purchased, anonymous cell lines, data in the public domain, or discussions of a classroom project that teaches research techniques and may collect some anonymous data that will not be widely disseminated or published outside the classroom, a HSPPO Executive manager may confirm that this does not meet the definition of human research. After discussing situations such as this, the HSPPO staff member involved, if it is clear that human subject research is not involved, may inform the person inquiring that the project, as described, does not constitute human research and does not require an IRB application.

It is the PI's responsibility to maintain documentation of a verbal (phone or in-person discussion) decision. If the PI submits an e-mail description, the request must include sufficient documentation of the activity to support the determination that the research does not meet the definition of human research as listed in 45 CFR 46 or 21 CFR 50. Formal submissions will receive a response by e-mail. E-mail submissions will receive a response by e-mail and a copy of the submitted materials will be scanned and these documents and the determination e-mail will be kept on electronic file in the "Not Human Research" file located at I:\vpresearch\USHC\Correspondence\Not Human Research.

When activities whose status relative to the regulatory definition of research, the involvement of human subjects, or eligibility for exemption may be in doubt, the appropriate University of Louisville IRB will make the final determination of whether or not the activity is human subjects research. To assist the IRB in making these decisions, the IRB may utilize documents and guidance provided by organizations like [CDC](#), the [Oral History Association](#), etc., that may conduct research in these gray areas such as [public health inquiries](#) or [oral history projects](#).

Biomedical IRB

Any biomedical research project involving human subjects, regardless of its source of funding, is reviewed by the Biomedical IRB if it is conducted in or involves patients or staff of the University of Louisville and its research affiliates or it is conducted by faculty, staff, or students in the Schools of Dentistry, Medicine, or Public Health and Information Sciences. This IRB also reviews projects from the School of Nursing when they involve physical, psychological or physiological interventions exceeding minimal risk.

SBE IRB

Any behavioral research project involving human subjects, regardless of its source of funding, is reviewed by the SBE IRB if it is conducted by faculty, staff, or students in the Colleges of Arts and Sciences, Education and Human Development, or Business and Public Administration, or in the Schools of Engineering, Law, Music, Social Work, or Nursing. This IRB reviews projects from the School of Nursing when they involve physical, psychological or physiological interventions that do not exceed minimal risk.

Referral to Other IRB

The chair of each of the IRBs may request that a study scheduled for review by their IRB be transferred to the other IRB if a meeting is cancelled for the IRB scheduled for review, the other IRB may be the more appropriate IRB for review, or if the IRB in question appears to have a conflict with a specific investigator or team of investigators.

Referral to an External IRB

If the University's Oversight Committee for the Management of Institutional Financial Interests in Research (OCMIFIR) identifies an apparent or real financial institutional conflict of interest that may or may appear to affect a proposed research project, the project may be referred to an external IRB for review and oversight. As new institutional conflicts are identified, the OCMIFIR may also recommend the transfer of existing approved projects to an external IRB. In these cases, the recommendation will be communicated with the IRB in order to facilitate the efficient transfer of all documentation without an interruption of research procedures.

Communication with Other IRBs

If a study is referred to an external IRB for review or if the study is reviewed by any other IRB (for example, the NEIRB, WIRB or CDC IRB), the University of Louisville Institutional Review Board(s) may consider signing an IRB Authorization Agreement with the external IRB.

Authority of the IRB

The authority conveyed to the Biomedical and SBE IRBs includes the following:

1. review, approve, and ratify all non-exempt human subject research covered by the Federal-wide assurance in which it is determined that the risks to participants are reasonable in relation to potential benefits to participants and society;
2. Approve pending receipt of specific required modifications. The IRB will draft correspondence to investigators requesting specific modifications to the protocol or the informed consent form. The requested modification must be specific enough to allow the IRB chair to determine whether the responsive materials provided by the investigator match the modifications required by the IRB. The IRB will be informed of these approvals at the next regularly scheduled meeting. When the convened IRB requests clarifications, requests for additional information, or modifications that cannot be described specifically, the protocol will be tabled, pending subsequent review by the convened IRB of responsive material;
3. review and determine the exempt status of new research projects;
4. defer pending further communication between the investigator and the IRB. Studies are deferred when the IRB has substantive concerns or significant requests for clarification. Responses to the IRB correspondence in this category must be returned to the full IRB for deliberation and review;

5. review and disapprove the initiation of new research projects in which it is determined that the risks to participants are not reasonable in relation to potential benefits to participants and society;
6. require from investigators revisions in research protocols and informed consent documents as a condition for initial or continuing approval;
7. monitor the activities in approved projects including regularly scheduled continuing review at least annually, and verification of compliance with approved research protocols and informed consent procedures;
8. develop mechanisms for prompt reporting to the IRB of any planned changes in approved projects prior to the implementation of those changes;
9. develop mechanisms for prompt reporting to the IRB of any adverse experiences occurring in approved projects, or reporting of unanticipated problems involving risks to subjects or others (UPIRTSO), in other projects related in context to the approved projects;
10. suspend or terminate previously approved research;
11. restrict aspects of research for the purposes of human subjects protection;
12. review and monitor the use of test articles (investigational drugs, biologicals and devices) for the purpose of treatment of serious or life-threatening illnesses (Biomedical IRB only);
13. serve as the privacy board of the University of Louisville's hybrid covered entity (HCE);⁵
14. recommend sanctions to the Office of the Executive Vice President for Research (OEVPR) for cases of non-compliance investigated and found actionable by the IRBs;
15. report human research guidelines violations to the appropriate state or federal agency.

Authority of Institutional Officials

The EVPR has the authority to review decisions of the IRB. In the case of an approval decision, should the EVPR conclude that a project does not fully comply with policies or obligations of the University of Louisville, the project may be disapproved, suspended, or terminated on behalf of the institution. In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the EVPR or any other officer or agency of the University of Louisville, state government, or federal government may not reverse the decision. In the case where the Oversight Committee for the Management of Institutional Conflicts of Interest in Research (OCMIFIR) has identified an institutional conflict of interest, the EVPR may refer the study to an external IRB for review and oversight. Affiliated Institutional officials retain the same authority as the University's Institutional Official for their respective organizations. Affiliated institutions will utilize their own internal policies and procedures to manage conflicts of interest unique to their institution.

The University of Louisville Privacy Officer may review the IRB Privacy Board decisions but has no authority over the actions of the IRB. Should the Privacy Officer and the Privacy Board disagree; the Privacy Officer and the Privacy Board will meet and review the research proposal and authorizations. The Privacy Officer and the Privacy Board, in consensus, will determine the appropriate authorization language.

If a project does not fully comply with policies or obligations of the University of Louisville, the project may be disapproved, suspended, or terminated on behalf of the institution.

V. RELATIONSHIP OF UNIVERSITY OF LOUISVILLE IRBS TO OTHER AGENCIES, INSTITUTIONS, OFFICES AND COMMITTEES

Compliance with Federal Regulations

⁵ HIPAA regulations – 45 CFR 160, 162, and 164

The University of Louisville (represented by the Office of the Executive Vice President for Research) has filed a Federal-wide Assurance ([FWA00002211](http://www.fda.gov/oc/ohrt/FWA00002211)) with the DHHS Office for Human Research Protections (OHRP) affirming that the University supports the principles of the *Belmont Report* and is in compliance with DHHS regulations governing the Food and Drug Administration (FDA), OHRP and the signers of the Common Rule. This assurance applies to all research conducted at the University of Louisville and its affiliated institutions involving human subjects regardless of funding source. The full text of the FWA is available in hard copy by contacting the Human Subjects Protection Program Office (HSPPO), and is posted on the HSPPO website⁶.

Based on the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the University of Louisville has designated itself as a hybrid covered entity and is subject to the regulations outlined in 45 CFR 160, 162, and 164. As part of the institution's compliance with the HIPAA Privacy Rule, the IRB has been identified as the Privacy Board.

Relationship with Other Affiliated Institutions

1. **Louisville Veterans Affairs Medical Center.** The University of Louisville and the Louisville Veterans Affairs Medical Center (VAMC) provide dual review for human subjects research conducted at the Louisville VAMC and the University of Louisville by University of Louisville faculty.
2. **Norton Healthcare, Inc.** The University of Louisville's two IRBS provide IRB review and oversight for all human subjects research conducted at Norton Healthcare, Inc.
3. **Jewish Hospital St. Mary's HealthCare, Inc.** The University of Louisville's two IRBs provide IRB review and oversight for human subjects research conducted at Jewish Hospital sites by University affiliated investigators. Research studies by Jewish Hospital affiliated investigators (not otherwise UofL affiliated) are reviewed and overseen by an external IRB.
4. **University Medical Center, Inc.** (including University of Louisville Hospital and the James Graham Brown Cancer Center). The University of Louisville's two IRBs provide IRB review and oversight for all human subjects research conducted at these sites.
5. **Jefferson County Public Schools (JCPS).** When possible, a representative of the Jefferson County Public Schools serves on the SBE IRB. The SBE IRB may provide informal expertise and consultation to the JCPS IRB.

Review of Human Subjects Research Activities by Other University Committees

University of Louisville IRBs coordinate reviews with other institutional committees as described below. None of these committees are a formal part of the UofL IRB structure, but there is communication between the committees regarding status of review and/or conditions of approval. Though other institutional committees share the responsibility for following guidelines in the collective effort to protect human subjects, the final authority for the determination of human subjects research falls on the IRB. Researchers are not required to wait for the approval of the other UofL institutional review committees before submitting a proposal to the IRB. However, IRB final approval will be held until documentation of approvals from other institutional review committees has been forwarded to the IRB. Investigators must submit other required institutional review committee approvals (Institutional Biosafety Committee, Radiation Safety Committee, Committee for the Review of Individual Financial Interests in Research, Oversight Committee for the Management of Institutional Financial Interests in Research, General

⁶ <http://research.louisville.edu/UHSC/>

Clinical Research Center, Clinical Scientific Review Committee, etc.) to the IRB. However, IRB final approval will be held until the investigator forwards documentation of approvals from other institutional review committees to the IRB. For research conducted at the University of Louisville under the University of Louisville IRB oversight, the IRB will review the approved management plan and give final approval to the proposed modification to the research protocol or consent. Research cannot be initiated until receipt of a final approval letter from the IRB.

1. University Radiation Safety Committee (RSC)

The RSC is administratively located in the Department of Environmental Health and Safety (DEHS) and provides expertise with regards to accepted radiation protections regulations and practices. This committee reviews any research that involves the use of X-ray, radioisotopes, or lasers. Approval by the IRB is contingent upon approval by the RSC; however, review by the two committees may occur concurrently.

The RSC is charged with ascertaining that all experimental or research uses of radioactive materials and/or ionizing radiation in or on human subjects conform to the currently accepted radiation protection regulations and practices, and the University of Louisville Radioactive Material License on file with the Kentucky Department of Public Health.

The Director, HSPPO is an ex-officio member of the RSC. The purpose of this appointment is to enhance communication and coordination between the RSC and the IRB to ensure that there is proper oversight and timely approval of all research involving radiation and human subjects. The Assistant Director, HSPPO acts as an alternate ex-officio member of the RSC in the absence of the Director, HSPPO. Either the Director or the Assistant Director will attend all scheduled RSC meetings and report the results of and discussion involving radiation safety and human subject research to the IRB and IRB chair for any necessary action.

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

2. Institutional Biosafety Committee (IBC)

The IBC is administratively located in the DEHS and ensures that research involving recombinant DNA complies with the National Institutes of Health (NIH) guidelines. All such research that is not exempt from NIH recombinant DNA guidelines must be registered with the University of Louisville DEHS. These registration documents are reviewed and approved by the IBC prior to initiation of research. The IBC notifies the IRB of its approval of projects using recombinant DNA, but deliberations of the IBC are not shared with the IRB unless there are specific subject protection issues raised by the IBC. IRB approval is contingent upon IBC approval when the research involves gene therapy.

The Director, HSPPO is an ex-officio member of the IBC. The purpose of this appointment is to enhance communication and coordination between the IBC and the IRB to ensure that there is proper oversight and timely approval of all research involving recombinant DNA and human subjects. The Assistant Director, HSPPO acts as an alternate ex-officio member of the IBC in the absence of the Director, HSPPO. Either the Director or the Assistant Director will attend all

scheduled IBC meetings and report the results of and discussion involving recombinant DNA and human subject research to the IRB and IRB chair for any necessary action.

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

3. Committee for Review of Individual Financial Interests in Research (CRIFIR)

The CRIFIR is appointed by the EVPR and is charged with reviewing cases of individual researchers with a significant financial interest that may affect or appear to affect their research. The committee is composed of faculty members representing various academic and research disciplines and is chaired by an Assistant Vice President for Research. The Committee provides management strategy recommendations to the EVPR. Management strategies that may be considered in addressing conflicts range from no action required other than disclosure, to that of disqualification of the investigator from participating in the project, as well as others. Approved management plans are forwarded to the IRB by the CRIFIR for information purposes and communicate any requirements for disclosure in informed consent documents.

4. Oversight Committee for Management of Institutional Financial Interests in Research (OCMIFIR)

The University of Louisville President appoints the OCMIFIR that operates administratively under the EVPR. The OCMIFIR is made up of two faculty members, one Executive administrator, and various non-affiliated community members, representing diversity of expertise needed to adequately review potential institutional conflicts of interest. This committee reviews cases in which an institutional official or the institution itself holds a significant financial interest that may affect or appear to affect the results of a research project and determines whether the research can be conducted at the University and any resulting management strategies. Management strategies are developed and implemented to address conflicts of interest and to assure that the institution may satisfy any research obligations in an objective manner and to avoid and/or mitigate concerns of bias. Approved management plans are forwarded to the IRB by the OCMIFIR to communicate any requirements for disclosure in informed consent documents or to provide direction that affected research projects must be transferred to an external IRB due to institutional conflict. The OCMIFIR may recommend referral to an external IRB for review, approval and oversight, or determine that the research may not be conducted at the University of Louisville.

5. Clinical Scientific Review Committee (CSRC)

The CSRC reviews all cancer clinical trials at the James Graham Brown Cancer Center. No investigator may have access to Cancer Center shared resources without full approval of the CSRC. All Cancer Center intramural studies, industry trials, or cooperative group studies are required to be sanctioned by the CSRC. IRB approval is contingent upon approval of the CSRC.

Review of Human Subjects Research Activities by Other University Offices

1. Office of Industry Contracts (OIC)

Staff of the HSPPO and the OIC will share contract and study information as necessary for each industry sponsored protocol to ensure that protocol, consent, and contract language are consistent with language required by 45 CFR 46.116 and 21 CFR 50.20 and .25

2. Research Integrity Office (RIO)

Staff of the HSPPO and the RIO share conflict of interests information as well as individual and institutional significant financial conflict of interest management plans. The HSPPO and RIO also work together and share information concerning possible research misconduct and violations of University of Louisville research oversight policies.

3. Privacy Office

Staff of the HSPPO and IRB members often consult with the University Privacy Officer on matters concerning the management of personal health information (PHI) as it relates to the enforcement of Health Insurance Portability and Accountability Act (HIPAA) of 1996 research regulations. Consultation is on an as-needed basis and may be initiated by the IRB, the HSPPO, or the Privacy Officer.

VI. THE MEMBERSHIP OF THE IRB

Appointment and Service of Members

The Executive Vice President for Research, considering advice from the Chairs of the Institutional Review Boards (IRBs) and the Director, Human Subjects Protection Program (HSPP), will appoint IRB members utilizing the following criteria:

1. Each IRB at the University of Louisville will be composed of no less than five and no more than twenty-one members sufficiently qualified through the experience, expertise, and diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
2. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
3. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, the reviewing IRB will include of one or more individuals who are knowledgeable about and experienced in working with these subjects. When reviewing research involving prisoners, the prisoner representative must be present and be a voting member. The prisoner representative must either be the primary reviewer of the protocol or a secondary reviewer whose comments or concerns are documented in the minutes.
4. No IRB will consist entirely of men or entirely of women. Qualified persons of both sexes will be considered so long as no selection is made to the IRB only on the basis of gender.
5. No IRB will consist entirely of members of one profession. Each IRB will consist of members of various professions including at least one scientist, one nonscientist, and one member who is not

otherwise affiliated with the institution, and who is not part of the immediate family of a person who is affiliated with the institution (community member).⁷

6. No IRB member will be knowingly appointed whose institutional responsibilities conflict or appear to conflict, with the primary goals of the IRB. This includes, but is not limited to the employees in the offices and programs under the EVPR (Sponsored Programs Financial Administration, Technology Transfer, Office of Industry Contracts, Office of Sponsored Programs Grants Administration, Sponsored Programs Development, Clinical Research Services and Support, HSPP, or the Research Integrity Program). University employees serving as university counsel, ombudsman, as a voting member of a similar compliance related committee (CRIFIR, OCMIFIR, IBC, RSC, IACUC, etc.), or those university employees responsible for business development are prohibited from concurrently serving as members, alternates, or ex-officio members on the IRBs. Well qualified community members, without any conflict(s) of interest, may serve in a dual capacity on some of the committees (CRIFIR, OCMIFIR) where university employees are not permitted to serve at the same time on both.

The existing UofL IRBs will not review classified research because their membership currently does not meet the minimum qualifications to review classified research.

The length of service for an appointed IRB member will be five years and can be renewed by the EVPR. No more than one fifth of membership may be considered for renewal/replacement each year. If a member resigns prior to the end of their term, a nominee may be appointed to complete the original term. Service on the IRB will be recognized by the OEVP on an annual basis. The recognition will consist of a letter to the member's home department detailing the hours of service for the previous year.

Newly appointed members or alternates are added to the appropriate IRB roster. Copies of revised rosters are sent to OHRP and are filed in the HSPP office.

During the first year of the IRB member's initial term, the IRB chair may assign an experienced committee member to serve as a mentor for the new appointee. This mentor will assist the new member, when requested, in preparing for committee meetings, contacting investigators for additional information, and working through any problems noted with the IRB submission, before the IRB meeting is held.

If the IRB member chooses to continue to serve on the IRB at the end of the five year term, the IRB member will submit a request, to the appropriate IRB chair, to remain on the committee. The IRB chair, in consultation with the Executive Vice President for Research, may extend an invitation for a committee member to remain.

Alternates, if appointed, are designated for a specific member. If both the alternate and the member attend a meeting, only one of these two may vote. In these cases, the minutes reflect who is in attendance as a voting member.

The Executive Vice President for Research may, at the EVPR's discretion, recruit non-voting (*ex officio*) members from among the academic or administrative staff of the University of Louisville or its research affiliates, if their presence at the meetings of the IRB would aid the IRB in conducting its duties. These members may take part in all meetings of the IRB and participate in the discussions but they may not vote on the decisions. Non-voting members are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of non-voting members, Human Subjects Protection Program Office (HSPPO) staff and visitors.

⁷ 45 CFR 46.107, 21 CFR 56.107

Members of the IRB may be removed before the end of their term if their participation in IRB activities is deemed to be inadequate, inappropriate, or damaging to the reputation of the University and its research activities. Removal may be initiated by the EVPR, at the recommendation of the chair of the IRB on which the member participates, or the chair of the member's department or dean of the college or school the member represents.

VII. MANAGEMENT OF THE IRB

IRB Members

The members of the University of Louisville IRBs (regular or alternate) are appointed by the EVPR⁸, to safeguard the rights and welfare of human subjects in research. All IRB members (regular, alternate, and non-voting) will be required to sign a confidentiality and conflict of interest disclosure agreement.

IRB chair

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

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

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

IRB chairs must disclose any conflicts of interest at least annually and notify the OEVP of any changes that occur between annual disclosures. These disclosures will be shared with the OCMIFIR to enable the committee to address any potential situations where an institutional official's individual financial interests could also be considered an "institutional conflict of interest."⁹

The chair votes only to break a tie vote or for the purpose of ensuring that a sufficient number of members eligible to vote are available to have a properly constituted quorum. IRB minutes will reflect that when the chair is not required to vote that the chair abstains from voting.

IRB chairs, vice-chairs, and appropriate HSPPO staff meet on an as needed basis with the EVPR and the Assistant Vice President for Research (AVPR) to discuss any items of concern. IRB chairs and

⁸ in accordance with 45 CFR 46 and 21 CFR 50

⁹ Oversight of Institutional Financial Interests in Research Policy is located at (<http://www.ori.louisville.edu/Policies/Research-policies.htm>)

vice-chairs serve at the discretion of the EVPR. The IRB Chairs performance will be evaluated each year by the EVPR during the University of Louisville's annual performance review period.

IRB Designee

Experienced IRB designees are IRB members with sufficient time served with the IRB and experienced in reviewing submitted research to act in lieu of the chair in reviewing, determining the status of research or approving exempt or expedited research. A chair determines that a member qualifies as an experienced designee by evaluating one or more of the following: a) their qualifications as a researcher, b) IRB service, and c) member knowledge of the regulations and guidance concerning human subjects in research. An IRB designee may, on occasion, act for the chair in situations that require the absence of the chair, i.e., conflict of interest, business emergencies, etc.

Administrative Designee

A chair may designate key members of the HSPPO staff to serve as their designee in the following types of situations:

- a. triage received applications to the chairs for exempt and expedited review;
- b. make assignment of protocols, in consultation with the IRB Chair, to primary reviewers for IRB meetings;
- c. review HIPAA authorizations; and
- d. any other tasks as assigned by the chair(s).

A chair determines that a HSPPO staff member qualifies as an experienced designee by evaluating their knowledge of IRB policies, procedures, regulations, and guidance.

Consultants/Ad hoc Reviewers

At its discretion, the IRB may invite scientists or non-scientists from within or outside the University of Louisville, who have special expertise, to function as consultants and ad hoc reviewers of a project application. Any individual asked to participate, as a consultant/ad hoc reviewer, will be required to sign a confidentiality agreement and declare in writing that they have no conflict of interest or financial conflict of interest in research for each consultation that relates to the protocol that they are asked to review. These individuals have access to all documents submitted to the IRB relevant to the specific project under review, may participate at the deliberations and make recommendations on the project, but may not vote¹⁰.

Consultants/Ad hoc Reviewers will be required to review the information listed in IRB Member and IRB Consultant Conflicting Interests below to determine if they may have a conflict that would prevent them from acting as a consultant.

Consultants/Ad hoc Reviewers are held to the same standards as IRB members when dealing with conflicts of interest of any kind.

IRB Member and IRB Consultant Conflicting Interests

No IRB member or consultant/ad hoc reviewer may participate in the IRB initial or continuing review of any project in which the member/consultant has a conflict of interest, except to provide information requested by the IRB¹¹. In cases where the assigned initial reviewer has a conflict of interest, the

¹⁰ 45 CFR 46.107(f) and 21 CR 56.107(f)

¹¹ 45 CFR 46.107(e) and 21 CFR 56,107(e)

reviewer must declare that conflict of interest and the study application will be re-assigned to another reviewer. The member will be asked to recuse themselves from committee discussions and voting. Minutes reflect that a conflict of interest has been disclosed and recusals required to manage the disclosed conflict are recorded. The type of conflict will be identified in the meeting minutes.

When the member has a protocol for review before the IRB (investigator-member), the member may be present at IRB meetings, like any investigator, only to provide information requested by the IRB. The investigator-member must be absent from the meeting room during the subsequent discussion and voting phases of the review and may not vote (e.g., abstain, approve, defer, disapprove) on the study. The absent member is not counted towards a quorum when the vote on the study in question is taken.

The chair and/or members should not serve as scientific or scholarly merit reviewer of a protocol for their department. In the event it is unavoidable for an IRB member to serve both on a departmental scientific or scholarly merit review committee and as the primary reviewer of the protocol for IRB discussion, the IRB member cannot vote to approve or disapprove the submitted protocol.¹²

The following defines the circumstances under which an IRB member or consultant/ad hoc reviewer is considered to have a conflicting interest:

“Conflict of interest” refers to a divergence between an individual’s personal financial, relational, or other interests and his/her professional obligations to the University of Louisville – whether through teaching, involvement in research, contracting, purchasing, or performing other administrative duties -- such that an independent observer might reasonably determine that the individual’s professional actions or decisions are, or potentially could be adversely affected, distorted or otherwise compromised by the individual’s personal interest. The term conflict of interest is broader and encompasses more professional activities than the term financial conflict of interest in research, defined below, which is the subject of this policy.

“Financial conflict of interest in research” is the existence of a significant financial interest that an independent observer might reasonably determine affects or compromises, or appears to affect or compromise, the design, conduct, reporting or management of research.

1. Interests of IRB members, consultants/ad hoc reviewers and their immediate families with the same financial interest as an investigator would cause the IRB to consider this a conflict of interest.
2. “Immediate Family Member” means any individual having a relationship to a person (whether by blood, law or marriage) as spouse, parent, child, grandparent, grandchild, stepchild, or sibling.
3. Financial and non-financial criteria may include but are not limited to;
 - a. Is a member of the research team;
 - b. Has a financial interest in the research with value that cannot be readily determined;
 - c. Has a financial interest in the research with value that exceeds a specified monetary threshold (\$10,000);
 - d. Has received or will receive compensation with value that may be affected by the outcome of the study;
 - e. Has a proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement;

¹² Department chairs are requested not to utilize IRB members from their departments as scientific or scholarly reviewers of protocols submitted to the IRB for review and approval.

- f. Has received payments from the sponsor that exceed a specified monetary threshold (\$10,000) in the past year;
- g. Has ownership interest (equity or stock options) of any amount when the value of the interest would be affected by the outcome of the research;
- h. Has compensation of any amount when the value of the interest would be affected by the outcome of the research;
- i. Is an executive or director of the agency or company sponsoring the research; or
- j. Has an interest that the IRB or the IRB member believes conflicts with his or her ability to objectively review a protocol;
- k. Has an interest that the IRB or IRB member or others perceive may conflict with his or her ability to objectively review a protocol.

How are conflicting interests identified?

1. It is the responsibility of the member to declare any real or perceived conflicts of interest (as previously described) he/she may have at least annually or within 30 days of a change in status.
2. It is the responsibility of the consultant/ad hoc reviewer to declare any real or perceived conflicts of interest (as previously described) he/she may have prior to initiating any requested review.

Describe the actions taken when an IRB member declares a conflicting interest:

1. An IRB member with a conflicting interest may be in the meeting room only to provide information requested by the IRB.
2. An IRB member with a conflicting interest will be asked to leave the meeting room before voting and/or discussion unless asked specifically to remain for providing information. In any case, the IRB member must leave the room prior to the vote.
3. If an IRB member declares a conflicting interest, that interest is documented in the minutes indicating the nature of the conflict. The minutes will note that the member declared the conflict and left the room prior to vote and/or discussion. If the member is asked specifically to remain for providing information, the minutes will note that the member remained during discussion at the request of the IRB for the purpose of providing information requested and then left the room before the vote.

Describe the actions taken when a consultant declares a conflicting interest:

A consultant/ad hoc reviewer with a conflicting interest may not provide information to the IRB.

Other requirements:

1. The name of the person with a conflicting interest must be recorded in the IRB meeting minutes for each applicable vote.
2. IRB members with conflicting interests cannot count towards quorum.
3. IRB members and consultants/ad hoc reviewers will follow the same University of Louisville [*POLICY FOR OVERSIGHT OF INDIVIDUAL FINANCIAL INTERESTS IN RESEARCH*](#) as researchers at the University.

Duties of IRB Members

Duties of members include reviewing human subject application materials in advance of meetings and being prepared to discuss issues related to human subjects protections, serving as primary reviewer

when requested by the chair, and having an understanding of the specific requirements of human subjects regulations. Member duties include:

1. Protecting the rights and welfare of research subjects.
2. Determining that risks to subjects are minimized.
3. Ensuring that the investigators:
 - a. use procedures that are consistent with sound research design and that do not expose subjects to risk,
 - b. whenever appropriate, use procedures already being performed on the subjects for diagnostic or treatment purposes, and
 - c. ensuring that the investigator follows a procedure for properly documenting informed consent (IRB members are encouraged to review chapter 4, Informed Consent in the University of Louisville Investigator's Guide for a comprehensive review of the informed consent process).
4. Determining that risks to the subjects are reasonable in relation to the anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB member should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB member should not consider possible long-range effects of applying knowledge gained in the research.
5. Determining that selection of subjects is equitable. In making this assessment, the following should be taken into account:
 - a. the purpose(s) of the research and the setting in which it is conducted.
 - b. the IRB members should be particularly cognizant of special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.
 - c. Women and members of minority groups and their subpopulations must be included in all clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the IRB that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.
 - d. The inclusion (recruitment process) of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

6. Determining if the informed consent is adequate and contains all other federally or locally mandated elements, and if not, request clarifications and changes in the consent form in order to adequately explain the purpose of the research, the risks and benefits entailed therein.
7. Determining that the research plan makes adequate provision for ensuring the safety of the subjects.
8. Determining that there are adequate provisions to protect the privacy of subjects and to maintain the privacy of the subjects and confidentiality of the data, in accordance with the DHHS and FDA regulations.¹³ Investigators who conduct research under the direction of the University of Louisville must develop a plan for each protocol submitted to protect the privacy and confidentiality of subjects. The conditions for maintaining confidentiality of the subjects and the research records are required for the life of the data. The assigned protocol reviewer is responsible for assessing the efficacy of the plan. The reviewer should assess the adequacy and comment in the *"IRB REVIEWER FORM INITIAL OR CONTINUING REVIEW"* on the ability of the investigator's plan to protect:
 - a. **Identifiable Personal Information** - No single item (except possibly a person's Social Insurance Number, which by law cannot be used except for very specific circumstances) can be relied upon to identify an individual with certainty. Names, addresses or telephone numbers may more directly identify an individual than postal codes, date of birth, age, occupation, initials, hospital or student number, ethnic group or religion. Although individual items may not by themselves permit identification of an individual, taken together in a given context and with a certain amount of effort and use of other sources, a combination of items may allow an individual to be identified. This means that all items of information relating to an individual may have the potential to identify that individual.
 - b. **Privacy** - Researchers have a duty to respect the privacy of prospective subjects. That is, the researcher allows the research subject to determine when, how, and to what extent information about him or her is communicated to others. Researchers usually protect an individual's right to privacy by obtaining free and informed consent before collecting personal information about him or her. The act of contacting potential subjects to seek free and informed consent to access private information may constitute a breach of privacy if the investigator does not have access to such individuals in the course of his or her usual professional activities. In general, someone the research subject would think has a reason to know why he or she might participate in the study should be the first to approach the research subject.
 - c. **Confidentiality** - Researchers have a duty to respect the confidentiality of personal information collected during research. Research projects vary substantially in the sensitivity of the information involved, the possibility of identifying particular individuals, and the magnitude and probability of harms that may result from identification of research subjects. Breaches in confidentiality may also have a negative impact on family and friends or the group to which the research subject belongs. A Certificate of Confidentiality may be considered to protect study data from disclosure of identifying information that could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. More information about the Certificate application may be found on the [NIH COC kiosk](#).

The researcher has a duty to protect research subjects from harm through unauthorized release of identifiable personal information. Confidentiality safeguards include assigning

¹³ 45 CFR 46, 160, 164 and 21 CFR 50

each research subject a code number and using that number on all data about the subject, and the use of locked rooms and filing cabinets for storage of data.

- d. **Anonymity** - When information collected through research is disseminated, research subjects normally are anonymous, unless identification has been agreed to or requested by the research subject. Often, data are presented in aggregate form, which also reduces the potential to link specific responses to individuals.
- e. **Limits** - In some instances, research results may be disclosed to the government, government agencies, the research sponsor, the IRB or its designees, a regulatory agency, or those individuals who may be responsible for financial oversight at the institution where the research is conducted. State statutes may require reporting of child abuse, sexually transmitted diseases, intent to murder, or suicidal thoughts. Additionally, in the cases of well-known individuals, those with very rare conditions, or research that requires presentation of photographs or videotapes, it may be impossible to present the data without identifying the research subject. Research subjects need to be aware of any limitations to anonymity in these situations.

In other cases, research records may be liable to subpoena in judicial and administrative proceedings, and data may be vulnerable to search warrants. Because researchers have a duty to protect the confidentiality undertaken in the free and informed process to the extent possible within the law, it is legitimate for the researcher and the institution to argue the issue in court. In fact, this may be the only legal option open to a researcher to protect the confidentiality of research data.

- f. **Plan Assessment** - The reviewer should summarize the investigator's plan and indicate, in the reviewer's opinion, whether or not the plan provides adequate physical protection of the data and subject's privacy. There are no absolute protections. For example, the plan should indicate that the data is coded or de-identified, that the subject's PHI is protected and only PHI and data necessary for the research is collected and retained, data is stored in a secured area or pass word protected computer and locked in a space that only the investigator or key study personnel who have a need may access. Other means of security may be identified or required dependent on the nature of the research and the sensitivity of the data collected.
9. Ensuring additional safeguards are in place to protect the rights and welfare of subjects that are likely to be vulnerable to coercion or undue influence, such as children, students, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.^{14,15}
 10. Before the IRB meeting, the IRB member should:
 - a. Review all required documentation in the application submission package before the assigned project(s) is/are presented.
 - b. Discuss any questions about the assigned projects with the investigator, other IRB members, or consultants prior to the IRB meeting.
 - c. Decide whether the investigator should attend the meeting to discuss any problems or concerns noted with the project.
 - d. Determine if specific changes are needed in the application, protocol or consent form, and come to the meeting with recommended wording to be transmitted to the investigator.

¹⁴ 45 CFR 46.111(a)

¹⁵ 21 CFR 56.111(a)

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

Attendance at Committee Meetings

Biomedical IRB meetings are held the first, third, fourth, and sometimes the fifth (determined by workload) Thursday of each month beginning at 12:15 PM EST. If a committee meeting date falls on a scheduled University holiday, the meeting will be rescheduled at a time more convenient for committee members and HSPPO staff. In December of each year, the list of committee meetings to be held in the New Year and submission deadlines are published on the HSPPO website. Additional committee meetings may be scheduled if necessary.

SBE IRB meetings are held the first Wednesday of each month beginning at 12:30PM EST. If a committee meeting date falls on a scheduled University holiday, the meeting will be rescheduled at a time more convenient for committee members and HSPPO staff. Additional committee meetings may be scheduled if necessary. Meetings may be canceled if no business requiring full board review is pending.

Copies of all applicable regulations are available for reference at every convened meeting of the IRB.

Educational IRB meetings may be held the second Thursday of every other month. All IRB members, Biomedical and Behavioral, are invited to attend. These meetings are organized to allow time for training, policy development and discussion of current issues identified in regular IRB meetings.

Regular committee members are expected to attend each scheduled committee meeting. The IRB welcomes alternate members to attend all committee meetings and copies of the agendas and meeting materials will be sent to all members and alternates who have indicated a desire to attend all IRB meetings.

If a situation arises where the committee member cannot attend, and the member has been assigned as a primary reviewer for the meeting, the member should contact the HSPPO and request that the project be reassigned to another primary reviewer. A primary reviewer unable to attend and failing to notify the HSPPO will cause the study review to be delayed until the following meeting. Unless reassignment is requested, the primary reviewer is expected to present the study at the next regularly scheduled meeting.

IRB members are encouraged to attend as many committee business and educational meetings as their schedule will allow. If a member cannot attend a scheduled meeting, the member is encouraged to notify the IRB coordinator assigned to the committee on which he/she participates and let them know that they will be unable to attend the scheduled meeting.

In order to begin an IRB meeting, a quorum of members must be present. A quorum is defined as one more than half of the appointed committee members. A qualified alternate serving for an absent member is counted as a member present. Those present must include one member whose primary concerns are in a nonscientific area.¹⁶ The quorum should have at least one unaffiliated member and one member who represent the general perspective of subjects present at convened meetings.

¹⁶ 45 CFR 46.108(b)

Members who represent the general perspective of subjects, the unaffiliated member, and the non-scientific members may be the same person, or may be represented by two or three different persons. When the convened IRB reviews research involving prisoners, the prisoner representative must be present.

Any actions taken at a meeting without the presence of a nonscientist or more than half of the IRB members are considered invalid. Should the quorum fail during a meeting, the IRB may not take further action or vote unless the quorum is restored.

Removal of Member

When a committee member consistently fails to attend IRB meetings or fails to meet expectations, the IRB chair and Director, HSPP, meet with the committee member to determine the cause. If the IRB member indicates an inability to continue to function effectively as an IRB member, the IRB chair or Director, HSPP, will work with the Dean and/or department chair in obtaining a replacement member to serve on the IRB. Members who do not adequately fulfill their responsibilities, as judged by the IRB chair, may be asked to step down from IRB membership by the Executive Vice President for Research.

Members of the IRB may be removed before the end of their term if their participation in IRB activities is deemed to be inadequate, inappropriate, or damaging to the reputation of the University and its research activities. Removal may be initiated by the EVPR, at the recommendation of the chair of the IRB on which the member participates, or the chair of the member's department or dean of the college or school the member represents.

IRB Chair and Member Training and Continuing Education Requirement

Once an IRB member has been appointed, the IRB member will meet with the IRB chairs and Director, HSPP, to learn about IRB forms and IRB review guidelines, and to receive an IRB member guide and policies and procedures manual. IRB members must fulfill the same training requirements expected of human subjects researchers at the University of Louisville within one year of appointment¹⁷.

IRB members are encouraged to attend one other local or regional IRB educational meeting during the course of each calendar year.

The HSPPO staff will prepare an application form for the IRB member to join the Applied Research Ethics National Association (ARENA), the membership arm of Public Responsibility in Medicine and Research (PRIM&R). This is a national association for IRB members and administrators. Annual dues for this organization will be paid for by the HSPPO.

New IRB members will be expected to attend new member offerings in their first year attending the ARENA/PRIM&R meetings. IRB members are strongly encouraged to attend the annual ARENA/PRIM&R meetings held each fall. Cost for attendance at these two meetings (held back-to-back) is a HSPPO expense. IRB members will be required to follow appropriate University travel regulations in order to obtain reimbursement for their travel to these meetings.

IRB members are provided educational reading material and opportunities for discussion at the majority of IRB meetings. Materials are circulated with the meeting agenda and are discussed at the beginning of the meeting. After discussion, each member present completes a short quiz. The HSPPO staff maintains a log of participation in this educational opportunity.

¹⁷ Effective March 1, 2004, current IRB members must complete the CITI Core Course commiserate with their committee assignment. In cases of members with dual appointments, the training may be staggered over two consecutive years.

The HSPPO also maintains a small library of materials that includes the OHRP Institutional Review Board (IRB) Guidebook, the *Belmont Report*, and other books and videotapes discussing ethical and regulatory issues relating to human subjects research. These materials are available to the entire campus community.

Compensation of IRB Members

Community members, who are not compensated by their sponsor or employer, will be paid for their service on the IRBs at the rate of \$25.00 per hour, unless waived by the committee member.

IRB Member Liability

IRB members function as employees and/or agents of the University of Louisville. As such, when acting in accordance with the University of Louisville IRB's Standard Operating Procedures, their actions are covered by the University of Louisville general liability coverage. Community members when acting in accordance with the University of Louisville's IRB Standard Operating Procedures are covered either by 1) the University of Louisville's general liability coverage or 2) by insurance from the other affiliated institutions.

Administrative Support - The Human Subjects Protection Program Office (HSPPO)

The University of Louisville Human Subjects Protection Program Office (HSPPO), a unit within the Office of the Executive Vice President for Research and reporting directly to an Assistant Vice President for Research, has been established to support the IRB process. The Human Subjects Protection Program Office:

1. assists in preparing agenda for and monitoring IRB meetings;
2. maintains files on all human subjects research (including copies of all correspondence between the IRB and investigators) that takes place at the University of Louisville;
3. maintains databases for tracking studies;
4. prepares meeting minutes;
5. maintains files of minutes of full board and subcommittee meetings;
6. screens research applications for completeness prior to initiating the IRB review process;
7. acts as a resource for investigators on general regulatory information, guidance with forms, and assistance in preparing an application for IRB review;
8. maintains the institution's Federal-wide Assurance and the IRB membership rosters;
9. provides staff support to the IRBs for all written correspondence;
10. sends notices of approval, study closure (other than closure of the study by the investigator), and termination;
11. generates and sends reminder notices to investigators of upcoming continuing reviews;
12. maintains information on federal regulations relating to human subjects research;
13. provides education regarding the IRB process and regulations to the University community;
14. provides education opportunities to IRB members;
15. maintains records of IRB membership including training;
16. conducts quality assurance and quality improvement for the HSPP;
17. assists in preparing and providing educational opportunities to subjects, prospective subjects, or their communities, to enhance their understanding of research involving human subjects.

All HSPPO staff will be required to complete a confidentiality agreement.

Study File Documentation

All documentation generated by IRB members or HSPPO staff and placed in a study file will be signed by the originator and dated. The use of post-it notes is discouraged but not prohibited. All other documentation required to be signed in the file should have either the principal investigator’s or key study personnel’s signature or initials on the document.

Resources

The University provides adequate facilities and equipment to support the operation of the IRBs and HSPPO in performing the functions described in this document. The HSPPO staff reviews and states resources needs and prepares an annual budget for review and approval by appropriate University of Louisville officials.

VIII. FUNCTIONS OF THE IRB

The IRB fulfills its function by adhering to federal regulations regarding the function and operations of IRBs.¹⁸ The HSPPO provides administrative support for the IRB in fulfillment of its function and operations. As noted, the IRB reviews proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in the nonscientific areas. In order for the research to be approved, it must receive the approval of a majority of those members present at the meeting. The IRB follows the criteria for review and approval of research as stated in federal regulations.¹⁹

DETERMINATION OF TYPE OF REVIEW

Levels of Review

The UofL IRB designates the chair or chair’s designee to review the entire application and make determinations as to whether a project constitutes human subjects research and, if so, the type of review (full board review, expedited review, or exempt). All applications are assigned to full board review unless they meet the criteria for exemption or being expedited. 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 either utilizing the appropriate paper Reviewer Form or the Protocol Review process in the BRAAN2 software.

Information Provide to Primary Reviewers and Board Members

	INITIAL REVIEW	CONTINUING REVIEW	FULL BOARD AMENDMENT
REVIEWER MATERIALS	A full copy of the submission containing; application, scientific review, Multi Institutional Research Application (MIRA), synopsis, consent(s), HIPAA documents, protocol,	A full copy of the submission containing; the progress report form, summary sheet of the last year since last review (filled out by the IRB Coordinator), study synopsis, full protocol, training	A full copy of the submission containing; the amendment request form, summary of amendment from the sponsor, full revised protocol, and revised

¹⁸ 45 CFR 46.103(B)(4) & 21 CFR 56.108(A) & (B)

¹⁹ 45 CFR 46.111 & 21 CFR 56.111

	Investigational Drug or Device Brochure (if applicable), advertisements, SAE's submitted, 1572 (if applicable), grant application (if applicable) training certification, CV's, and any other documents that might be required depending on the research.	certification, any recent literature related to the research, copies of the last 5 signed consents and research authorizations from their subjects, new consent(s) to approve for the upcoming year, and the whole file to have for the review.	consent(s) and HIPAA document(s) (if any).
BOARD MEMBER MATERIALS	A copy of the; Application, scientific review, billing table from the MIRA, study synopsis, consent(s), and HIPAA documents.	A copy of the; Progress report form, the summary sheet of the last year since last review (filled out by the IRB coordinator), study synopsis, and new consent(s) to approve for the upcoming year.	A copy of the; Amendment request form, sponsor's amendment summary, and revised consent(s) and HIPAA document(s) (if any).

Conducting Initial Review

The Institutional Review Board will consider the following when reviewing requests to involve human subjects in research:

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 study²⁰.

Considering Risk

Assessing risk is an important component of the review process. As stated earlier, one aspect is to ensure that risks have been minimized, risks are appropriate given the expected benefits, and benefits are maximized. Each greater than minimum risk protocol submitted must contain a data and safety monitoring plan (DSMP) detailing how confidentiality is protected and, to the extent possible, risks are reduced to a minimum. This plan does not need to be complicated but should be appropriate for the risks associated with the study.

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

²⁰ Payment for participation in research is not considered a benefit.

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.

For detailed information regarding the definition and differing requirements for SR and NSR devices, as well as a partial list of devices considered by the FDA as SR and NSR, please see the [FDA](#), that is available in your member packet and on-line.

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 overstating 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.

Special Consideration for Projects Involving Vulnerable Populations²¹

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 protections²². 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.

The IRB considers for approval research projects involving vulnerable populations if one of the following conditions is met:

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

²¹ 45 CFR 46, Subparts B, C and D

²² 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.

- 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.

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. The IRB chair or designee will assign the primary reviewer.

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 following guidance provides direction on obtaining from a Legally Authorized Representative (LAR)²³ decision maker the valid informed consent to participate in research for a subject who is a child, cognitively impaired, lacks capacity, or suffers a serious or life-threatening disease.

LAR consent for participation in a research study should be employed only to the extent that it is consistent with the intent of 45 CFR 46, 45 CFR 46 and 21 CFR 50 and all other federal and state laws and regulations pertaining to protecting human subjects participating in research.

While no specific set of criteria can encompass all conceivable situations in which the use of LAR consent complies with the intent of 45 CFR 46 and 21 CFR 50, the following criteria should be viewed as fundamental guidelines to be used by the UofL IRBs when determining whether to permit the use of LAR consent for participation in a research study.

- a. LAR consent should be considered only in research studies relating to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research subject.
- b. LAR consent is a protocol-specific request of the investigator, and must be reviewed and approved accordingly by the IRB.

²³ Informed consent by a subject is one of the key cornerstones of the system protecting human subjects in research. It has traditionally been recognized that consent by someone other than the subject is not the same as the subject's own consent. There are instances, however, in which a subject may be unable to consent. [Federal regulations](#) allow for consent by the individual or his/her Legally Authorized Representative (LAR). LAR means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Therefore, researchers, as suggested by University of Louisville legal counsel, are encouraged to utilize the same decision process to determine a LAR for research as would be utilized to determine a LAR for medical care (see footnote 42). Consent by a LAR should involve all the same considerations that informed consent from a competent subject involves. It also involves identifying a proper representative and ensuring to the extent known that the research decision reflects the wishes of the subject.

- c. LAR consent is requested through the application process for new research studies or through the modification process for an existing protocol.
- d. As in all human subjects research, the IRB must consider carefully the risk/benefit ratio of the particular study for the targeted population.
- e. As with all mental health research conducted by the University, subject confidentiality and privacy must be protected.
- f. The IRB may consider whether the frequency of a specific protocol's review cycle should be reasonably modified when LAR consent is implemented.
- g. The IRB application/amendment form should detail the criteria under which LAR consent may be sought.

The investigator shall include a protocol-specific plan for the assessment of the decision-making capacity of the subject in the protocol or amendment request. If the investigator determines that the subject lacks decision-making capacity, the investigator shall, consistent with the standard consent process 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.

Determining the decision-making capacity of the subject

Whenever possible, investigators will attempt to obtain informed consent directly from the subject.

The application reviewed by the IRB must detail a protocol-specific plan for the assessment of the decision-making capacity of the subject that will be conducted by the investigator for any subject who may qualify for LAR consent. While there are no standardized measures for determining capacity to consent, subjects may be assessed on their ability to understand and to express a reasoned choice concerning the:

- a. Nature of the research and the information relevant to his/her participation;
- b. Consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- c. Consequences of the alternatives to participation.

The capacity to understand all of these concepts may not be necessary in order to consent to participate in a particular research protocol -- greater capacity is required for higher-risk protocols. This standard should be used for determining the capacity of the LAR as well, if necessary.

In protocols in which a LAR's consent has been approved by the IRB, assessment of the decision-making capacity of the LAR should be implemented only when the investigator has reason to believe that the LAR's decision-making capacity may be impaired.

Determination of who may act as a LAR

In a non-emergency room environment, LAR consent may be obtained from any of the following potential LARs who has reasonable knowledge of the subject, in the following descending order of priority:

- a. The judicially-appointed guardian of the person, if the guardian has been appointed and (for biomedical research) if medical decisions are within the scope of the guardianship;

- b. The attorney-in-fact named in a durable power of attorney, if the durable power of attorney (for biomedical research) specifically includes authority for health care decisions;
- c. The parent or spouse of the person;
- d. If the person is incompetent, an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation;
- e. The nearest living relative of the person, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives.

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:

- a. Posting IRB approved advertisements throughout the university to recruit subjects from a broad base of students.
- b. Offering students the opportunity to participate in "mass screenings" with follow-up with those who meet research criteria. It should be clearly stated that participation in the screening, as well as participation in the research is voluntary.
- c. Avoiding any personal solicitations by students, faculty, GTAs or RAs for fellow students or faculty.
- d. Providing a number of research projects from which to chose, if participating as a research subject is a course requirement.
- e. Providing alternative and equal methods for meeting course credit (or extra credit) requirements, such as attending a series of research presentations by faculty, writing a brief paper, 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.

Identification of Subjects 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.

The Informed Consent Process

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.

The FDA, but not HHS, provides for an exception from the informed consent requirements in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in 50.23. Accordingly, the IRB carefully reviews the consent process and consent

documents. In considering a consent process, a reviewer should bear in mind the requirement that consent should be sought only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate, and that minimize the possibility of coercion or undue influence. The information that is given or orally communicated to the subject or the representative shall be in language understandable to the subject or the representative (6th-8th grade level). Informed consent, whether oral or written, may not include any exculpatory language, through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights. It may also not release or appear to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Qualifications

The IRB will examine the Review of Scientific or Scholarly Merit Form and other qualifications of investigators. Procedures requiring special skills on the part of the investigators, licensure, accreditation, and/or experience in qualifying the investigator for the performance of the proposed procedures are reviewed by the IRB. In addition, the IRB will consider the facilities and equipment used to conduct the research and maintain the rights and welfare of subjects.

Additional Review

The IRB will determine whether a project requires more than annual review and may require an appropriate monitoring procedure that could include monitoring of the consent process, observation of the research procedures, formulation of a data and safety monitoring plan, and review of research related records. In some instances, the IRB may refer review of the research to an additional committee. However, final authority for additional review lies with the IRB.

Conflict of Interest

A conflict of interest refers to a divergence between an individual's personal financial, relational, or other interests and his/her professional obligations to the University of Louisville whether through teaching, involvement in research, contracting, purchasing, or performing other administrative duties such that an independent observer might reasonably determine that the individual's professional actions or decisions are adversely affected, distorted or otherwise compromised by the individual's personal interest. The term conflict of interest is broader and encompasses more professional activities than the term financial conflict of interest in research, defined below, the identification and management of which is the subject of this section of the IRB Standard Operating Procedure (SOP).

Financial Conflict of Interest in Research

Financial conflict of interest in research is the existence of a significant financial interest that an independent observer might reasonably determine could affect or compromise, or appears to affect or compromise, the design, conduct, reporting or management of research. The effect or compromise contemplated might relate to the collection, analysis, and interpretation of data, the hiring of staff, the procurement of materials, the sharing of results, the choice of protocol, the involvement or consenting of human participants, and/or the use of statistical methods.

Payment for Subject Participation In Research

The nature, amount, and method of payment or other remuneration should not constitute undue inducement to participate (i.e., the payment should not serve as sufficient inducement for the subject to volunteer). The IRB will consider the impact participation poses on the daily life of the

potential subject. For example, the IRB will consider reimbursement of subjects for inconvenience posed by the research, such as: the time required to participate; travel involved and/or parking costs; lost time from work, babysitters, etc. Investigators should include provisions in the protocol for addressing these concerns, especially for research that poses little or no direct benefit for the subjects.

Special precautions should be taken when payment is offered to a third party for the participation of someone else in the research. The IRB is concerned that such payments may constitute undue coercion from the third party to the actual research participant. For example, a parent may be offered remuneration for volunteering their child to participate in a research project. In these cases, precautions should be taken to clearly separate the payment to the third party from the consent/assent process with the actual research participant. Final approval for participation rests solely with the research participant and their consent/assent takes precedence over that of the person to whom payment is offered.

Since subjects reserve the right to withdraw their participation from the research without prejudice, payment to subjects should be prorated, i.e., partial participation in a research activity would obligate partial payment. The IRB will review both the amount of the payment, to whom it is offered, and the proposed method of disbursement to ensure that payment for participation does not constitute coercion or undue influence. Investigators should explain the payment schedule in the informed consent document.

Payment for Research

Finder's fees and other financial incentives paid by a sponsor or by an investigator to others related to the recruitment of research subjects are prohibited. No one may receive any incentive for the purpose of encouraging individuals to participate in research. All payment by sponsors for research conducted under the auspices of the University of Louisville must be made directly to the University of Louisville Research Foundation, Inc. (ULRF) or the University of Louisville and will be managed by the Foundation or University. Payments should never go directly to investigators, key personnel or subjects without first going through the ULRF or the University.

Surveys, Questionnaires, Interview Materials, or other Testing Instruments

These materials may be in written or electronic format. If electronic, investigators should provide a hardcopy of the material. These materials should be reviewed to ensure that they adequately reflect the purpose and procedures in the study and handle sensitive issues appropriately. If the materials ask for information that, according to local law, would require reporting (e.g., elder or child abuse), the consent form should explain this exception to the promise of subject confidentiality. There are, however, a variety of psychological and other measures that are considered "standard" and, while they cannot be modified, reviewers should still indicate if use of a given measure is appropriate for a particular study. In particular, reviewers should consider if survey answers, if known, would impact a subject's reputation, insurability, etc.

The No Child Left Behind Act of 2001(Public Law 107-110)²⁴ identified eight categories of protected information for survey, questionnaires, interview materials, or other testing instruments responses:

1. political affiliations of student or student's parent;

²⁴ <http://www.ed.gov/policy/elsec/leg/esea02/pg122.html>

2. mental or psychological problems of student or student's family;
3. sex behavior or attitudes;
4. illegal, anti-social, self-incriminating or demeaning behavior;
5. critical appraisals of others with whom students have close family relationships;
6. legally recognized privileged or analogous relationships;
7. religious practices, affiliations or beliefs of student or student's parent; and
8. income.

Research involving any of the eight identified categories requires written parental informed consent prior to participation of a child, even if the research meets the exempt criteria.

Deception or Withholding Information

The basic principles that guide the ethical conduct of research, as previously outlined in “*The Foundations of 45 CFR 46: [The Belmont Report](#)*” are (1) respect for subjects, (2) beneficence; and (3) justice. The requirements for complete informed consent strongly favor comprehensive, honest, and understandable disclosure of all elements of the subject’s participation in research. There are times, however, especially in behavioral research, when investigators plan to withhold information about the real purpose of the study or purposely give subjects false information about some aspect of the research. As a result, the subject cannot give prospective fully informed consent. The use of deception or incomplete disclosure imposes special responsibilities on the investigator and the IRB. Occasionally, a study will involve degrees of deception. Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results, can be acceptable, provided the subject is fully debriefed after participation. Risks stemming from major deception, such as leading the subject to believe that she/he has committed a crime or has a disease, must be clearly counterbalanced by the benefits of the research.

The Federal regulations do not allow the IRB to waive some or all of the elements of informed consent, including a fair and comprehensive description of all elements of the research, if the study involves more than minimal risk. In addition, the waiver of the elements of consent must not adversely affect the rights and welfare of subjects, and must be essential to the ability to carry out the research.

Incomplete disclosure or the use of deception cannot be used as a means to secure the participation of subjects in research. The IRB may not approve research that entails more than minimal risk and withholds information that is material to the subject’s decision to participate in the study. The IRB is required to consider whether the withheld information would influence the decision of potential subjects to participate in the research. The IRB cannot approve a study that presents more than minimal risk where subjects are deceived or not given complete information that they would consider material to the decision to participate.

Use of Deception

The employment of deception by an investigator(s) for the purpose of securing subject participation and/or to prevent potentially biased reporting of data/information by the subject is permissible provided all of the following conditions exist:

- a. Deception is necessary due to the lack of alternative procedures for data collection not involving deception;
- b. The deceptive procedures will not place subjects at significant financial, physical, legal, psychological, or social risk;

- c. The data collection/experiment will be followed by careful debriefing sessions whereby the subjects are fully informed of the nature and purpose of the deception; and
- d. The procedures for deception must meet the guidelines established by the discipline of the investigator through its professional code of ethics.

Debriefing

In order for the IRB to adequately review the research, investigators should justify, in detail, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of: (a) the necessity for deceiving subjects; (b) how potential benefits of the research justify the use of deception; and (c) how the investigators will conduct the debriefing. In addition, investigators should include a debriefing script or statement that indicates the information subjects will receive regarding their participation in the research.

The IRB in collaboration with the investigator will determine whether subjects should be debriefed either after unwittingly participating in the research or after knowingly participating in research that involved deception. The IRB may require debriefing when it contributes to the subject's welfare, i.e., when it corrects painful or stressful misperceptions, or when it reduces pain, stress, or anxiety concerning the subject's performance. For example, if a subject is lead to believe through participation in deception research that she/he has committed a crime or has a disease, a debriefing session may correct the induced stress, pain, and/or anxiety.

Recruitment Tools

Recruitment tools (advertisements, etc.) are not approved or valid without an IRB approval stamp containing the approval and expiration dates. Audio and video tools may be excepted from this requirement. When reviewing recruitment tools the IRB must review the final mode of its communication, including the final copy of printed advertisements and the final audio or video advertisements.

Only IRB approved advertisements, considered fair, honest and appropriate by the IRB, may be used in the conduct of subject recruitment. Recruitment materials should be included with your initial and continuing review applications. If the material is not ready at the time of the initial application, investigators may submit the material as an amendment to an already approved project. Requests for approval of recruitment materials following initial IRB review of the protocol should allow sufficient time for any necessary revisions prior to publication. Advertisements, press releases, etc., may qualify for expedited review.

All recruitment materials are required to have IRB review and approval prior to implementation. The tools may not be used to recruit subjects until the investigator receives final IRB approval. Prior to use, each recruitment tool should have an approval and expiration date on the tool. When recruiting subjects from another institution with an IRB, investigators are required to gain IRB approval from that institution. In institutions without an IRB, investigators are required to obtain a letter of agreement on the facility's letterhead indicating the research can be conducted at the site and the agency or institution will review, abide by and comply with the procedures approved by the UofL IRB.

A recruitment tool informs potential subjects of a research activity and provides them with an opportunity to contact the researcher. A recruitment tool may include, but is not limited to, post-cards, flyers, advertisements, press releases, brochures, and postings on the Internet. Investigators are required to use the following guidelines when developing recruitment tools:

- a. name and address of the clinical investigator and/or research facility (letterhead is acceptable).
- b. the condition under study and/or the purpose of the research.
- c. in summary form, the criteria that will be used to determine eligibility for the study.
- d. a brief list of the benefits of study participation, (if any) i.e. a free health examination.
- e. time or other commitments required.
- f. the location of the research and the person or office to contact for further information;
- g. in drug or device studies, no claim should be made as to the superiority, safety or effectiveness of the drug or device. Proprietary names of study products may not be used.
- h. do not provide excessive monetary or other incentives that could be interpreted as inappropriate or coercive.
- i. are consistent with protocol.

The recruitment tool should not:

- a. state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- b. include exculpatory language.
- c. emphasize the payment or the amount to be paid, by such means as larger or bold type.
- d. promise “free treatment” when the intent is only to say subjects will not be charged for taking part in the investigation.

When following FDA regulations and guidance the recruitment tool should not:

- a. make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling.
- b. use terms, such as “new treatment,” “new medication,” or “new drug,” without explaining that the test article is investigational.
- c. allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Due to contractual obligations, recruitment tools should not include any proprietary identifiers, contain therapeutic or outcome claims or mention the corporate sponsor by name.

An investigator may request assistance from the HSPPO in developing UofL Today submissions to ensure that their announcement meets the above guidelines as well as the 75 word limit imposed by UofL Today.

Primary Reviewer

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

The primary reviewer conducts in-depth review of all items required for IRB submission of a new application (see XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB), including the Informed Consent Document(s), and all supplemental materials (including, if applicable, the entire grant

application²⁵, protocol, and investigator's brochure). 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. Primary reviewer responsibilities include reviewing the grant application or the pharmaceutical company 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. The primary reviewer leads the discussion of the new project or continuing review application. The primary reviewer may not have a conflict of interest regarding the project under review and must notify the chair of any conflict.

Primary reviewers are provided an initial review checklist to ensure that all criteria for approval of research have been fulfilled. Each primary reviewer is expected to return this checklist to the HSPPO staff to assist in documenting minutes and electronic communications with the investigator.

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

Consultants

At the time of preliminary review of a new project application or modification, the IRB chair or primary reviewer may determine that the study requires further review by a consultant with expertise outside of the current IRB membership. This determination may be made based on the scientific design of the study, the ethical issues of the study, the potential risks or benefits of the study, specific privacy and confidentiality concerns, or considerations relative to a particular study population. If the services of a consultant are needed, the IRB Chair and HSPPO Director consult with AVPR and request that the EVPR provide the level of funding required.

Upon identifying the need for a consultant review, the chair and/or primary reviewer, in consultation with the chair, will identify a consultant with appropriate expertise and experience based on the particular issues to be addressed. Consultants are identified by the chair of the IRB based on their type of review required and/or the expertise in the discipline of the submission. For issues requiring only simple clarification, a written set of questions will be developed for submission to the consultant. The consultant's written response to these questions will be provided to the full IRB for review at the time of the convened meeting. For issues requiring more than simple clarification, the consultant may also be invited to attend the full board meeting during the review of that particular study. The consultant will leave prior to the final vote by the IRB. Documentation of the discussion with the consultant will be included in the meeting minutes and the protocol review files.

No person with a conflict of interest will serve as a consultant for the purposes described in this section. Any individual asked to participate, as a consultant, will be required to sign a confidentiality agreement and declare in writing that they have no conflicts of interest involving the study for each consultation.

Expedited Review

²⁵ 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](#)

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 chairperson utilizing the IRB Reviewer Form (Biomedical or Behavioral, depending on the type of research), or by one or more experienced reviewers designated by the chairperson 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 remanded to the full IRB for review at its next scheduled meeting.

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.²⁶

Projects involving classified research cannot be completed by exempt or expedited review.²⁷

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. **(See XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB)**

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

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.

Studies approved by the Expedited Review process are subject to at least annual review and this information is communicated electronically to the principal investigator in the approval letter (.pdf).

Expedited Review Process

The Secretary, DHHS, has established, and published as a Notice in the [Federal Register](#), a list of categories of research that may be reviewed by the IRB through an expedited review procedure. A protocol may be reviewed utilizing the expedited review process if the research falls within one of the

²⁶ [Categories of research that may be reviewed by the IRB through an expedited review: Applicability \(D\)](#).

²⁷ [Categories of research that may be reviewed by the IRB through an expedited review: Applicability \(D\)](#).

categories of research that may be reviewed by expedited review. The categories in this list apply regardless of the age of subjects, except as noted. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, DHHS, in the Federal Register. A copy of the list is available from the Office for Human Research Protection, DHHS, Bethesda, Maryland 20892.

The IRB chair, or designated experienced IRB member in accordance with the requirements set forth in 45 CFR 46 will review the protocol submission utilizing the information provided in the following guidance and determine if the research meets the criteria for expedited review. The expedited review process may be used for projects involving a) no more than minimal risk, and b) only those procedures listed in one or more of the following categories:

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 application²⁸ 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) application²⁹ 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 saliva 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;

²⁸ 21 CFR Part 312

²⁹ 21 CFR Part 812

- (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 echo-cardiography;
- 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 UofL IRBs will keep members advised by providing written documentation of all expedited approvals at full board meetings and will note this advisement in the meeting minutes utilizing the following statement. "The IRB was advised at the meeting on (current full board meeting-month/day/year) of all expedited research proposals approved by this procedure since the last full board meeting on (month/day/year)."

University of Louisville officials³⁰ may restrict, suspend, terminate, or choose not to authorize an IRB's use of the expedited review procedure.

Exempt Human Subjects Research

All applications are assigned to full board review unless they meet the criteria for exemption or being expedited. 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 or chair's designee of the Institutional Review Board. 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).

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 the chair has a conflict of interest, the appearance of a conflict of interest or a member is better qualified to make the

³⁰ Institutional Official (EVPR), or designee

determination. If the activity does not qualify for exemption, the investigator is notified by the Institutional Review Board.

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 (e-mail or BRAAN2) 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 (e-mail or BRAAN2). 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 IRB Standard Operating Procedures.
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.

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 IRB Committee review. Research involving prisoners can be approved under expedited review procedures. However, because of the vulnerability of prisoners, OHRP recommends that all research involving prisoners be 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.

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:

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. Educational³¹ 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

³¹The 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.

numbers, is insufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject's anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small or the research setting is identified, anonymity can be threatened or compromised even when the names are removed from the data.

Observational Research

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

Breach of Confidentiality

Additional consideration for exemption includes whether there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review of exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of 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 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. As with quality control or quality assurance information, the data collected by educational agencies is usually not reviewed by the IRB. The IRB becomes involved when researchers wish to access this information for research purposes.

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 prospectively, or prior to the procedure, request for research purposes, the obtaining of 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,
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.

If, in the opinion of the IRB chair or 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, 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 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.³²

University of Louisville officials³³ 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 Request Form](#) found on the HSPPO website under Forms. If the protocol remains exempt, the investigator will be notified of the decision. If the change(s) require(s) that the research must be reviewed using expedited or full board review, the investigator will be notified and asked to submit the appropriate additional documentation for this review.

Establishing Continuing Review Parameters for Approved Protocols

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 board³⁴. This review takes place no less than annually, and may require more frequent review or reports as determined by the IRB. For projects receiving full board review, the length of approval is calculated from the date of the full board review. When a primary reviewer has been assigned, that reviewer is asked to provide a recommendation for the length of approval. The appropriate length of approval is considered as a part of the full board discussion of known or potential study risks. The initial reviewer of a protocol will be assigned the continuing review responsibility. If the initial reviewer is unavailable, the IRB chair will determine the most qualified reviewer. That review may take place up to thirty days (30) prior to expiration.

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.

When determining the interval for continuing review, members should consider:

1. studies that are pilot studies and for which little preliminary data exists.
2. the experience of the investigator.
3. studies that pose a special risk to the subject.
4. studies where there may be little preliminary human data.
5. emergency waiver of consent protocols.
6. studies in which the subjects are gravely ill and the risk/benefit ratio is unclear (e.g. sepsis trials).
7. studies in which the preliminary data indicate a special element of risk for the subject.

Projects requiring review more frequently than annually may include:

1. Experimental therapies in which the clear potential for significant adverse experiences have been identified at the time of review;
2. Non-therapeutic projects based on risk information provided at the time of initial review;
3. Projects in which new information provided during the duration of the study (including at the time of continuing review) indicates a high probability of significant adverse experiences not previously reported; or

³² [Categories of research that may be reviewed by the IRB through an expedited review: Applicability \(D\).](#)

³³ Institutional Official (EVPR), or designee

³⁴ 45CFR46.109(e)

4. Projects in which local or outside adverse experience reports create new concerns regarding the need for closer project scrutiny.

In such cases, approvals may be granted for time periods less than one year or, as may be more appropriate, for a limited number of subjects over a period not to exceed one year.

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](#)³⁵ or if it should be scheduled for full-board review. If the review is to be a full-board 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. 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. In addition to the files located in the HSPP office, reviewers receive the progress report, 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.

³⁵ Expedited Review Category (8): Under Category (8), an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows: (a) Where: the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and 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. Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure. For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source. [Expedited Review Category \(9\)](#): Under Category (9), an expedited review procedure may be used for 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 meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened 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 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).

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.

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.

Investigators are notified electronically (e-mail or BRAAN2) 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 study 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.

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.

Urgent Review of Applications

Urgent review procedures may be invoked only under unusual circumstances. This does not include urgency that is a result of negligence or delay on the part of the investigator or his/her staff to submit human subjects applications in a timely fashion.

On occasion, however, an investigator is faced with an immediate deadline beyond his or her control. If the chair permits urgent review of a protocol, the materials are distributed as soon as possible to IRB members to allow sufficient time for review prior to the meeting. The investigator may be required to attend the meeting to answer any questions that arise.

A copy of the informed consent document is stamped approved by the IRB through the study expiration date and returned to the investigator for use.

Revisions Prior to Final Approval

Revisions to new and continuing human subjects applications may be required. Correspondence is sent to the investigator detailing requests for revisions, clarification, or additional information as well as information regarding continuing review. The investigator has 60 days to respond to the revisions requested. If the investigator does not respond in 60 days, the application is deactivated and returned. If the investigator wishes to conduct a study that has been deactivated, the investigator must submit a new application, incorporating comments from the prior IRB review.

When specific changes are requested in the protocol and/or consent document(s), these are reviewed for compliance by the chair or designee before final approval is given. When the IRB specifies condition for approval of a protocol that are to be verified by the IRB Chair or designee, continuing review must occur no more than one year from the date of review at the convened meeting. In instances where extensive/general revisions are requested during a full board review, the revised documents are returned to the full board for its review and approval. The application receives final approval when all required changes have been submitted and approved.

Upon receipt of final approval, the HSPPO staff stamps approved documents given to subjects (e.g., Informed Consent Document(s), Assent(s), HIPAA document(s), advertisements, letters to subjects) with the IRB approval stamp, the date of approval, and the date of expiration. All other submitted documents (attached in BRAAN2 in MISC. ATTACHMENTS under Approval Attachments) will not be stamped but will be referenced (as named in the Approval Attachments Description) in the approval letter as approved. The stamped, approved documents are sent to the principal investigator along with the final approval letter that includes information on the date of human subjects expiration of approval. The 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.

Rebuttal or Appeal of IRB Decisions

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 BRAAN2) 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 or any other officer or agency of the University of Louisville, state government or federal government.

Suspension or Termination of IRB Approval

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, 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.

There are situations where an unexpected event, related or possibly related to participation in the research, and suggesting that the research places subjects or others at a greater risk of harm than was previously known or suspected, requires an immediate change to a protocol in order to relieve an apparent immediate hazard to research subjects.

Any suspension or termination of approval includes a statement of the reasons for the IRB's action and is reported promptly to the investigator, the investigator's department chair, and the Office of Sponsored Programs Grants Management, and/or the Office of Industry Contracts (when the study is externally funded).³⁶ The IRB may require remedial action or education as deemed necessary for the investigator or any other key personnel. Federal regulatory agencies are notified as required by federal regulation.

Suspension is the temporary closing of a human research project or discontinuing an investigator's privilege to conduct human subject research. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the research may proceed. The IRB will make this determination.

Termination is the ending of all activities related to a human research project or an investigator's privilege of conducting human subject research at the University of Louisville except for the continuation of follow-up activities necessary to protect subject safety.

For additional information view the policy [Suspension or Termination of Previously Approved Research](#) located on the HSPPO website under Research Related Policies.

Submission of a Protocol to a Second IRB after Disapproval from another IRB

If an investigator submits a protocol to a University of Louisville IRB or to another IRB outside the University and the reviewing IRB disapproves the study, and it is subsequently sent to another IRB for review, that IRB must be told of the original disapproval.

When an IRB disapproves a study, it must provide a written statement of the reasons for its decision to the investigator and the institution³⁷. If the study is submitted to a second IRB, a copy of this written statement should be included with the study documentation so that it can make an informed decision about the study. Federal regulations³⁸ require an IRB to "... review ... all research activities...." The FDA regulations do not prohibit submission of a study to another IRB following disapproval. However, all pertinent information about the study should be provided to the second IRB.

³⁶ 45 CFR 46.113 & 21 CFR 56.113

³⁷ 21 CFR 56.109(e)

³⁸ 21 CFR 56.109(a)

Reporting to Federal Oversight Agencies

The Human Subjects Protection Program Office notifies the Office for Human Research Protections (OHRP) of any changes in IRB membership.

The IRB chair notifies the Office of the Executive Vice President for Research and they together notify OHRP (in accordance with the terms of the University of Louisville FWA) and the FDA (for projects subject to 21 CFR Parts 50 and 56) in a timely manner of any:

1. serious or continuing non-compliance;
2. unanticipated problems involving risks to subjects or others; or
3. suspension or termination of IRB approval for a project. Any suspension or termination of approval will include a statement of the reasons for the IRB's action.

In cases of corporate-sponsored research, the University of Louisville coordinates its notification to federal regulatory agencies with the sponsor. See the [Institutional Review Board](#) policy for reporting guidelines.

IX. OPERATIONS OF THE IRB

Many protocols submitted to the IRB will require full IRB review. Submissions requiring full board review must be received by the submission deadline posted on the HSPPO website for consideration at the next scheduled [Biomedical](#) or [Social Behavioral Educational \(SBE\)](#) IRB meeting.

Currently, Biomedical IRB meetings are held the first and third, fourth, and fifth Thursday of the month. Any biomedical research project involving human subjects, regardless of its source of funding, is reviewed by the Biomedical IRB if it is conducted in or involves patients or staff of the University of Louisville and its research affiliates or it is conducted by faculty, staff, or students in the Schools of Dentistry, Medicine, or Public Health and Information Sciences. This IRB also reviews projects from the School of Nursing when they involve physical, psychological or physiological interventions exceeding minimal risk.

SBE IRB meetings are held the first Wednesday of the month. Any SBE research project involving human subjects, regardless of its source of funding, is reviewed by the SBE IRB if it is conducted by faculty, staff, or students in the Colleges of Arts and Sciences, Education and Human Development, or Business and Public Administration, or in the Schools of Engineering, Law, Music, Social Work, or Nursing. This IRB reviews projects from the School of Nursing when they involve physical, psychological or physiological interventions that do not exceed minimal risk.

If a committee meeting date falls on a scheduled University holiday, the meeting will be rescheduled at a time more convenient for committee members and HSPPO staff. Individual meetings may be cancelled by the chair due to a) insufficient applications requiring full board review, b) University holiday, c) inability to secure a quorum for attendance, or d) other reasons as may arise that make a scheduled meeting unnecessary or otherwise inappropriate.

Notification of Meetings and Distribution of Materials

The agenda and application materials are distributed to IRB members sufficiently in advance of the meeting date to allow time for review, generally a week in advance. Primary reviewers receive the initial submission packet prior to the distribution of the agenda. The agenda indicates the date, time, and place of the meeting. For both new project and continuing review full board meetings, IRB members

receive the application form, informed consent and/or assent document(s), recruitment materials, other correspondence with subjects (if applicable), and other materials as determined by the chair or designee. Complete file documentation is available to all IRB members upon request.

In December of each year, the list of [committee meetings](#) to be held in the new year and submission deadlines are published on the HSPPO website. Additional committee meetings may be scheduled if necessary.

Meeting Procedures

The IRB meeting is called to order when a quorum of members is in attendance.. A quorum consists of more than half of the members. Approval of an action requires a majority vote of the members when a quorum is present. The meeting ends when business is finished or is suspended whenever a quorum of members is no longer present for deliberations. IRB meetings are conducted by the IRB chair and the meeting agenda is arranged to place less controversial issues at the beginning of the meeting. Education informational items, information on expedited and exempt reviews, continuing reviews and amendments are discussed by the chair and assigned primary reviewer(s). Members receive this information with adequate time to review prior to the meeting and sufficient time is allowed to discuss any issues they may wish to raise concerning this information. More comprehensive or complex issues, including initial, continuing review and amendments that may require significant committee discussion are placed at the end of the agenda.

Each presenter is asked to organize and present the item within ten minutes, adequate discussion and the IRB action follows. If the reviewer requires additional time for presentation, the chair and committee are notified prior to the start of the presentation. Primary reviewers are requested to complete the appropriate review checklist and, if necessary, contact the investigator to resolve questions prior to presentation. If the primary reviewer believes that the issues related to the protocol cannot be resolved in a reasonable amount of time, the reviewer may recommend that the protocol be deferred and the reviewer will continue to work directly with the investigator to resolve any outstanding issues.

At the discretion of the chair and/or primary reviewer, the investigator(s) may be invited to attend the meeting for the purpose of additional clarification or discussion. The investigator(s) is (are) required to leave the meeting for subsequent discussion and voting.

At the discretion of the chair, voting may be by written ballot, a show of hands, or voice vote. The official meeting minutes record, without individual identification, the number of votes to approve, disapprove, defer, or abstain. If vote(s) to disapprove is cast, the minutes should reflect the reason(s) for the disapproving vote(s). In the event a member of the IRB elects to abstain, the minutes record such and identify the individual who did not vote. A majority vote of the members present at the meeting is required for approval. Proxy votes, written, electronic, or telephone, are not allowed.

Investigators are notified electronically (e-mail or BRAAN2) of the decision of the IRB and any changes required. If minor specific changes are required by the IRB, the changes may be reviewed and approved by the chair or designee, once returned to the HSPPO. Minor specific changes (e.g., address change, addition or deletion of study personnel, change in number of subjects to be recruited, substitution of specific words and/or phrases etc.) may be approved by the IRB chair or his/her designee without return to the full board for review.

Auditing Activities

Professional staff in the Human Subjects Protection Program Office, acting on behalf of the IRB, may conduct a monitoring visit. The reason(s) for on-site review may include, for example, (1) random

selections, (2) complex projects involving unusual levels or types of risks to subjects, (3) projects conducted by an investigator who previously failed to comply with IRB determinations, or (4) projects where continuing review or reports from other sources have indicated that changes without IRB approval may have occurred or subjects were consented inappropriately, (5) HIPAA non-compliance, (6) subject or whistleblower complaints, or (7) a request by an IRB member and with approval by the IRB.

Auditing of Research Projects

The conduct of an on-site review may include but is not limited to: (1) requests for progress reports from investigators, (2) examinations of research records, including signed informed consent documents, protocol amendments, grant and IRB applications, unanticipated problems, and local (occasionally external) serious, and/or related adverse experience reports, (3) contacts with research subjects, or (4) observation of the consent process and/or research procedures.

A written record of auditing activities is maintained in the study file and in the HSPPO office. Any of the following may occur as a result of an audit report:

1. Suspension of some or all research activities;
2. Suspension of processing of grant applications;
3. Suspension of supervision or mentoring of graduate students;
4. Suspension or withholding of grant or operating funding;
5. Removal as a principal or co-principal investigator in particular or all research activities;
6. Loss of improperly collected data;
7. Suspension of laboratory privileges;
8. Mandatory submission to monitoring or oversight;
9. Imposition of a requirement to obtain additional appropriate training;
10. Imposition of a mandate and timetable for corrective or remediating action;
11. Follow-up action with successor institution in the case of investigator leaving the University for such institution;
12. Any action that may be required by applicable law or regulation;
13. Any appropriate personnel action up to and including termination;
14. Notification of affiliated research offices and sponsors, if any;
15. Notification of privacy officer for a HIPAA violation; and
16. Any other sanction deemed appropriate by the IRB.

The monitoring report is reviewed at a convened meeting of the IRB. When accepted by the IRB, the report findings and committee recommendations are forwarded to the principal investigator for response and resolution of any outstanding issues, the EVPR, and others, including federal regulatory agencies, as deemed necessary by the IRB.

AUDITING NOT FOR CAUSE

The HSPP auditors are responsible for selection of the protocols for the “not for cause” audits. For purposes of auditing, the term “not for cause auditing” is defined as selection of research protocols for review which have no current noncompliance investigation pending. The HSPP has set a goal of conducting 48 limited scope, not for cause audits annually.

Not for cause audits will be selected for review on a monthly basis based on the month of Continuing Annual Review (CAR). These will be chosen by the 10th day of the previous month. Protocols will be selected for review among investigators based on the month of CAR. If the investigator had an audit in the past 12 months they will be removed for the Not For Cause Audit list. The audit team will randomly

draw 10 studies per committee for the month. There will be a division between the Biomedical and Social Behavioral Education (SBE) CAR's due in that particular month. A minimum of 3 Biomedical and 2 SBE studies will be selected monthly.

Auditing for Cause

Information regarding non-compliance³⁹ in human subjects studies may come to the attention of the IRB in several ways. These include information contained in new applications, continuing reviews, adverse event reports, and reports from collaborators, employees, the public, or subjects.

The chair makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing non-compliance with IRB determinations or federal regulations⁴⁰. In such cases, the chair may suspend the study procedures pending a timely investigation and review by the full IRB. At the discretion of the chair or committee, a study may continue while minor incidents of non-compliance are under investigation. The chair may elect to discuss an allegation of non-compliance with the IRB prior to suspending the protocol if it is apparent that there is no increased risk to subjects. The Director, HSPPO, may suspend studies when the violation is a clear violation of the regulations, a violation of university policy, or there is imminent danger to subjects. The chair and/or the IRB will confirm this action as soon as possible.

Investigations by the IRB focus on the protection of study subjects. In cases that involve allegations of research misconduct, the chair contacts the University of Louisville Research Integrity Officer (RIO) for further action. This does not preclude the chair or any member of the IRB from independently contacting the RIO about any allegation of research misconduct⁴¹. Inquiries or investigations into research misconduct do not preclude IRB review and actions.

The conduct of an on-site review may include: (1) requests for progress reports from investigators, (2) examinations of research records, including signed informed consent documents, protocol amendments, unanticipated problems, and local serious, and/or related adverse experience reports, (3) contacts with research subjects, or (4) observation of the consent process. Examples of when observation of the consent process could occur are: (1) the full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party; (2) the IRB is made aware of a complaint or concern with regard to the informed consent process; or (3) the IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

The audit report is reviewed at a convened meeting of the IRB. Following the initial review, a copy of the preliminary audit report is forwarded to the principal investigator (PI). The PI has ten working days to provide any clarifications, explanations, or rebuttals to the IRB. The IRB will consider any additional information provided and finalize the report findings and committee recommendations. The final report is forwarded to the PI, EVPR, and others, including federal regulatory agencies as deemed necessary by the IRB.

The following are the recommended procedures for resolving alleged non-compliance:

1. In most cases (occasionally, notices will be sent directly to the HSPPO auditing section), when made aware of a potential problem, HSPPO staff compiles file information and presents

³⁹ See University of Louisville IRB Noncompliance Policy.

⁴⁰ See Allegation of Noncompliance IRB Chair/HSPPO Director Checklist in HSPPO Audit Policy and Procedure.

⁴¹ Research misconduct, in this context, refers to fabrication, falsification and plagiarism only.

concerns to the appropriate IRB chair or incorporates the findings into the continuing review summary presented to the IRB.

2. The chair may make a determination to refer the matter to a HSPP representative to contact the principal investigator. The purpose of such contact is initial fact-finding, i.e., to determine whether the problem is intentional, unintentional and/or the result of mistake or oversight.
3. If deemed serious enough, the chair may temporarily halt enrollment and/or data collection until full board review occurs (with consideration of effect in therapeutic trials). However, when an audit is recommended based on the consents or authorizations submitted with the progress report and the chair has determined there is no increased risk to the subjects; the study may continue and no corrective action will be required by the researchers until the audit is accepted by the IRB.
4. The IRB Compliance Auditor, at the direction of the Chair, should document the outcome of any communications and discussions in writing, by either e-mail or paper memo with a copy to the IRB files. Such documentation should be factual and objective.
5. When the initial inquiry does not result in resolution of the matter, the IRB may request a meeting with the principle investigator as soon as possible. The IRB compliance auditor should document results of the meeting.
6. Any discussions, findings, efforts to achieve resolution and sanction recommendations are presented at the next IRB meeting by the chair or IRB compliance auditor to the IRB. The IRB granted authority to recommend sanctions to the compliance auditor.
7. At a convened meeting, a quorum of IRB members will discuss the findings, recommend actions, and vote to approve the recommended actions.
8. The IRB has the authority to suspend or terminate IRB approval of protocols that are found to be non-compliant with institutional policies and procedures, state statutes, and/or federal laws or regulations.
9. The HSPPO sends written notification⁴² of actions taken to the principal investigator with copies to the departmental chair, Executive Vice President for Research, and the research offices of other affiliated institutions, as determined by the IRB. To the extent that any action includes suspension or termination, in cases of externally funded programs, notice will be sent to the Office of Sponsored Programs Grants Management or the Office of Industry Contracts. Federal regulatory agencies are notified of actions as required by federal regulation.

Quality Assessment/Quality Improvement of the Human Subjects Protection Program

As a Quality Assessment/Quality Improvement (QA/QI) process, the Institution, organizations within the Institution or the Human Subjects Protection Program (HSPP) will periodically conduct an audit, survey or other method to assess the quality, efficiency, and effectiveness of the HSPP. The process should identify strengths and weaknesses of the HSPP in order to make improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program.

The plan will include methods:

1. to achieving targeted levels of quality, efficiency, and effectiveness of the HRPP;
2. to measure or measures of quality, efficiency, and effectiveness; or
3. to assess quality, efficiency, and effectiveness and make improvements.

For example, measures related to quality, efficiency and effectiveness could include:

1. quality - post approval investigator satisfaction survey - analyze to make improvements.
2. efficiency - review times - if needed aim to reduce certain times in the review/approval process.

⁴² See *INSTITUTIONAL REVIEW BOARD REPORT OF FINDINGS* policy and procedure for reporting requirements and timelines.

3. effectiveness - analyze consent forms reading level and make suggestions for improve readability.

X. IRB RECORD REQUIREMENTS

IRB Membership Roster

A current roster of IRB members and their areas of expertise may be found on the [HSPPO](#) website. The roster is updated as committee membership changes.

Committee Members Coming and Going

If a committee member arrives late note that they have arrived and if the number of voting members has been affected.

Committee members will leave the room for three reasons, please record as follows:

1. Committee member left the room due to a conflict of interest.
2. Committee member left the room for a personal break and will be returning
3. Committee member left the meeting for good and will not be returning.

Meeting Minutes

Members and alternates of IRBs receive minutes of full board meetings and monthly reports of IRB business for their respective board. Minutes include written notification of all new projects approved (full board and expedited), projects determined to be exempt, continuing reviews (full board and expedited), modifications (full board and expedited), and reportable adverse experience.

Minutes are generated that record the following information:

1. attendance at each meeting including voting and non-voting members or attendees;
2. The IRB was advised at the meeting on (current full board meeting-month/day/year) of all expedited research proposals approved by this procedure since the last full board meeting on (month/day/year).
3. actions taken by the board including initial and continuing review of research;
4. the vote on actions taken including the number for, against, with reason for the against vote, to defer, and abstaining (The IRB chair, as a matter of policy votes only to ensure a quorum or to break a tie vote. If not voting, the chair will be listed as abstaining in the recording of each vote.),
5. notation when a member declares a conflict to interest and leaves the room and when the member returns (the minutes will state the reason the member left the room),
6. notation when a member leaves the room for reasons other than a conflict of interest and when the member returns,
7. the basis for requiring changes in or disapproving research;
8. the length of time of an approval;
9. a written summary of the discussion of controverted issues and their resolution;
10. specific comments relevant to inclusion/exclusion of certain populations;
11. amendments or modifications that require full board review;
12. documentation and review reports of adverse reactions reports;
13. Report from the Institutional Biosafety Committee (IBC) on research involving human subjects;
14. Report from the Radiation Safety Committee (RSC) on research involving human subjects; and

15. in addition to the review of pending applications, meeting minutes may include information regarding expedited approvals, modifications, terminations, emergency/single patient use, adverse experiences, and any other business appropriate for board meetings.

DHHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as:

1. approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)];
2. approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207);
3. approving research involving prisoners (see 45 CFR 46.305-306); or
4. approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings.

OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB Chairperson or other designated reviewer elsewhere in the IRB record.

Study File and Minutes Maintenance

The HSPPO maintains file copies of all research proposals reviewed, scientific evaluations, if any, approved sample informed consent documents, progress reports, UPIRTSOs, local serious adverse event reports, emergency use reports, budget and accounting records (if required for IRB review, these records are available from other offices within the OEVPR), statements of significant new findings provided to subjects (if any), meeting minutes showing attendance, action taken, vote with number of members voting for, against, to defer, or abstaining, the basis for requiring changes in or disapproving research, a written summary of the discussion of controversial issues and their resolution, and other correspondence pertaining to IRB operations.

IRB meeting minutes, once approved, are forwarded to the Executive Vice President for Research. These minutes include findings and actions, decisions to approve, disapprove, or require modifications to secure IRB approval of research activities and any other business the IRB considers necessary to report.

Reports of suspension or termination of research not conducted in accordance with the regulations, statutes and principles or IRB's requirements, or occurrences that have been associated with an event that is unexpected, 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 will be included. Observations of, or having a third party observe, the consent process, observations of, having a third party observe, the conduct of the research may also be included.

Privacy Board actions and concerns related to University of Louisville investigators' adherence to the HIPAA Privacy Rule as it relates to research will be reported when these issues appear before the Privacy Board.

Record Retention by the IRB

Electronic records on human subjects research are maintained by the HSPPO for a minimum of three years after notice of study closure and records relating to research which is conducted shall be retained for at least three years after the completion of the research (45 CFR 46.115, 21 CFR 56.115).

The HSPPO maintains a permanent record of all closed project files on four external hard-drives held in the HSPPO and the AVPR office that supervises the HSPPO (studies closed since August, 2003) or in BRAAN2. Access to the hard-drive records is limited to HSPPO staff, IRB members, and individuals who have official reasons for reviewing the files. The four hard-drives are stored in a locked area in the HSPPO and the AVPR office. The AVPR office is in a different building separate from the HSPPO office. If requested, the records shall be accessible for inspection and copying by authorized representatives of the OHRP and FDA at reasonable times and in a reasonable manner.

Data Retention when Subjects Withdraw/are Withdrawn from Human Subjects Research

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. In these circumstances, questions sometimes arise about: (1) whether the investigator may use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the investigator; and (2) whether the investigator can continue to obtain data about the subject and if so, under what circumstances. The guidance below addresses these and related questions. OHRP recommends that investigators plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols and informed consent documents.

When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the

subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

For additional guidance on this subject see the OHRP document "[Guidance](#) on Withdrawal of Subjects from Research: Data Retention and Other Related Issues."

Data Retention when Subjects Withdraw/are Withdrawn from Human Subjects Research Regulated by the FDA

According to FDA regulations, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

FDA law and regulations recognize that a complete and accurate risk/benefit profile of an investigational product depends upon the data from every subject's experience in the clinical trial. For example, if a subject's data could be withdrawn from a study, a sponsor would not have access to data on adverse events experienced by the subject and would be unable to evaluate whether changes to the protocol or the informed consent documents are needed to ensure the rights, safety, and welfare of other trial subjects.

FDA regulations (21 CFR 312.62 and 812.140(a)(3)) require investigators to prepare and maintain adequate case histories recording all observations and other data pertinent to the investigation on each individual treated with the drug or exposed to the device. The agency needs all such data in order to be able to determine the safety and effectiveness of the drug or device.

Data collected on study subjects up to the time of withdrawal must remain in the trial database in order for the study to be scientifically valid. If a subject withdraws from a study, removal of already collected data would undermine the scientific, and therefore the ethical, integrity of the research. Such removal of data could also put enrolled subjects, future subjects, and eventual users of marketed products at an unreasonable risk. Finally, removal of data would fundamentally compromise FDA's ability to perform its mission, to protect public health and safety by ensuring the safety and effectiveness of regulated products.

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

For additional guidance on this subject see the FDA document “Guidance for Sponsors, Clinical Investigators, and IRBs: [Data Retention](#) When Subjects Withdraw from FDA-Regulated Clinical Trials.”

XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB

Qualifications for Principal Investigator/Project Director Status

The University of Louisville will allow anyone with a formal relationship with the University to act as a Principal Investigator (PI)/Program Director (PD) on an extramurally funded project. That relationship can be as a faculty, staff, post-doctoral fellow or adjunct faculty. The individual must also meet all of the University guidelines for eligibility.

If an individual is not a permanent employee of the University of Louisville, the term of appointment must be sufficient in length to complete the proposed project. Such individuals must obtain formal approval by the appropriate chair and/or dean to submit the application in the name of the University with assurances that adequate resources and supervision will be available for the project to be successful should it be funded. Gratis Faculty with research appointments who wish to conduct Human Subjects Research and act as a PI on a study may also require EVPR approval. This is determined on a case by case basis and the final decision is made by the EVPR.

In most circumstances, all paid and gratis faculty with research gratis appointments of the University, who conduct human subjects research associated with their appointment, must utilize the University's IRBs for review, approval and continued oversight of the research. In certain circumstances, individual or institutional conflicts of interest may require the utilization of an independent IRB. Requests for use of an independent IRB must be made to the EVPR or the University IRB and approved by the EVPR.

Employees of Norton Healthcare who are principal investigators and do not have a paid or gratis faculty appointment with the UofL may utilize Western IRB for their human subjects review when conducting research in Norton Healthcare property. If the research is conducted in the investigator's private office and the investigator makes no claim of affiliation with the University of Louisville, he/she may utilize Western IRB. These investigators may not use the University's name or claim affiliation with the University to solicit research.

If those Norton Healthcare employees who have a UofL gratis faculty with a research appointment, desire to utilize their University affiliation, they are required by Norton Healthcare and UofL policy to utilize the University's IRBs for approval of their research.

Investigators who are affiliated with Jewish Hospital St Mary's Healthcare (JHSMH) and the University must utilize the University IRBs for their research oversight. Investigators, who are affiliated with JHSMH but not the University of Louisville, may elect to utilize Western IRB. These investigators may not use the University's name or claim affiliation with the University to solicit research.

For additional information, OHRP has a list of frequently asked questions ([FAQs](#)) about investigator responsibilities.

The Basic Application

A complete submission for IRB review includes:

1. Application for Human Subjects Review and any required appendices or BRAAN2 submission;
2. Protocol summary in lay language;

3. Consent Form (created from template or in BRAAN2 consisting of all the applicable checklist items), if applicable;
4. Consent Form checklist (BRAAN2 presents the check list in the form of questions) with each item location in consent appropriately referenced, if applicable;
5. Recruitment Tools (Advertisements, Information Items and other materials) to be used to recruit subjects, if applicable;
6. Industry-sponsored protocol and Investigator's Brochure (attach in BRAAN2), if applicable;
7. Investigator-initiated Final Protocol, if applicable;
8. Grant Application for non-industry sponsored research and Final Protocol (attach in BRAAN2), if applicable;
9. Review Certification Form (attach in BRAAN2), if applicable;
10. Completed and appropriately signed Scientific or Scholarly Merit Review of Research Protocols Involving Human Subjects (a part of BRAAN2);
11. Approval from appropriate organizational official to conduct research at another site (health department, hospitals, nursing homes, schools, etc.), if applicable;
12. Disclosure of Significant Financial Interest (UofL SFCOI - include for PI and all key personnel);
13. Current Curriculum Vitae (include for all key personnel);
14. Certification of current Human Subjects Protection Training (BRAAN2 automatically checks) for all key personnel;
15. Certification of HIPAA IN RESEARCH Training (BRAAN2 automatically checks) for all key personnel, if applicable;
16. Applicable HIPAA documentation (if any):
 - a. HIPAA authorization form;
 - b. HIPAA partial waiver form;
 - c. HIPAA waiver of authorization form;
 - d. HIPAA revocation form;
17. Billing Compliance Table (BCT) from the Multi-Institutional Research Application (MIRA) form, if applicable;
18. Completed Submission Checklist.

The application to submit a human subjects research protocol for review to the University of Louisville IRB is in the BRAAN2 protocol submission software. The BRAAN2 electronic submission process guides the PI or key personnel through the submission process and does not require a separate checklist. Properly answering all questions in the process and attaching all required documents assures that the submission is complete.

The following is an expanded explanation of each item in the submission checklist.

1. Application for Human Subjects Review

The application for Human Subjects Review may be found at the [BRAAN2](#) production site. Additional information about the use of the BRAAN2 software is located on the [BRAAN2 website](#).

2. Protocol summary in lay language

This summary should include a non-technical description of the research questions, methods, and procedures. The IRB is required by federal regulations to include members from various backgrounds, at least one member from the community at-large, and at least one non-scientific member. This summary should explain the research for the lay reader.

3. Informed Consent/Assent Form (created from template or in BRAAN2 consisting of all the applicable checklist items), if applicable

Sample consent and assent forms are found on the HSPPO website. There are sample consent forms for medical research and non-medical research, and a sample assent form for research with children between the ages of seven and 18. All consent/assent forms are required to reflect the IRB format and style. Only UofL IRB reviewed, approved, stamped, and dated consent and/or assent forms can be used to acquire subjects' consent to participate in the proposed research.

4. Consent form checklist (BRAAN2 presents the check list in the form of questions) with each item location in consent appropriately referenced, if applicable

The consent form checklist consists of items and language required by the IRB for inclusion into medical and non-medical consent/assent forms.

5. Recruitment Tools (Advertisements, Information Items and other materials) used for recruitment or retention of subjects

Recruitment tools (advertisements, etc.) are not approved or valid without an IRB approval stamp containing the approval and expiration dates. When reviewing recruitment tools the IRB must review the final mode of its communication, including the final copy of printed advertisements and the final audio or video advertisements.

Only IRB approved advertisements, considered fair, honest and appropriate by the IRB, may be used in the conduct of subject recruitment. Recruitment materials should be included with your initial and continuing review applications. If the material is not ready at the time of the initial application, investigators may submit the material as an amendment to an already approved project. Requests for approval of recruitment materials following initial IRB review of the protocol should allow sufficient time for any necessary revisions prior to publication. Advertisements, press releases, etc., may qualify for expedited review.

All recruitment materials are required to have IRB review and approval prior to implementation. The tools may not be used to recruit subjects until the investigator receives final IRB approval. Prior to use, each recruitment tool should have an approval and expiration date on the tool. Audio and video tools may be excepted from this requirement. When recruiting subjects from another institution with an IRB, investigators are required to gain IRB approval from that institution. In institutions without an IRB, investigators are required to obtain a letter of agreement on the facility's letterhead indicating the research can be conducted at the site and the agency or institution will review, abide by and comply with the procedures approved by the UofL IRB.

A recruitment tool informs potential subjects of a research activity and provides them with an opportunity to contact the researcher. A recruitment tool may include, but is not limited to, post-cards, flyers, advertisements, press releases, brochures, and postings on the Internet. Investigators are required to use the following guidelines when developing recruitment tools:

- a. name and address of the clinical investigator and/or research facility (letterhead is acceptable).
- b. the condition under study and/or the purpose of the research.
- c. in summary form, the criteria that will be used to determine eligibility for the study.
- d. a brief list of the benefits of study participation, (if any) i.e. a free health examination.

- e. time or other commitments required.
- f. the location of the research and the person or office to contact for further information;
- g. in drug or device studies, no claim should be made as to the superiority, safety or effectiveness of the drug or device. Proprietary names of study products may not be used.
- h. do not provide excessive monetary or other incentives that could be interpreted as inappropriate or coercive.
- i. are consistent with protocol.

The recruitment tool should not:

- a. state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- b. include exculpatory language.
- c. emphasize the payment or the amount to be paid, by such means as larger or bold type.
- d. promise “free treatment” when the intent is only to say subjects will not be charged for taking part in the investigation.

When following FDA regulations and guidance the recruitment tool should not:

- a. make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling.
- b. use terms, such as “new treatment,” “new medication,” or “new drug,” without explaining that the test article is investigational.
- c. allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Due to contractual obligations, recruitment tools should not include any proprietary identifiers, contain therapeutic or outcome claims or mention the corporate sponsor by name.

An investigator may request assistance from the HSPPO in developing UofL Today submissions to ensure that their announcement meets the above guidelines as well as the 75 word limit imposed by UofL Today.

IRB Review of Research Websites

When information posted on a research website goes beyond directory listings with basic descriptive information, such information is considered part of the informed consent process and therefore requires IRB review and approval.

Basic descriptive information includes:

- a. study title
- b. purpose of the study
- c. protocol summary
- d. basic eligibility criteria
- e. study site location(s), and
- f. how to contact the study site for further information.

Information exceeding such basic listing information includes descriptions of study risks and potential benefits, or solicitation of identifiable information. If you wish to use a website to

recruit subjects for a study and more that the above basic information is included, you must have IRB approval of the website prior to making it available to the public.

6. Industry-sponsored protocols & Investigator's Brochure (attach in BRAAN2), if applicable

A detailed research protocol is required for IRB review. All submissions should include a complete protocol that includes an explanation of the following information:

- a. Background, including a brief literature review
- b. Objectives of the research
- c. Significance of the research
- d. Thorough description of how human subjects will participate in the research
- e. How the study population is determined and how they will be [equitably](#) recruited
- f. Eligibility (inclusion) and exclusion requirements for subjects
- g. Design/methodology including all survey instruments, questionnaires, etc. Omission of any of these items, if applicable, may delay research approval.
- h. Treatment regimen(s) (*for medically invasive research*)
- i. Clinical information (when applicable) (*for medically invasive research*)
- j. Statistical analysis of the collected data
- k. Data and Safety Monitoring Plan
- l. References
- m. Investigator's Brochure for drugs or devices - The IRB is required to examine the Investigator's Drug Brochure and/or device guide in order to adequately assess the risk/benefit ratio for subjects participating in the research.

7. Investigator-initiated Final Protocol (attach in BRAAN2), if applicable

Investigator-initiated protocols should include all items listed in the industry-sponsored protocol except the Investigator's brochure.

8. Grant Application for non-industry sponsored research and Final Protocol (attach in BRAAN2), if applicable

Grant applications for sponsored research should include all items listed in the industry-sponsored protocol plus a completed grant application form. Where a grant proposal involves the use of human subjects in research, a copy of the entire grant proposal must be forwarded to the IRB along with all other documentation. When the investigator's institution is the primary awardee of the grant, HHS regulations require that the IRB review the actual application or proposal for HHS support. The IRB's review should ensure that all research described in the application or proposal is entirely consistent with any corresponding protocol(s) submitted to the IRB. No work may be initiated on a grant, funded or not, prior to receipt of approval from the IRB and any other applicable University of Louisville committee (i.e., Institutional Biosafety Committee, Radiation Safety Committee, etc.). The information in the various components of the submission application to the IRB must match information submitted in the grant application.

9. Review Certification Form (attach in BRAAN2)

The [Sponsored Study Billing Information](#) (in BRAAN2), should be completed when the research budget for the project is over \$10,000 and is funded by an industry sponsor.

10. Completed Scientific or Scholarly Merit Review (a part of BRAAN2)

A [Scientific or Scholarly Merit Review](#) must be completed by the principal investigator's chair/dean/dean's designee. The form is assurance to the IRB that the proposed research has been found to have scientific or scholarly merit, is supported by the principal investigator's chair/dean, and the principal investigator has adequate resources and expertise to conduct the research.

11. Approval to conduct research from appropriate organization official (when the study involves LMHD, JCPS, etc.), if applicable

This is a document from an organization/external facility, outside of the University of Louisville or its affiliated institutions, indicating that the principal investigator has permission from the organization to conduct research at the organization/external facility.

12. [Disclosure of Significant Financial Interest](#) (UofL SFCOI - include for PI and all key personnel)

University of Louisville Policy requires that all covered individuals, involved in research, complete the disclosure form at least on an annual basis. If using the paper submission format, the PI and key personnel must provide copies of the completed form. If utilizing the BRAAN2 system, the software automatically checks to see if a current disclosure form is on file.

13. Current Curriculum Vitae (include for all key personnel)

A Curriculum Vitae includes a summary of educational and academic backgrounds as well as teaching and research experience, publications, presentations, awards, honors, affiliations and other details.

14. Certification of current Human Subjects Protection Training (BRAAN2 automatically checks) for all key personnel

This is training required by the University of Louisville for each key personnel in order to conduct research under the auspices of the University of Louisville and its affiliated institutions. If utilizing the BRAAN2 system, the software automatically checks to see if training is current.

15. Certification of [HIPAA IN RESEARCH](#) Training (BRAAN2 automatically checks) for all key personnel, if applicable

This is training required by the University of Louisville to document the knowledge for each key personnel concerning the Health Insurance Portability and Accountability Act of 1996 that ensure privacy of protected health information. If utilizing the BRAAN2 system, the software automatically checks to see if training is current.

16. Applicable HIPAA documentation (if any)

- a. HIPAA authorization form
- b. HIPAA partial waiver form
- c. HIPAA waiver of authorization form
- d. HIPAA revocation form

17. [Multi-Institutional Research Application](#) (MIRA), if applicable

This form is required for all studies conducted in a University of Louisville affiliated local hospital.

18. Completed Submission Checklist (not required in BRAAN2 as the software documents the list)

A checklist located at the end of each IRB application form indicating that all applicable items have been addressed.

If the application is incomplete or otherwise not fully prepared for review, it is returned to the investigator or a request is made for necessary changes or to provide additional information. The HSPPO staff or an IRB representative may contact the investigator by phone, e-mail, or through BRAAN2 requesting clarification of protocol issues or revisions in consent document(s) prior to referral to the IRB.

Additional Items that may need to be Addressed at Application Submission

Instruments

The IRB is required to review all research instruments including standardized instruments such as surveys, questionnaires, inventories and assessments to be used in the proposed research. Please include the instruments and case report forms, if available with your initial application. Investigators may submit draft versions of investigator initiated study instruments or sponsor initiated data collection forms for the IRB to review. The IRB is required to review any modifications to research instruments. Please submit an addendum to the IRB when requesting changes to previously approved instruments. If draft instruments are submitted, the instruments cannot be used until they are approved by the IRB.

Data and Safety Monitoring Plans

Appropriate oversight and monitoring of clinical trials is necessary to ensure the safety of the participants and the integrity of the study data. The extent of monitoring varies by the risk/benefit ratio of the study and by the size, complexity and nature of the study.

The IRB requires a data and safety monitoring plan (DSMP) for all studies greater than minimal risk. For externally sponsored studies, the DSMP is normally incorporated into the protocol. For an investigator-sponsored study greater than minimal risk, the principal investigator is responsible for creating and implementing a data and safety monitoring plan.

The IRB will review the proposed level of risk and monitoring plan and will accept or amend the DSMP for every study. Any proposed change to the IRB approved DSMP must be reviewed and approved by the IRB. External board plans will be reviewed and approved by the IRB including GCRC and NIH plans.

For federally funded trials, NIH has issued two notices on data and safety monitoring (June 10, 1998, and data and safety monitoring for [phase I and phase II trials](#) (June 5, 2000), and a [Decision Tree](#) for Data and Safety Monitoring for Clinical Trials regarding data and safety monitoring in Phase I, II, and III clinical trials.

Investigator as a Sponsor

If an investigator is the developer of the drug, biologic or medical device, and no commercial manufacturer is involved, then either the investigator or the investigator's institution may be the sponsor for the purposes of designing and organizing clinical trials. The sponsor is responsible for submitting

an IND or IDE application to the FDA and providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. Faculty contemplating the dual role of sponsor-investigator should consult with the IRB about the additional responsibilities that entails.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

Should an investigator associated with the University of Louisville or the University sponsor a multi-site study, the sponsor is required to meet all the responsibilities of a sponsor as determined by DHHS guidance. A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations. The sponsor is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution. The sponsor must submit all required documents including the FDA forms 1571 and 1572 to the FDA and an IRB application, as described above to the IRB as well as ensure that investigators at other research sites submit and follow requirements directed by their local IRBs. The sponsor must declare any [individual financial](#) conflict(s) of interests in the research and develop a management plan that is approved by the University. The University of Louisville IRB will not review a research protocol where the institution may have an [institutional](#) financial interest in the research. The research oversight will be delegated to an independent IRB with appropriate expertise and experience to review the research.

When the University of Louisville is the coordinating center for a multi-site protocol, the IRB will require the UofL PI to ensure that IRB approval has been obtained at each participating site prior to initiation of the research at that site. At the time of initial review, the IRB will assess the procedures for dissemination of protocol information (e.g. unanticipated problems involving risks to subjects or others, protocol modifications, interim findings) to all participating sites.

IRB policies and procedures from each approving institution will be followed by researchers at that site. All required reports will be provided to the local IRB as per their policy. The coordinating PI at the University of Louisville will be responsible for providing local information as well as unanticipated problems involving risks to subjects or others, protocol modifications, or interim findings that may affect the UofL IRB's continuing approval of the research.

Informed Consent Document

Signed informed consent is required on all human subjects research that is not exempt from IRB review except as provided in this section.

The HSPPO has developed an Informed Consent Document template that provides investigators with guidance in developing this form. The template prompts the investigator to add details about the study, levels of risk, and other issues as indicated. The format and language in the template have been approved by the IRB. These documents are available from the HSPPO and may be downloaded from the HSPPO website or produced using the informed consent builder in the BRAAN2 electronic protocol submission software.

Initials and Date On Informed Consent Document

The informed consent form builders in BRAAN2 have a space at the bottom of each consent page for subject initials and date. This is programmed into the software and can not be removed. Some sponsors or researchers may wish to include the initials and date on each page of the consent. Others do not. The IRB does not require that subjects/LARs initial and date each page of the consent document. The use of these blanks is at the discretion of the researcher and/or sponsor. If they are completed on an informed consent form or left blank, the IRB does not care.

Content of the Informed Consent Document

All consent processes should include the basic elements of consent.

1. A statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures, which are experimental⁴³.
 - a. This section should provide a clear and accurate statement of the scientific purpose, the objectives of the research, the reasons why the study is being conducted, and a description of the background supporting the activity.
 - b. This section should clearly identify the procedures that will be followed during the course of the research activity. The procedures should be presented to the subject in the order of their occurrence and should detail the approximate duration for each activity the subject is expected to complete⁴⁴.
 - c. There are certain situations where the difference between clinically indicated and experimental interventions must be explained for subjects in the "Procedures" section of the consent form. These sections should contain a clear statement regarding which procedures are experimental and which procedures are standard care.
2. A description of any reasonably foreseeable risks or discomforts to the subject;
 - a. The consent form is required to provide subjects with a clear understanding of any risks or discomforts which are reasonably anticipated during the participation in the research⁴⁵. All foreseeable risks and/or discomforts of participating in a research study should be addressed in the "Risks/Discomforts" sections. Risks should not be understated or overstated. In some cases it is appropriate to cite statistical probability of risk occurrence, risk prevention measures, reversibility and treatment. Appropriate disclosure of the potential risks associated with an intervention can be particularly difficult in clinical regimens where decisions are based upon available data.
 - b. It is OHRP's and FDA's position that this phrase (A description of any reasonably foreseeable risks or discomforts to the subject) applies to the risks or discomforts associated with the research activity(s) and not to clinical intervention(s) that would have occurred otherwise unless the research intervention in some manner modifies the risks or discomforts associated with the clinical intervention.⁴⁶
 - c. A principal element of the informed consent process is a Subject making an informed decision regarding their willingness to undertake the risks of a project.

⁴³ 45 CFR 46.116(a)(1), 21 CFR 50.25(a)(1)

⁴⁴ 45 CFR 46.116(a)(1), 21 CFR 50.25(a)(1)

⁴⁵ 45 CFR 46.116(a)(2), 21 CFR 50.25(a)(2)

⁴⁶ <http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm>, <http://www.fda.gov/oc/ohrt/irbs/informedconsent.html#children>

- d. If the study is a “pilot” study or “Phase I” study the consent form should indicate that the subject is one of the first to participate in the process, treatment or intervention.
3. A description of any benefits to the subject or to others, which may reasonably be expected from the research;
 - a. This section of the consent form should state whether there are any direct benefits to the subject that may reasonably be expected as a result of participation in the research. Examples of direct benefit to the subject may include treatment of an illness, or knowledge of value to the subject (e.g., results of a cardiac stress test, results of an educational test, etc.). The potential benefits to the subjects should not be overstated, coercive, or guaranteed. If there are no direct benefits to the subject, this should be clearly stated⁴⁷.
 - b. This section is suggested to ensure fair representation of potential benefits to prospective subjects. All research should have some underlying potential benefit to society (e.g., advancement of knowledge, health benefit to others, etc.). This section should not address payment issues as a benefit.
 4. A disclosure of appropriate alternative procedures or courses of treatment (including no treatment), if any, that might be advantageous to the subject; a statement under alternatives similar to: "Other treatments for your disease include different drugs and drug combinations with similar side effects. You may choose to continue whatever treatment you are receiving. Another alternative treatment plan is comfort care only, where treatments are directed only at reducing symptoms, relieving suffering, and maximizing comfort, dignity, and control. (In comfort care only, treatment is not directed at curing, slowing, or reversing your disease.);
 - a. In clinical research, all consent forms are required to indicate any therapeutic alternatives available to the subject in the non-research and/or research context that may be of reasonable benefit to the subject. When appropriate, the relative risks/benefits of the therapeutic alternative vs. the research should be stated⁴⁸. It is important to remember that an alternative could be supportive care or “watchful waiting” only. Medical protocols which are not therapeutic should state, “Since this protocol is not therapeutic in nature, the only alternative to participation is not to participate in this research.” For studies involving alternative therapies, the research alternatives as well as other available treatments should be clearly distinguished and described.
 - b. In non-medical research, the consent form should state any alternatives that may be advantageous to the subjects. For instance, if subjects are students who will receive extra credit for participation, the consent form must describe the alternatives available to earn equivalent academic credit.
 5. A statement describing that confidentiality will be maintained and the mechanisms being used to preserve it. It should also state, however, the rights of study sponsors and the regulatory and other agencies, such as the FDA, to review study data, including records identifying subjects;
 - a. This section should state that any information obtained in connection with the research and that could identify the subject will remain confidential and will be disclosed only with the subject’s permission or as required by law. It should detail the extent to which

⁴⁷ 45 CFR 46.116(a)(3), 21 CFR 50.25(a)(3)

⁴⁸ 45 CFR 46.116(a)(4), 21 CFR 50.25(a)(4)

confidentiality will be adhered to and how specific records identifying the subject will be maintained⁴⁹.

- b. Depending on the subject matter of the research, there may be limits to the investigator's promise of confidentiality to the subject. An example would be if a subject reveals information about possible child or elder abuse, or if the investigator and/or research staff discover the possibility of abuse.
 - c. Under Kentucky law, the privilege of confidentiality does not extend to information about sexual or physical abuse of children, spouses or elders. If any member of the program staff has or is given such information, he or she is required to report it to the authorities. The obligation to report includes alleged or probable abuse as well as known abuse.
 - d. Investigators are required to protect and/or disguise an individual subject's identity when using photographs, videos, or audiotape recordings. Statements regarding the use of photographs, videos, or audio recordings should be consistent in both parental permission forms and children assent forms. For example, if the child's assent form indicates that the photographs, videos, or audiotapes are confidential and only the investigators will have access to the material, then the parental form should not indicate that the parent/guardian will have access to the tapes of photographs. The investigator should clearly outline in the consent form whether the tapes will be used for classroom presentations, conventions, presentations, or possibly release to outside agencies. The consent form should also indicate when the tapes and/or photographs will be destroyed. In addition, the consent form should indicate the provisions for masking the subjects' identity.
 - e. If the investigator intends to release any information⁵⁰, the standard statement of confidentiality should be modified to state the person(s) or agency to whom information will be furnished, the nature of the information, the purpose of the disclosure, and whether the subject's name will be used.
6. For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained;
 - a. Cash payments (if any) should be described in dollar amounts. Subjects should also be told how much of the payment they will receive if they do not complete the research. The IRB, in compliance with the stated position of the FDA, encourages adoption of a pro-rated payment system whenever possible.
 - b. The nature, amount, and method of payment or compensation must not constitute undue inducement to participate (e.g., the payment alone should not serve as sufficient inducement for the subject to volunteer). Reimbursement may be provided for costs of participation (parking fees, travel, lost work time, baby-sitters, etc.). Therefore, partial participation in a research activity would obligate partial payment. Also, any anticipated

⁴⁹ 45 CFR 46.116(a)(5), 21 CFR 50.25(a)(5)

⁵⁰Required UofL IRB approved language addressing confidentiality: "The sponsor, the Institutional Review Board (IRB), the Human Subjects Protection Program Office (HSPPO) and other appropriate regulatory government agencies may inspect your research/medical records. The Investigator will supply your information to those responsible for regulatory and financial oversight of research subjects. Those responsible for financial oversight of research participants at this institution may review your research records. This is necessary so that any claim(s) for benefits arising from services rendered to you either as an inpatient or outpatient can be completed and submitted appropriately."

delays in processing payment (i.e., “it will take up to six weeks to receive your check”) should be mentioned.

- c. Researchers should carefully consider the potential for coercion when payment is offered for research participation. This is especially true when parents are offered payment for the participation of their children. Parents may exercise undue influence on their children in order to receive the promised payment. The primary issue in these situations is the assent of the child. Assent must be obtained from the child by the researcher without interference of the parent. If the child declines assent, the researcher is obligated to honor the child’s wishes and participation ends at that point. Payment for research participation in these situations, then, is predicated, not on the parent’s consent for the child’s participation, but on the child’s own assent to participate. If the child does not assent, payment for parent consent should not be offered. If payment will be in the form of class credit that will be awarded for research participation, the amount and type of credit should be clearly stated as well as any required conditions for credit. If the student does not wish to participate in the research, reasonable equivalent methods of credit must be offered.
- d. A statement regarding “Emergency Care and Compensation for Injury” is a required element of the consent form for all research that presents more than minimal risk as determined by the IRB⁵¹. “Minimal risk,” as defined by the Federal regulations, is “where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”⁵². For example, the risk of drawing a small amount of blood from a healthy adult for research purposes is no greater than the risk of doing so as part of a routine physical examination. Investigators should explain in the consent form whether any compensation/medical treatments are available in injury occurs and, if so describe the extent and nature of the compensation, and provide an estimate of the cost of the medical treatments. As a general rule, sponsors and researchers are responsible for the costs of medical care for subjects injured in the course of research participation.

Research Related Injury

Choose one of the following three options in bold. If industry sponsored, pick the option that best matches the proposed contract language.

- a. Sponsor pays for injury

If you are injured by being in this study treatment is available. The sponsor will pay for any necessary medical costs related to the treatment of your injury. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor.

Instruction:

- a. If limiting treatment sites, the investigator must state specifically where the treatment will be provided.

⁵¹ 45 CFR 46.116(a)(6), 21 CFR 50.25(a)(6)

⁵² 45 CFR 46.102(i), 21 CFR 50.3(k)

b. If the sponsor attaches conditions state them, e.g., if the subject has followed all the instructions of the investigator, or if the investigator has followed all the procedures in the research study.

b. Sponsor pays what insurance does not pay for injury

If you are injured by being in this study, treatment is available. Your insurance will be billed for the cost of treatment. The sponsor will pay for any necessary medical costs related to the treatment of your injury due to your taking part in the study and not paid by your insurance or any other payor. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor.

Instruction:

a. If limiting treatment sites, the investigator must state specifically where the treatment will be provided.

b. If the sponsor attaches conditions state them, e.g., if the subject has followed all the instructions of the investigator, or if the investigator has followed all the procedures in the research study, or will pay for whatever your insurance will not cover.

c. Sponsor does not pay for injury

If you are injured by being in this study treatment is available. The sponsor, the study site, or your study doctor has not set aside money to pay for treatment of any injury. You and your insurance will be billed for the treatment of these injuries. Before you agree to take part in this research study you should find out whether your insurance will cover an injury in this kind of research. You should talk to the study doctor or staff about this. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor.

The investigator is responsible for selecting the correct paragraph to match the study contract language. If there is disagreement on the language between the sponsor and the IRB and the sponsor agrees that one of the three paragraphs previously approved by the IRB is acceptable, then the IRB allows the Chair or Vice-Chair to approve this minor change in the consent form.

Studies Requiring Cabinet for Health And Family Services (CHFS) IRB Approval

Use the following language for studies that recruit from CHFS clients (wards and foster children) if the study is greater than minimal risk:

"If you are injured by being in this research study, the study doctor will arrange for you to get medical treatment. You do not give up your legal rights by signing this form. If you are injured during the research because of negligence⁵³ on the part of the researcher or the sponsor, you

⁵³ Negligence - Failure to exercise the degree of care considered reasonable under the circumstances, resulting in an unintended injury to another party.

can still pursue all opportunities available through Kentucky law. If you think you have a research related injury, please call your study doctor."

For studies that recruit from CHFS clients and are less than minimal risk or minimal risk, do the following per direction of the CHFS IRB. Do not include any language concerning the availability of treatment for injury since the "Common Rule" does not require information to be given for minimal risk studies;

7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and a consent form must include a section explaining who can be contacted for answers to questions about the research, such as the results, and whom to contact in the event of a research related injury⁵⁴. The "Identification of Investigators" section should clearly identify the members of the study team who may be contacted and a contact telephone number that can be used (24 hours a day, 7 days a week, for greater than minimal risk studies);
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled;
 - a. federal regulations require a clear statement in all consent forms that participation in the study is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subjects may discontinue participation at any time without loss of benefits to which the subject is otherwise entitled⁵⁵. For research involving prisoners, the consent form should clearly state that participation and/or withdrawal from participation will not affect the subjects sentencing or parole status, and;
 - b. when appropriate, the consent form should state the consequences of a subject's decision to withdraw from the research. If applicable, the consent form should also state any anticipated circumstances under which the subject's participation may be terminated by the investigator or sponsor without regard to the subject's wishes.

The following additional statements may be required by the IRB:

9. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant), which are currently unforeseeable. if contact with a male subject can induce harm to a significant other (or to the embryo or fetus, if the significant other may become pregnant), which are currently unforeseeable⁵⁶;
10. Anticipated or unanticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
11. Any additional costs to the subject that may result from participation in the research. This section of the consent form is required for medical (including physical therapy and occupational therapy), dental, psychological research, etc., and should clearly state all financial obligations the subject may incur as a result of participation in the study (e.g., physician's fees, hospital charges, medications, pharmacy dispensary charges, laboratory tests, post-treatment follow-up, etc.). In addition, this section should also indicate if drugs, devices, tests or services will be

⁵⁴ 45 CFR 46.116(a)(7), 21 CFR 50.25(a)(7)

⁵⁵ 45 CFR 46.11(a)(8), 21 CFR 50.25(a)(8)

⁵⁶ 45 CFR 46.116(b)(1), 21 CFR 50.25(b)(1)

provided free-of-charge. The consent form should disclose all potential additional costs to the subject as a consequence of procedures carried out for research purposes (e.g., extended hospitalization, additional tests, etc.). Potential subjects should be advised that many health benefit plans do not cover experimental treatments, and they must be told if their insurance companies will be billed;

12. Consent forms should also indicate if there might be medical or other consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
13. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. The following are examples of reasons that might affect a subject's willingness to continue participating in a research project:
 - a. new toxicity data,
 - b. change in the risk/benefit ratio,
 - c. new alternatives to participation,
 - d. negative media attention,
 - e. unexpected findings of a DSMB,
 - f. moving the visit sites for the research a significant distance from the original site,
 - g. loss of study data,
 - h. failure to maintain confidentiality,
 - i. suspension or termination of the research by the IRB (the IRB will make a case-by-case decision),
 - j. suspension or termination of an investigator or key personnel (the IRB will make a case-by-case decision), and
 - k. other yet unknown and/or unanticipated information that may have significant impact on the subject's willingness to continue to participate;
14. The approximate number of subjects involved in the study⁵⁷. If a multi-site study, include local as well as total numbers;
15. A provision for subjects to be given a signed copy of the consent form, if the consent is written;
16. Identification of the sponsor in sponsor-initiated studies;
17. If blood is to be withdrawn, the consent form should include blood withdrawal information, such as: amount of blood to be withdrawn (in teaspoons or tablespoons); number of times; period of time covered; potential hazards, such as "a bruise at the site of vein puncture, inflammation of the vein and possible infection," and a statement that "care will be taken to avoid these complications;"
18. If subjects are being recruited only from Jewish Hospital Healthcare Services, Norton Healthcare, or UofL Health Care, the name of the hospital should be included with the University of Louisville at the beginning of the consent. If subjects are recruited from multiple sites, then list all the sites in the consent plus the University of Louisville;
19. If subjects are being followed for survival, the consent form must indicate the investigator's intent to do so;

⁵⁷ 45 CFR 46.116(b)(6), 21 CFR 50.25(b)(6)

20. Phase I studies, especially cancer chemotherapy studies, must include language which directly conveys the following: that the study is being done solely to ascertain the safety and/or toxicity of the drug or agent; that a therapeutic response is not the goal nor the expectation of the study; that some subjects will experience important or serious toxicities, and that these are more likely to occur at higher doses; and that the study will be discontinued when specified toxicities occur;
21. Reviewer should consider given the target recruitment populations, the necessity of consent forms in languages other than English;
22. Subjects have the right to know if material such as tumor tissue, bone marrow, blood, etc. will be turned into a commercial product. As a result, investigators are required to inform subjects in the consent form if any human materials (tumor tissue, bone marrow, blood, etc) may be used to establish a commercially useful product (e.g., a cell line). Subjects should also be informed that they may not benefit from the development of the commercial product;
23. When appropriate, a statement should be detailed in the consent form that the research is being done as partial fulfillment of the requirements for a Master's degree or doctoral degree.

The FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study. While HHS has the right to inspect records of studies it funds, it does not impose that same informed consent requirement.

For studies that involve FDA regulated products, the IRB shall require documentation of informed consent in accordance with Sec. 50.27, except as follows: (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. However, Federal regulation (21 CFR 50) requires that clinical investigations that support applications for research or marketing permits for FDA regulated products comply with its written informed consent requirement. This includes studies conducted after marketing but required as part of Premarket approval. IRBs should be aware of the requirements of informed consent when reviewing post approval studies that are required by the FDA as a condition of a marketing permit; or (2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.

Generally, all FDA regulated research involving drugs and devices require written informed consent by the subject or legally authorized representative. Some emergency research may be excepted.

The HSPPO and the chair or designee reviews the Informed Consent Document as a part of the triage process to determine if all basic elements of consent are contained in the document. Consent document(s) that are determined to be clearly inappropriate (e.g., significant deficiencies, too complex) are returned to the investigator for re-writing prior to being scheduled for IRB review. The reviewer must ensure there are no discrepancies between the protocol, application, and informed consent documents regarding the purpose, risks and benefits of the research.

The investigator receives written notice of required changes in the Informed Consent Document prior to final IRB approval. Final approval is not granted until all required changes have been made and submitted for review and approval.

The approved Informed Consent and Assent Documents are stamped with the IRB ID number, the date of approval, and the date of expiration.

Short Form Consent

A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative (LAR) or research LAR. When this method is used, there will be a witness to the oral presentation. The IRB will approve a written consent summary (see short form definition) of what is to be said to the subject or the LAR. The subject or the LAR signs only the short form. However, the witness signs both the short form and a copy of the consent summary, and the person actually obtaining consent will sign a copy of the consent summary. Thus, three types of persons are involved in this specific consent process; the subject or legally authorized representative or parent(s) of a child who is a subject, the person obtaining consent, and the witness. A copy of the consent summary will be given to the subject or the representative, in addition to a copy of the short form. Additional information about [short form consents](#)⁵⁸ may be found on the OHRP website.

Non-English Consent Forms

Investigators often face the situation where research participants do not read/speak English. The IRB recommends that when non-English consent forms are necessary, the translation should occur AFTER the English version of the consent form has incorporated all IRB requested changes and has received approval. The investigator must have a written translation of the entire consent form available in a language understandable to the subject. The investigator bears the responsibility of verifying the accuracy of translation of all consent forms submitted. The translated document must be accompanied by an Affidavit of Accuracy⁵⁹, which, with the translated document, will be provided to the IRB and the sponsor (if applicable).

The IRB approved informed consent documents should be available in English and other languages as appropriate to the subject population(s). For investigators proposing to use non-English consent documents, quality assurance procedures should be developed such as translation of the consent document from English to the second language and then back to English by a second translator, if available, proficient in the second language, to ensure that the information is correctly conveyed. The IRB is required to review all non-English consent forms and recruitment tools. The role of cultural norms of subjects should be addressed. This information should be provided is a clearly identifiable form for the IRB to review.

Non-English Speaking Subjects

Investigators may seek informed consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate. It is therefore critical that the information in the informed consent document be written in language that is understandable to the subject. The informed consent documents should be available in English and other languages as appropriate to the subject population.

⁵⁸ <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm>

⁵⁹ Affidavit of Accuracy – a document signed by a qualified translator in which the translator who performed or verified the translation affirms that the entire document has been translated, that nothing has been omitted or added, and that the translation is true and correct. A qualified translator is an officer or employee of an official translation bureau or agency or a professor or instructor who is teaching the translated language in an accredited college or university in the United States. The type of course being taught must be included in the Affidavit of Accuracy, which must be on official school stationery and notarized.

Federal regulations require the translation of consent forms into the language that is most easily understood by potential research subjects. The UofL IRB requires that researchers develop foreign language consent documents when enrolling subjects whose native language is not English.

Consent forms should be available in English and other languages as appropriate to the subject population(s) anticipated for a particular research project. Development of non-English language consent forms will typically necessitate translation of the original consent from English to the second language and then back to English. Back translation is necessary to ensure that the information is correctly conveyed. A certificate of accuracy from the qualified translator should be submitted.

The following guidelines should only be used if a non-English speaking subject is encountered unexpectedly:

If a non-English speaking subject is encountered unexpectedly, investigators may rely on an oral translation of the English language consent form but should take extra care in the informed consent process to ensure that the subject has understood the study procedures, risks, benefits, etc.

The research subject should be provided with a short form consent document, written in the subject's native language that summarizes the basic elements of the informed consent.

Consent procedures:

- a. The standard (i.e. IRB approved, full description) informed consent document should be presented verbally to the subject in his/her native language and all questions must be answered.
- b. With the agreement to participate in the research study, the subject should sign and date the translated "short form" consent document and the witness to the informed consent process should sign and date the "short form" consent document and the standard consent document. The investigator or person obtaining informed consent should sign and date the standard informed consent document.
- c. Copies of the signed "short form" consent document and the standard informed consent should be given to the subject with the originals of both documents retained in the investigator's research records.
- d. A statement in the research records should indicate that the translation took place; the name of the translator; and the translator's belief that the subject understands the study and the consent process.
- e. Investigators should consider that in obtaining clinical consent, family members most often shield their loved ones from bad news (i.e. risks of study). A proper medical translator is an important safeguard that should not be set aside lightly.

When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

English Speaking Subjects Unable To Sign Consent Form

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document. A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire

consent process and sign the consent document. A video tape or audio tape recording of the consent interview is recommended.

Process of Obtaining Informed Consent

The protocol reviewer should consider the following description of the process of obtaining informed consent and determine if the "Informed Consent Document" submitted accurately reflects the research and provides the necessary information for a potential human subject to truly give informed consent.

Informed consent is understood as an on-going process, which starts with the initial presentation of a research activity to a prospective subject by the investigator and continues through the research activity until the subject ends his/her participation or the study closes. Research subjects are rarely aware of research activities prior to an initial presentation by the principal investigator or a member of a principal investigator's research team. The initial phase of consent requesting participation in a research activity commonly begins with the first contact between the subject and the investigator. Many subjects make their decision regarding whether to participate in research during this initial contact. As a result, the greatest potential for misunderstanding exists in the initial consent process. Researchers must provide sufficient time for a potential subject to reflect on the nature of participation during the important initial presentation of a research activity. When subjects are presented with numerous research and clinical options, the consent process must include a clear description of the possible known ramifications resulting from each option presented. Subjects must also be made aware of the possibility of unforeseen risks resulting from participation in the research project. The presentation must not include specific "leading" information about whether to participate in any particular project.

By providing a potential subject with information understandable to the subject in an initial session regarding complex research issues, potential subjects should have an improved comprehension of the elements within the consent form and provide a more informed consent for participation in the research.

The next step in the consent process is the presentation of the consent forms to the subject. In biomedical research the investigator should separate the research consent form from any other clinical information or hospital admission forms. Subjects should not be asked to sign hospital admission paperwork or hospital consent documents for clinically indicated procedures at the same time as the presentation of the research consent form. The presentation of the research consent form should be a separate process. The principal investigator or a member of the research team should ensure that the subject or legally authorized representative (LAR) reads the consent form⁶⁰. After the subject or LAR reads the consent form, the principal investigator or member of the research team should ask the subject or LAR if he/she has any questions regarding the information contained in the consent form.

⁶⁰ Informed consent by a subject is one of the key cornerstones of the system protecting human subjects in research. It has traditionally been recognized that consent by someone other than the subject is not the same as the subject's own consent. There are instances, however, in which a subject may be unable to consent. Federal regulations allow for consent by the individual or his/her Legally Authorized Representative (LAR). LAR means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Therefore, the University of Louisville IRBs recognize the similar method of choosing a responsible party authorized to make health care decisions in [Kentucky statutes](#) will suffice for choosing a legally authorized representative for subjects unable to consent. If it has been determined that a person is a child or a person who does not have decisional capacity any one (1) of the following responsible parties, in the following order of priority if no individual in a prior class is reasonably available, willing, and competent to act, shall be authorized to make decisions on behalf of the person: (a) The judicially-appointed guardian of the person, if the guardian has been appointed and if medical decisions are within the scope of the guardianship; (b) The attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for health care decisions; (c) The parent or spouse of the person; (d) if the person is incompetent, an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation; (e) The nearest living relative of the person, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives. Consent by a LAR should involve all the same considerations that informed consent from a competent subject involves. It also involves identifying a proper representative and ensuring to the extent known that the research decision reflects the wishes of the subject.

In situations where the ability of the subject to understand the form is in question, for example, the form includes complex scientific information or the subject is possibly educationally or mentally challenged, the investigator or member of the research team may wish to ask questions of the subject to ensure an understanding of the basic elements of the consent form. In performing an assessment of the subject's comprehension of the consent form, an investigator should request that the subject indicate the risks of participation, how the subject may withdraw, and what alternatives exist to participation in the research. The decision-making capacity of subjects with psychiatric disorders or cognitive deficits (such as dementia) should be evaluated by a practitioner not otherwise affiliated with the research.

The person presenting the informed consent document should ensure that the potential subject is fully informed that his participation in research is a voluntary process and that he does not have to participate in order to obtain any care he is eligible to receive. All efforts should be made to offer the potential subject or LAR sufficient time to consider the information contained in the consent form. The potential subject or LAR should be given the opportunity to take the consent form home and sign the form on a return visit or be left alone to consult about enrollment with family or friends. If the individual decides to participate, he/she is asked to sign the consent form. The person obtaining the subject's informed consent must also sign the form. The subject must be given a copy of the form the subject signed. The IRB does not normally require a witness to observe the subject's signature but, the IRB may require a witness to document the process if the IRB feels there is sufficient reason to do so. If the investigator is not the person who obtains the signed informed consent from the subject, then, in compliance with University of Louisville IRB policy, an investigator on the study must sign the consent document within two weeks of the subject's giving written informed consent. 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. The FDA, but not HHS, provides for an exception from the informed consent requirements in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in § 50.23. The original consent is retained in the investigator's files.

Research is an on-going process, which involves the constant re-evaluation of current information and procedures. Therefore, investigators are ethically obligated to keep subjects apprized of all issues related to their participation in the study. New information should be presented to research subjects in a written form and the subjects should be asked to sign a copy of the form or to sign a revised consent form. Serious adverse events or unanticipated problems may occur during a research activity that would directly affect whether prospective or enrolled subjects would wish to continue in a particular research activity.

Subjects must receive the new information as a part of the continuing consent process. Investigators should note that the IRB requires IRB review and approval prior to an investigator providing subjects with new research information. Information also may arise regarding the study that should be shared with previously enrolled subjects after the completion of a study, or a specific treatment or procedure. For example, dysfunctional families may participate in qualitative research examining parenting techniques. Following data analysis, the investigator finds that a specific technique is superior to the other study arms of the project. As agents of a health care and educational institution, investigators are ethically obligated to provide this valuable new information to research participants.

It is difficult to be confident that volunteers truly understand the nature of their participation in research when they are confronted with volumes of complex scientific details in a brief and isolated session. Creating an on-going consent process will facilitate an exchange of information between subjects and investigators in a scientific environment of increasing complexity. By providing subjects with the opportunity to give effective and on-going informed consent in a process that incorporates the free

exchange of information between both the researcher and the subject, investigators will continue to set standards for the conduct of ethical research.

Informed Consent (Assent) with Children

For research involving the participation of children (ages 7-18), a subject assent document is required. The investigator will prepare and submit for approval a document that describes the research detail in general terms understandable to the child subjects participating in the proposed project. The IRB may determine that the informed consent document requires a single parental signature or dual parental signatures for a particular project based on the level of risk involved. This document should be written to the parent(s) or research LAR who will give permission for the child.

The IRB shall determine that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under [§46.404, 50.51](#) or [§46.405, 50.52](#). Where research is covered by [§46.406, 50.53](#) and [§46.407, 50.54](#) and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Guidance for Investigators for the Use of LAR Consent for Children

Children in Kentucky under age 18 (unless Emancipated) must have consent given by a LAR. The LAR may be determined by the following:

1. The judicially-appointed guardian of the child, if the guardian has been appointed and (for biomedical research) if medical decisions are within the scope of the guardianship;
2. The attorney-in-fact named in a durable power of attorney, if the durable power of attorney (for biomedical research) specifically includes authority for health care decisions;
3. The parent or parents of the child;
4. An adult sibling of the child, or if the child has more than one (1) sibling, the majority of the adult siblings who are reasonably available for consultation;
5. The nearest living relative of the child, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives.

Waiver of Parental or Guardian Permission

The IRB may waive parental permission under limited conditions:

1. When the consent of parents is not a reasonable requirement because it poses additional risk to the potential subject, or the parents' interests may not adequately reflect the child's interests (for example, research concerning neglected or abused children), the IRB may waive the requirement for parental or guardian consent. The researcher should propose an alternative mechanism in the application and explain how it will protect the child. The IRB may require an alternative mechanism for protecting the rights and welfare of children. The choice of an appropriate alternative mechanism depends on the nature and the purpose of the research, the risks and the anticipated benefit to the child, and the age, maturity, status, and condition.
2. When the subject is emancipated. Investigators should be aware that the definition of an emancipated child in the Kentucky Revised Statutes might vary, depending on the child's situation. The investigator is advised to review the Statutes before attempting to determine if a

person under the age of 18 meets the definition of emancipated as it relates to the proposed research. Generally, a person under the age of 18 in Kentucky is considered as emancipated when;

- a. he/she becomes self supporting,
- b. joins the armed forces,
- c. is released from the control and supervision of his or her parents or guardian by the courts, or
- d. has a valid marriage.

Pregnancy does not emancipate a female unless other conditions are met. For example, moving out of the parents' or guardian's house and into an apartment, setting up housekeeping with a partner, and having a baby can be emancipating, because the totality of the circumstances shows an intent to be free of the parents' custody, control, and support. However, the emancipation status will still be determined by the courts and is generally controlled by the contention that the female is free from the supervision and control of her parents or guardian and she has become self supporting, not that she is pregnant.

Informed Consent with Cognitively Impaired Persons

The IRB will determine that adequate provisions are made for seeking the assent of the cognitively impaired person, as well as the informed consent of the person's LAR or SR, when in the judgment of the IRB the person is capable of providing assent. In determining whether the cognitively impaired person is capable of assenting, the IRB will take into account the age, maturity, and psychological state of the person involved. This judgment may be made for all cognitively impaired persons to be involved in research under a particular protocol, or for each individual, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the cognitively impaired persons is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the individuals and is available only in the context of the research, the assent of the persons is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A. This document should be written to the agent designated by a health care power or attorney, or some other legally authorized representative who will give permission for the subject.

Signing the Informed Consent Document

Federal regulations require the subject's or subject's LAR signature [45 CFR 46.117(a)] and date of signature [21 CFR 50.27(a)] as the only required signature on the informed consent document to be a valid informed consent document. The International Conference on Harmonization (ICH) Good Clinical Practices Guidelines (ICH GCP 4.8.8.) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Standards [RI 2.180 (primary standard) and MM 7.40] require that a research informed consent document be signed and dated by the subject or LAR and signed and dated by the person who explained the document and obtained the subject's or the subject's LAR signature. The University of Louisville requires these signatures and dates on each consent form. The University of Louisville requires that the investigator also sign the informed consent form within 14 days if the investigator is not the person obtaining the subject's signature on the informed consent form. This University of Louisville requirement is mandated to ensure that investigators are aware of individuals who have been recruited to participate in research studies where the University of Louisville IRB is the IRB of record.

Modifying the Consent Process

Written informed consent is a basic principle in the protection of human subjects. The Federal regulations allow the IRB to waive or alter the requirements only under special conditions. As a result, the waiver of informed consent is one of the most misunderstood provisions of the Federal regulations. There is oftentimes confusion as to whether an investigator is requesting waiver of documentation of informed consent or a waiver to all or part of the consent process.

All research, whether reviewed by the full IRB or by way of expedited review, must conform to the applicable requirements for obtaining and documenting prospective informed consent. The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent. Information on the conditions for waiving, excepting, or otherwise altering the informed consent requirements that are set forth in 45 CFR 46.116(b)(c)(d) and 117, 21 CFR 50.23 and 24, or 21 CFR 56.109(c).

For studies that involve FDA regulated products, the IRB shall require documentation of informed consent in accordance with Sec. 50.27, except as follows: (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. However, Federal regulation (21 CFR 50) requires that clinical investigations that support applications for research or marketing permits for FDA regulated products comply with its written informed consent requirement. This includes studies conducted after marketing but required as part of pre-market approval. IRBs should be aware of the requirements of informed consent when reviewing post approval studies that are required by the FDA as a condition of a marketing permit; or (2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.

Waiver of Consent or Elements of Consent

The IRB may approve a consent procedure, that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by, or subject to the approval of, state or local government officials, and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

The IRB may approve a consent procedure, that does not include, or that alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. the research could not practicably be carried out without the waiver or alteration; and
4. whenever appropriate, the subjects will be provided with additional pertinent information after participation.

DHHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.

The Federal regulations do not allow a waiver of the conditions of informed consent because the conditions make it difficult to enroll subjects in the research. The FDA does not allow for a waiver of written informed consent for any product it oversees except in certain instances of emergency research. IRB review and approval in this very narrow instance is necessary prior to the beginning of any research. Certain criteria must be met before approval. The minutes of the IRB meeting must document protocol specific findings that justify the IRB's waiving or altering the elements of subject informed consent.

Waiver of Documentation of Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects, if it finds either:

1. The only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
2. That the research presents no more than minimal risk of harm to subjects, and involves no procedures for which written consent is normally required outside of the research context.⁶¹
3. The requirements for written informed consent cannot be waived or altered for research involving drugs or devices except for previously approved emergency research.

In cases, in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. If the IRB waives the documentation requirement, the waiver determination will be documented in the study file as well as on correspondence provided to the investigator. The minutes of the IRB meeting must document protocol specific findings that justify the IRB's waiving or altering the elements of subject informed consent.

Approval of research that uses deception or passive consent requires approval as a waiver or alteration of the consent process.

Protocol Changes (Amendments/Modifications), Deviations, Exceptions and Violations

Investigators are responsible for conducting human-subjects research in accordance with all applicable federal and state regulations, UofL IRB policies and procedures. During the conduct of the study, changes to the protocol may be proposed or unintentional changes may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by federal regulations and UofL IRB policies and procedures.

Amendments are submitted for review utilizing the Study [Amendment Request](#) Form or the amendment process in BRAAN2. The amendment and any required modifications to the protocol, consent or other study documentation are submitted at the same time. The amendment reviewer has access to the same documentation as the initial or continuing reviewer and is expected to conduct the review with the

⁶¹ 45 CFR 46.117(c) & 21 CFR 50.27

same diligence as an original or continuing review regardless of whether or not the review is expedited or full board review.

The federal regulations specifically require the IRB to review proposed changes in a research activity, and to ensure that such changes in approved research are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45CFR46.103(b)(4)(iii) and 21CFR56.108(a)(4)]. Research activity includes all aspects of the conduct of the research study, e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc. - all of the information outlined in the protocol submission and reviewed and approved by the IRB. Non-compliance with these regulations, UofL IRB policies and procedures, or UofL IRB requirements during the conduct of a research study results in a protocol violation, and as such must be reported to the IRB.

Planned changes to the IRB-approved protocol, protocol deviations and protocol exceptions, must be submitted as formal protocol amendments or protocol exceptions to the IRB and must be approved prior to initiation or implementation of the change. Any protocol deviation that is not approved by the IRB prior to initiation is a protocol violation and must be reported to the IRB as outlined below. The appropriate forms can be found on the [HSPPO website](#) or through the BRAAN2 software.

Investigators must report planned changes in the conduct of a study and receive approval from the IRB prior to implementing these changes. The approval documentation sent to investigators notifies them of the need for submitting any changes (via a [Study Amendment Request Form](#) or through BRAAN2) in their research projects, prior to initiation, to the IRB for review and approval. Regulations⁶² permit the use of expedited procedures for review of minor changes to previously approved research during the period for which the approval is authorized. Modifications that alter the risk/benefit ratio are assigned to a primary reviewer and presented to the full committee at a convened meeting. The essence of the study should be summarized by the reviewer for IRB members and the reviewer should state what the proposed modification is and how it will affect the conduct of the study, the risk/benefit ratio, and whether or not the amendment should be approved as written. If the amendment requires a change in the informed consent document, then the reviewer must review that change and recommend appropriate committee action. Amendments submitted to the IRB, along with supporting correspondence, are entered into the HSPPO or BRAAN2 database, and placed in the study file.

Investigators are notified electronically of the decision of the IRB and of any changes required. Modification approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent a modification approval letter indicating the date of the next study expiration. The IRB may only approve modifications through the current approval expiration period, unless considered at the time of continuation review. The modification approval letter reminds the investigator that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects. Upon receipt of the approval for the amendment, the investigator may initiate the modification.

Investigators will promptly report within five (5) business days proposed changes in previously approved human subject research activities to the IRB. 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.

When changing personnel including principal investigators, researchers must submit a Study Amendment Request Form or utilize the BRAAN2 software, indicating the change in responsibility.

⁶² 45 CFR 46.110(b)(2)

Changes in principal investigators and other key personnel may qualify for expedited review of the proposal.

Reporting Requirements

All major protocol violations must be reported to the IRB by letter within five (5) working days of discovery. Minor violations are to be reported at continuing review. It is the responsibility of the Principal Investigator (PI) to determine whether a violation is major or minor and to ensure proper reporting to the IRB. Reports of protocol violations should be submitted to the sponsor as outlined in the sponsor's protocol.

Major Violations

Examples (the list of examples is intended as a guide and is not all-inclusive):

1. Failure to obtain informed consent or research authorization, i.e., there is no documentation of informed consent/research authorization or Informed consent/research authorization obtained after initiation of study procedures
2. Informed consent/research authorization for IND/IDE studies obtained by someone other than individuals authorized by IRB to obtain consent/research authorization, e.g. someone other than a licensed physician investigator or key personnel
3. Inappropriate documentation of informed consent/research authorization, including missing subject signature, missing signature of person who obtained informed consent
4. Enrollment of a subject who did not meet all inclusion/exclusion criteria
5. Performing study procedure not approved by the IRB
6. Failure to report an unanticipated problem or serious adverse event to the IRB and/or sponsor
7. Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
8. Drug/study medication dispensing or dosing error
9. Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety
10. Failure to follow safety monitoring plan
11. Enrollment of subjects after IRB-approval of study expired
12. Failure to submit continuing review application to the IRB before study expiration
13. Use of invalid consent form, i.e. consent form without IRB approval stamp, or outdated/expired consent form/research authorization
14. Omitting an approved portion of the protocol

Minor Violations

Examples (the list of examples is intended as a guide and is not all-inclusive):

1. Implementation of unapproved recruitment procedures except for the purpose of subject safety
2. Missing original signed and dated consent form/research authorization (only a photocopy available)
3. Missing pages of executed consent form/research authorization
4. Copy not given to the person signing the form/research authorization
5. Someone other than the subject dated the consent form/research authorization
6. Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity
7. Study procedure conducted out of sequence
8. Failure to perform a required lab test
9. Missing lab results
10. Enrollment of ineligible subject (e.g., subject's age was 6 months above age limit)

11. Study visit conducted outside of required time frame
12. Failure of subject to return study medication
13. Over-enrollment.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The PI is responsible for following the UofL Unanticipated Problems Involving Risks to Subjects or Others Policy (UPIRTSO) when reporting unanticipated problems to the IRB using the Event Report Form found at the forms link on the HSPPO website or through BRAAN2. Principal investigators may also report events by e-mail or letter by providing the same information as requested in the Event Report Form but are encouraged to use one of the available electronic formats.

All local fatal or life-threatening events **MUST** be reported to the IRB electronically (e-mail or BRAAN2) within 72 hours of their discovery. The PI or any member of the research team must report all other reportable events to the IRB within five (5) workdays after becoming aware of an unanticipated problem or simultaneous with reporting to the sponsor or any other agency or organization, whichever occurs sooner.

Additional Investigator Reporting Responsibilities

A principal investigator or designee must promptly report any of the following events:

1. Voluntary hold placed on a study either by the principal investigator or sponsor,
2. Notice or appearance of an FDA, OHRP, or other Federal Agency auditor for the purpose of conducting a Routine/Surveillance or For Cause/Directed audit,
3. Study suspension, termination or closure by anyone other than the UofL IRBs,
4. Problems that required prompt reporting to the sponsor or funding agency,
5. Accidental or unintentional change to the IRB approved protocol that involved risks to subject or others, or that has the potential to recur,
6. Changes to the protocol taken without prior IRB review to an eliminate apparent immediate hazard to a research subject,
7. Information (publication in the literature, safety monitoring report, interim result, or other finding) that indicates a change to the risks or potential benefits of the research,
8. DSMB summary reports that indicate a change to the risks or potential benefits of the research,
9. Breach of confidentiality of research data,
10. Incorrect labeling of study medication/test article,
11. Incorrect dosing of study medication/test article,
12. Study medication/test article accountability discrepancies that trigger a study subject to be withdrawn from a study,
13. Breach of privacy/confidentiality/data security/loss of study data/sequestration⁶³ of study data due to non-compliance,
14. Unauthorized use or disclosure of protected health information (PHI),
15. Subject complaints, including those that indicate an unanticipated risk, or that cannot be resolved by the research staff,
16. Incarceration of a subject while participating in research,
17. Unexpected pregnancy of a subject or subject's partner (pregnancy is not considered to be an unanticipated problem),
18. Suicide attempt related to participation in a research study,

⁶³ Sequestration of study data means to remove any "non-allowed data" from study files. This data will be maintained in a secure location by the investigator separate from the study files from which it was removed. The investigator must sign an assurance to the IRB that the data will not be used as a part of the study results, will be maintained for as long as necessary, and destroyed when appropriate according to federal regulation and University of Louisville policy.

19. Death of a healthy volunteer while participating in research or within 30 days of participation,
20. Injury (needle stick, drug ingestion, chemical exposure, etc.) of study personnel related to preparation or administration of study drug,
21. Any other problem not previously described which in the opinion of the principal investigator was:
 - a. unanticipated,
 - b. related, and
 - c. affects the safety and welfare of current or future subjects.
22. Unanticipated adverse device effect (UADE), or
23. Anything not previously mentioned that the investigator or key personnel may think important for the IRB to know.

There are situations where an unexpected event, related or possibly related to participation in the research, and suggesting that the research places subjects or others at a greater risk of harm than was previously known or suspected, requires an immediate change to a protocol in order to relieve an apparent immediate hazard to research subjects. In these situations, the principal investigator may implement a change necessary to protect the welfare of the research subject prior to obtaining IRB approval. Investigators are encouraged to contact the IRB prior to implementation of the protocol change if they can. If not, investigators are required to notify the IRB in writing or electronically, by submitting an amendment, detailing the change within five (5) work days. Include a written description of the change and events, which necessitated immediate implementation.

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 Grants Management, and/or the Office of Industry Contracts (when the study is externally funded). Federal regulatory agencies are notified as required by federal regulation.

Study Closure

The HSPPO provides, upon request or through their website, a form that an investigator uses to notify the IRB/HSPPO of study closure. Once an investigator has closed a study, this form should be completed and forwarded to the HSPPO. HSPPO staff will document the study closure by entering the date of closure in the database maintained in the HSPPO. If the investigator has not submitted a completed continuation application or a study closure form to the HSPPO by the continuing review date, the HSPPO sends a memo to the investigator, explaining that IRB approval has lapsed. This memo includes a reminder that no human subjects research activities may be conducted until IRB approval is obtained. For therapeutic studies where subject safety is a concern, federal regulations allow some flexibility towards the continued treatment for currently enrolled subjects. However, no new subjects may be contacted, recruited, or enrolled in the study until the investigator obtains current IRB approval. A copy this letter is placed in the study file. The investigator has 30 working days from the memo date to submit the continuing review application. Failure to submit a continuing review application results in notification of study closure to the investigator and appropriate supervisor by the IRB.

In cases of on-going externally funded projects, the Office of Sponsored Programs Grants Management or the Office of Industry Contracts 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

OGM or OIC 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.

XII. EMERGENCY RESEARCH CONSENT EXEMPTION

The IRB may consider an "Emergency Research Consent Waiver" for a class of research consisting of activities, each of which have met the following strictly limited conditions. For additional information on emergency research, refer to the document [Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research](#)

Research subject to FDA regulations

The IRB responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented:

1. that the research activity *is subject* to regulations codified by the Food and Drug Administration (FDA) (see Federal Register, Vol. 61, pp. 51498-51531) at Title 21 CFR Part 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and
2. that the requirements for exception from informed consent for emergency research detailed in 21 CFR Section 50.24 have been met relative to those protocols, or

Research not Subject to FDA regulations

The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research *is not subject* to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OPRR that the following conditions have been met relative to the research:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, that may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible because:
 - a. the subjects will not be able to give their informed consent as a result of their medical condition;
 - b. the intervention involved in the research must be administered before consent from the subjects' LAR is feasible; and
 - c. there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
 - a. subjects are facing a life-threatening situation that necessitates intervention;
 - b. appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - c. risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of

- standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The research could not practicably be carried out without the waiver.
 5. The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.
 6. The IRB has reviewed and approved informed consent procedures and an informed consent document in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. These procedures and the informed consent document are to be used with subjects or their LAR in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (b)(7)(v) of this waiver.
 7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - a. consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
 - b. public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;
 - c. public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
 - d. establishment of an independent data monitoring committee to exercise oversight of the research; and
 - e. if obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a LAR, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, the IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a LAR of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document.

The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a LAR of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a LAR or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a LAR or family member can be contacted, information about the research is to be provided to the subject's LAR or family member, if feasible.

For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

For investigations involving an exception to informed consent under 21 CFR 50.24, the IRB shall promptly notify electronically (e-mail or BRAAN2) the investigator and the sponsor of the research when the IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under Sec. 50.24(a) or because of other relevant ethical concerns. The notification shall include a statement of the reasons for the IRB's determination.

XIII. RESEARCH USING FDA REGULATED PRODUCTS

Research involving an Investigational Drug or Device

The following information applies to PIs and to PIs who may also be sponsors holding an Investigational New Drug (IND) or Investigational Device Exemption (IDE) for the test article under study.

1. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an IND or IDE may be required. If an IND or an IDE is required, it is the investigator's responsibility to submit the appropriate application to the FDA, obtain the necessary documentation, and provide this documentation to the IRB as a part of the approval process.
 - a. An IND may not be necessary if all of the conditions stated in 21 CFR 312.2(b)(1) have been met. If the PI does not already have an IND, the PI will be notified electronically (e-mail or BRAAN2) that IRB approval is pending receipt of an IND. If there is a debate regarding the need for an IND, the IRB will require that the PI contact the Food and Drug Administration (FDA) to obtain written documentation that an IND is not necessary.
 - b. The IRB will review protocols involving investigational devices to determine if the device is a "Significant-Risk device" (SR) or a "Non-Significant Risk"(NSR) device. If the IRB determines that the research involves a SR device, an IDE is necessary. If the PI does not already have an IDE, the PI will be notified electronically (e-mail or BRAAN2) that IRB approval is pending receipt of an IDE.
2. Protocols involving an Investigational Drug (IND) or Investigational Device (IDE) require consideration and satisfaction of the pertinent FDA and the DHHS regulations (21 CFR 50). When the UofL PI is acting as the sponsor of research involving an investigational drug, the IRB requires that the PI submit documentation that the proposed drug preparation has been reviewed and compliance with Current Good Manufacturing Practices has been confirmed. In addition, when a UofL PI is acting as the sponsor of research involving an investigational drug or device, the IRB suggests that the PI review the reporting and record-keeping responsibilities as stated in 21 CFR 312 and 21 CFR 314 (for investigational drugs) or 21 CFR 812 and 21 CFR 814 (for investigational devices).
3. The PI is responsible for assuring the IRB that investigational drugs and devices are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor, and affiliated research institutions' storage requirements for drugs or devices of the type under study. Whenever possible, the storage of drugs and biologics should be under the supervision of a registered pharmacist and stored in the pharmacy in a limited access, locked area. Devices should be stored according to manufacturer's specifications and maintained in a

limited access area. Access to the test devices must be limited only to those authorized to use the devices.

4. The PI is responsible for ensuring that test articles (drugs, biologics, or devices) are controlled so that they are not used outside of a research study. An investigator shall administer the drug or device only to subjects under the PI's personal supervision or under the supervision of a sub-PI responsible to the PI. The PI shall not supply the investigational drug or device to any person not authorized under this part to receive it.
5. The protocol for the study should outline the security and storage plan for the test article(s) indicating that the plan meets the sponsor's storage and security requirements. The plan should include whether or not control will be through a hospital pharmacy and under the supervision of a registered pharmacist or held in a proper and secure storage area by the investigator. The protocol should detail how the test article is used in human subjects, indicate who may have access to the test article(s) and outline the accountability plan for the test article(s) to ensure that there is no unapproved access to or use of the test article(s).
6. A PI who is also a sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation. Review Appendix E for more extensive documentation on a monitor's qualifications.
7. Protocols involving an IND or IDE will undergo initial and continuing review at a convened meeting that includes at least one physician or pharmacist unless the protocol meets the criteria for expedited review (i.e., all treatment components complete, in follow-up only, data analysis only).
8. Consent for studies involving an IND and/or IDE will be obtained. Although FDA regulations allow waiver of consent if research meets the criteria specified in 21 CFR 50.23 or 21 CFR 50.24 and DHHS regulations allow a waiver of consent if research meets the criteria specified in 45 CFR 46 "Waiver of Informed Consent Requirements in Certain Emergency Research," consent is required for all non-emergency research that falls under FDA regulations or involves experimental treatment, tests, or drugs. In addition, the consent form will identify the test article as investigational and will inform participants that the FDA may inspect research records.
9. The PI who is a sponsor will provide the IRB with all documentation provided by the FDA indicating whether or not that sponsor has complied with FDA regulations dealing with sponsor responsibilities.
10. In addition to this documentation, the IRB, utilizing the HSPPO auditors, will, upon request, ensure through a preliminary audit of the production and storage area for the test article that the sponsor/investigator has met all the sponsor responsibilities as detailed in [21 CFR 312](#) for drugs or biologics and [21 CFR 812](#) for test devices.
11. The PI/sponsor will provide the IRB with a final report from the PIs at the close of a study (PI must file Study Closure Form).

Determination of Need for an IND

Studies that involve FDA-regulated products that are submitted without a valid IND number will be reviewed with respect to determining the need for an IND, based on the investigator's response to questions contained in the application form.

If the IRB determines that the study is exempt from an IND and approves the study, the study may begin without submission of an IND application to FDA. If the IRB determines that an IND is needed, the investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination (IND number) to the IRB before the IRB approves the study.

The IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
2. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
3. The investigation does not involve a route of administration or dosage level or use in a patient population (e.g., children, prisoners, pregnant women and fetuses) or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. The investigation is conducted in compliance with the requirements for institutional review and with the requirements for informed consent; and
5. The investigation is conducted in compliance with the requirements with regard to promotion and charging for investigational drugs in [21 CFR 312.7](#).⁶⁴

A clinical investigation involving an in vitro diagnostic biological product that is a blood grouping serum, reagent red blood cells, or anti-human globulin is exempt from the requirements for an IND if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21 CFR 312.160.

A drug intended solely for tests in vitro is exempt from the requirements of an IND if it is shipped in accordance with 21 CFR 312.160.

A clinical investigation involving use of a placebo is exempt from the requirements of an IND if the investigation does not otherwise require submission of an IND.

Determination of Significant Risk (SR) vs. Non-significant Risk (NSR) for Non-Exempt Medical Devices

For determination of the need for an IDE, the convened IRB will address the applicability of FDA regulations under 21 CFR 812.2 and, if necessary, make a significant risk determination.

A Significant Risk (SR) device study is one that presents a potential for serious risk to the health, safety, or welfare of a subject and

1. is intended as an implant; or
2. is used in supporting or sustaining human life; or

⁶⁴ 21 CFR 312.2(b)

3. is for use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A Non-significant Risk (NSR) device investigation is one that does not meet the definition for a SR study.

The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB considers the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure is considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR.

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

To help in the determination of the risk status of the device, an investigator is asked to include the sponsor's (including the investigator on investigator-initiated studies) assessment of whether or not a device study presents a significant or non-significant risk. The investigator must provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The investigator must inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The investigator must inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

Abbreviated IDE Requirements

An exemption from certain regulations described in the medical device amendments that allows the shipment of an unapproved device for use in a clinical investigation. The sponsor of an SR device is required to apply to the FDA for an IDE before the clinical research may begin. There are abbreviated requirements for NSR devices that do not involve filing with the FDA.

- a. The device is not a banned device.
- b. The sponsor labels the device in accordance with 21 CFR 812.5.
- c. The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device was not a significant risk device, and maintains such approval.
- d. The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation was waived.
- e. The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
- f. The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10).

- g. The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
- h. The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

Responsibilities of an Investigator as a Sponsor for Significant Risk Device Investigations

This section is intended to assist investigators (hereafter referred to as sponsors) who are also sponsors in identifying and complying with their responsibilities in connection with the conduct of clinical investigations of medical devices that are deemed "significant risk" by the reviewing IRB or by FDA. For a complete description of their responsibilities, sponsors should refer to the actual text of the regulations cited below. In addition, sponsors should be aware that a clinical investigation must be conducted in accordance with any requirements imposed by the reviewing IRB, by institutional policies, or by state law.

General Duties

1. Submitting the IDE application to FDA
2. Obtaining both FDA and IRB approvals for the investigation and submitting certification of IRB approval to FDA before shipping the device to any investigator
3. Obtaining FDA approval and IRB approval for a supplemental application before beginning that portion of the investigation
4. Selecting qualified investigators
5. Ensuring proper monitoring
6. Ensuring patient informed consent is obtained

Selection of Investigators

1. Assuring selection of investigators qualified by training and experience
2. Shipping the investigational device only to participating investigators
3. Obtaining a signed investigator's agreement containing:
 - a. investigator's curriculum vitae
 - b. statement of investigator's relevant experience, including dates, location, extent, and type of experience
 - c. if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination
 - d. statement of the investigator's commitment to:
 - I. conduct the investigation in accordance with the agreement, the investigational plan, Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA
 - II. supervise all testing of the device involving human subjects
 - III. ensure that the requirements for informed consent are met (21 CFR Part 50)
4. Providing investigators with the necessary information to conduct the investigation including, but not necessarily limited to:
 - a. the investigational plan
 - b. the report of prior investigations

Monitoring

Selecting monitor(s) qualified by training and experience to monitor the progress of the investigation;

1. Securing compliance of all investigators in accordance with the signed investigator's agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any condition of approval imposed by the reviewing IRB or FDA. If compliance cannot be secured, shipment of the device to the investigator and the investigator's participation in the investigation must be discontinued;
2. Ensuring that significant new information about the investigation is provided to all reviewing IRBs, FDA, and investigators;
3. Evaluating all unanticipated adverse device effects and terminating the investigation, or portions of it, if that effect presents an unreasonable risk to subjects (reporting requirements are listed below.)
4. Resuming terminated investigations only after both FDA and IRB approvals are obtained.

Controlling Distribution and Disposition of Devices

Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (see 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (§ 812.43(b)). Sponsors must also maintain complete, current, and accurate records pertaining to the shipment and disposition of the investigational device (§ 812.140(b)). Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

To further ensure compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at § 812.140(a). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (§ 812.110(c)).

Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

1. Promotion or test marketing of the investigational device;
2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;
3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,
4. Representing that the device is safe or effective for the purposes for which it is being investigated.

Supplemental Applications

Supplemental applications are required to be submitted to, and approved by, FDA in the following situations:

1. Changes in the investigational plan: FDA approval is required for any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety or welfare of the subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.
2. Addition of new institutions: IRB approval is also required for new institutions. The investigation at the new institution(s) may not begin until both FDA and IRB approval(s) are obtained, and certification of IRB approval is submitted to FDA.

Maintaining Records

A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

1. Correspondence with another sponsor, monitor, investigators, an IRB or FDA
2. Records of shipment, including:
 - a. name and address of consignee
 - b. type and quantity of device
 - c. date of shipment
 - d. batch numbers or code marks
3. Records of disposition, describing:
 - a. batch number or code mark of devices returned, repaired, or disposed of by the investigator or other persons
 - b. reasons for and method of disposal
4. Signed investigator agreements
5. Adverse device effects (whether anticipated or unanticipated) and complaints
6. Any other records that FDA requires by regulation or by specific requirement for a category of investigation or a particular investigation

Submitting Reports

A sponsor shall prepare and submit the following complete, accurate, and timely reports.

1. Unanticipated adverse device effects (with evaluation) to FDA, all IRBs, and investigators within 5 working days after notification by the investigator. Subsequent reports on the effect may be required by FDA.
2. Withdrawal of IRB approval
3. Withdrawal of FDA approval
4. Current 6month investigator list
5. Annual progress report see format for IDE progress report
6. Recall and device disposition (within 30 working days after the request was made)
7. Final report see format for progress reports
8. Use of device without obtaining patient informed consent
9. Significant risk determinations by the IRB when proposed to be nonsignificant risk
10. Other reports requested by the IRB or FDA

Inspections

Sponsors are required to permit FDA to enter and inspect (at reasonable times and in a reasonable manner) any establishment where devices are held (including any establishment

where devices are manufactured, processed, packed, installed, used, or implanted or where records or results from use of devices are kept). FDA may also inspect and copy all records relating to an investigation including, in certain situations, records that identify subjects.

The IRB may agree or disagree with the investigator/sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made and the initiation of the study must be delayed until FDA approval of an IDE application has been granted.

If the IRB decides the device/study is significant risk, it notifies the investigator of this decision. The IRB must be provided with notice that an IDE has been granted, and the IDE number must appear on the investigator's IRB application prior to final full board review.

Once the SR/NSR decision has been reached and proper documentation provided, the IRB considers whether the study should be approved or not. Full IRB review is required for all studies involving investigational devices. The criteria for deciding if SR and NSR studies are approved are the same as for any other study. Minutes of IRB meetings document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

Device Studies in Pediatric Populations

Because the pediatric population represents a particularly vulnerable group, specific measures are needed to protect the safety of pediatric study subjects. Adult devices may be inappropriate for use in pediatric subjects for a variety of reasons, or may require specific design changes and/or specific labeling to accommodate their use in pediatric subjects. We recommend that you consider the following when you develop devices or plan a clinical trial for devices intended for pediatric subjects:

1. height
2. weight
3. growth and development
4. disease or condition
5. hormonal influences
6. anatomical and physiological differences from the adult population
7. activity and maturity level
8. immune status.

Pediatric Subgroups

If clinical data are needed to support a pediatric indication, you should make every effort to gather data that adequately addresses each targeted pediatric subgroup. In some cases, the expected benefit and safety can be determined without separate studies in each subgroup. That is, it may be extrapolated from one age group to another. In other cases, such as with neonates, clinical data gathered specifically in that subgroup will likely be needed. You should be prepared to provide data for each targeted subpopulation or a justification as to why it is either not needed or can be

Please review the FDA publication *Premarket Assessment of Pediatric Medical Devices* for additional information about research involving pediatric medical devices.

Emergency Use Of an Investigation Drug or Biologic

The emergency use of test articles frequently prompts questions from Institutional Review Boards (IRBs) and investigators. The following paragraphs address three areas of concern: emergency Investigational New Drug (IND) requirements; IRB procedures; and informed consent requirements.

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.36].

FDA Contacts for Obtaining an Emergency IND

Product	Office/Division to Contact
drug products	Division of Drug Information (HFD-240) 301-827-4570
biological blood products	Office of Blood Research and Review (HFM-300) 301-827-3518
biological vaccine products	Office of Vaccines Research (HFM-400) 301-827-3070
On nights and weekends	Office of Crisis Management & Emergency Operations Center (HFC-160) 301-443-1240

Emergency Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

- a. Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- b. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Institutional procedures may require that the IRB be notified prior to such use; however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must both convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, some IRBs have sent to the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing in the patient/subject's medical record all of the following [21 CFR 50.23(a)]:

- a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
- b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- c. Time is not sufficient to obtain consent from the subject's legal representative.
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Emergency Use of Unapproved Medical Devices

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360(e)]. An unapproved device may be

used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520(g) of the Act [21 U.S.C. 360(j)(g)] and 21 CFR part 812. Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices which require an IDE.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies in writing to FDA that an emergency actually existed.

Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

- a. the patient is in a life-threatening condition that needs immediate treatment;
- b. no generally acceptable alternative for treating the patient is available; and
- c. because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the FDA Office of Emergency Operations (HFA-615) 301-443-1240.

FDA would expect the physician to follow as many subject protection procedures as possible. These include:

- a. obtaining an independent assessment in writing, documented in the patient/subject's medical record by an uninvolved physician;
- b. obtaining informed consent from the patient or a legal representative;
- c. notifying institutional officials as specified by institutional policies;
- d. notifying the Institutional Review Board (IRB); and
- e. obtaining authorization from the IDE holder, if an approved IDE for the device exists.

After-Use Procedures

After an unapproved device is used in an emergency, the physician should:

- a. report to the IRB within five days [21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [21 CFR part 56];

- b. evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
- c. if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing in the patient/subject's medical record all of the following [21 CFR 50.23(a)]:

- a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
- b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- c. Time is not sufficient to obtain consent from the subject's legal representative.
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Reporting the Use of a Test Article (Drug, Biologic or Device) to the IRB

The investigator's written report is presented at the next appropriate IRB meeting. When an IRB receives a report by an investigator of an emergency use, the IRB examines the case to assure that the emergency use was justified and that the emergency use complied with FDA regulations. Using FDA guidance, the IRB will determine if the emergency use was justified and document the IRB's decision in the minutes of the meeting. The five-day report will be initially reviewed by an IRB chair/vice-chair if no Biomedical IRB is scheduled in the 5 day window. If the IRB cannot review, the chair/vice-chair determination will be reported at the next convened IRB meeting.

The written report submitted to the IRB must include a cover letter explaining the medical condition, reason for use, and date administered as well as a copy of the signed Informed Consent Document. The investigator must also include any manufacturer information available on the product (e.g., drug brochure).

Once the investigator has provided written notice, the use is assigned a University of Louisville IRB tracking number, and the chair or his/her designee responds in writing that the information has been received.

Although this procedure is designed to permit only a single emergency use of a test article for the treatment of one patient by one physician within the University or affiliated institutions, it is not intended to limit the authority of a physician to provide emergency care in a life-threatening situation. Should a situation arise that would require the emergency use of the test article for a second patient, either by the same or a second physician, for the same test article, subsequent emergency use should not be withheld for the purpose of gaining IRB approval. If it appears probable that similar emergencies will require subsequent use of the test article at the University or affiliated institutions, every effort should be made either to sign on to the sponsor's protocol or to develop a protocol for future use of the article at the institution. Either of these protocols would need to be prospectively reviewed and approved by the IRB for future use of the test article.

Treatment Use of an Investigational Drug or Device

The IRB reviews the use of investigational drugs/devices if the investigator provides evidence that a treatment IND or IDE has been obtained or as single patient use (below). In all cases, treatment use of an investigational drug or device requires prospective IRB approval as well as subject informed consent.

1. Single Patient (Non-emergency Use)

In non-emergency situations, physicians may obtain investigational drugs for use outside of a controlled clinical trial for a single patient. This is often referred to as "compassionate use." Usually, the patient is in a desperate situation and unresponsive to other therapies, or no approved or generally recognized treatment is available. There may be little evidence that the proposed therapy is useful, but it is thought to be plausible on theoretical grounds or anecdotal evidence. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment.

IRB approval is also required prior to administration of the investigational drug. The approval is granted for the treatment of a single patient. When an investigator desires to obtain single patient use approval, the investigator submits an application and the study is assigned a University of Louisville IRB identification number and sent through the new application procedure. The treatment use may occur only after IRB approval is obtained. Subsequent treatment use requires FDA approval for a treatment IND or IDE.

Every single patient use must be reviewed and approved by the IRB as well as the FDA, and all requirements for informed consent must be met. Although the FDA may waive local IRB review for a Single Patient Use, the University of Louisville IRB Policy does not permit such waivers and will not allow a Single Patient Use without the prior review and approval of the IRB.

Additional information related to the use of a HUD may be found in the FDA document [Humanitarian Device Exemption \(HDE\) Regulation: Questions and Answers.](#)

2. Humanitarian Use Device (HUD)

Humanitarian use of investigational devices is prospectively reviewed by the IRB. The investigator is required to submit a new application for review. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA. These projects are subject to the same new and continuing review requirements as research projects as outlined in this document. The use of such devices is approved only for the purposes noted in the FDA approval letter.

3. Treatment IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) the trial sponsor is actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

4. Group C Treatment IND

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105]. Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review.

5. Parallel Track Studies

The FDA provides another mechanism for making promising investigational drugs and biologics available as quickly as possible for persons with AIDS and other HIV-related diseases, while generating data on the safety and effectiveness of the drugs. Under Parallel Track provisions, individuals with AIDS and HIV-related diseases for whom standard therapy is unsuitable or no

longer effective, and who are not able to participate in on-going controlled clinical trials, have access to promising investigational drugs. Recipients of new drugs under Parallel Track provisions are actually participating in the studies although without concurrent control groups. This mechanism is therefore called "Parallel Track Studies."

Parallel Track protocols are considered a subset of the treatment IND and are processed according to the treatment IND procedures described above. They are distinguished from other treatment INDs merely by the amount of evidence of effectiveness required for FDA approval. Both are designed to make promising new agents available to persons with life-threatening diseases who cannot participate in controlled clinical trials and for whom there are no satisfactory alternative therapies. But while treatment INDs permit access to drugs in late Phase 2 and early Phase 3 stages of clinical trials, Parallel Track provisions permit access to AIDS drugs during late Phase 1 and early Phase 2 stages of clinical investigation. All Parallel Track requests must be reviewed by the IRB and the FDA.

In addition, Parallel Track studies are required to comply with the regulations governing informed consent, IRB review, and reporting requirements. Although the FDA may waive local IRB review for Parallel Track studies, the University of Louisville IRB Policy does not permit such waivers and requires IRB review and approval before any patients are treated under Parallel Track provisions. When submitting an application to use an investigational drug or biologic in a treatment protocol, the investigator should:

Identify the drug or biologic and provide the IND number under which it is currently being studied elsewhere (or under which it has been studied, if Phase 3 studies have been completed).

Explain the scientific basis for believing that the product may be useful for treating the patient's condition and that it will not be unduly harmful.

Describe the patient population that would qualify for treatment with the product under the following criteria:

- a. The patients are suffering from a serious or immediately life-threatening or severely debilitating disease, and
- b. There is no comparable or satisfactory alternative drug or therapy available to treat the stage of the disease in the intended population.

Submit a treatment protocol describing how the drug would be administered to qualified patients (including dosage, frequency, and mode of administration) and data that will be collected their response to treatment.

Attach the consent form to be used. The only exception to the requirement for informed consent is if the drug must be administered in the emergency room or under similar emergency conditions.

Adverse event reports must be submitted as usual to the FDA and the Sponsor (and to the IRB, if they meet the definition of unanticipated problems or SAE) and a report on the outcome of each patient treated must be provided to the IRB at intervals established by the IRB in conformance with the regulations of the FDA, as well as to the drug sponsor and the FDA as they may require.

XIV. EDUCATION AND TRAINING

Educational Activities Aimed at the Community at Large

The HSPP Office has developed a brochure: *"I want to know more about being in a research study"* aimed at the general population in Louisville and the surrounding communities explaining about research. The brochure lists a number of questions a potential subject may wish to ask if approached to be a subject in a study.

Educational Activities Aimed at the Research Community at Large

The IRB and HSPPO provide services to inform the research community on issues related to use of human subjects in research and ethics in research, and to make researchers aware of applicable Federal regulations.

The HSPPO maintains an internet website that contains detailed information on the University of Louisville human subjects review process as well as links to federal regulations and regulatory agencies, the human subjects Federal-wide Assurance document on file with OHRP, the OHRP Institutional Review Board (IRB) Guidebook, the *Belmont Report*, and other guidance documents.

The HSPPO also maintains a small library of materials that includes the OHRP Institutional Review Board (IRB) Guidebook, the *Belmont Report*, and other books and videotapes discussing ethical and regulatory issues relating to human subjects research. These materials are available to the entire campus community.

Application materials are provided with appropriate guidance (e.g., templates) as a means of educating investigators regarding the proper process for conducting human subjects research.

The HSPPO schedules and advertises educational workshops throughout the calendar year directed at investigators and their research associates. These workshops cover topics that include University of Louisville policies and procedures as well as federal regulatory requirements.

Effective July 1, 2000, all investigators and key personnel involved in the conduct of human subject research must show evidence of completing University-approved education in human subjects protections annually.

Members of the IRB or HSPPO staff may present information at meetings in academic departments or give lectures in University classes, to emphasize selected aspects of human subject research, and to keep various constituencies abreast of activities of the IRB.

Educational Activities Aimed at Members of the IRB

At the time of induction of a new member, the chair of the IRB and/or professional staff from the HSPPO review with the member all procedures of the IRB and the general regulatory framework from which procedures and policies are derived.

Information offered by the HSPPO includes the University of Louisville human subjects website containing detailed information on the University of Louisville human subjects review process as well as links to federal regulations, the University of Louisville human subjects Federal-wide Assurance document on file with OHRP, the OHRP Institutional Review Board (IRB) Guidebook, the *Belmont Report*, and other guidance documents.

If an IRB member or HSPPO staff does not know the answer to a question or how to proceed with respect to a particular problem, the IRB member or HSPPO staff should consult with Executive HSPPO staff or appropriate IRB chair. If the answer is insufficient, the Executive HSPPO staff or chair will consult responsible regulatory agency.

IRB members are encouraged to fulfill the same training requirements as investigators and should do so within one year of appointment to the IRB. Chairs and members are encouraged to attain certification as an IRB professional. The HSPPO supports these efforts by paying the registration for any member who wishes to take the test.

HSPPO professional staff members are required to obtain Certified IRB Professional ([CIP](#)) credentialing immediately upon eligibility. Information on CIP can be obtained at the following website: <http://www.primr.org/Certification.aspx?id=74>

HSPPO staff members will not be scheduled to complete external continuing educational training until after completion of their provisional period. Once the staff member has become a regular status employee, the supervisor(s) will inform the staff meeting of upcoming educational/training activities for which they are qualified to attend.

Educational Activities Aimed at Members of the University Administration

The University of Louisville provides the opportunity for professional staff members of the Human Subjects Protection Program Office and professional staff from the Office of the Executive Vice President for Research to attend, at least annually, conferences or workshops on human subject issues in research. Upon return, these individuals may be asked to brief appropriate members of the University community on relevant information obtained.

DEFINITIONS

Adjuvant Therapy – Therapy provided to enhance the effect of a primary therapy; auxiliary therapy.

Adverse Event – An undesirable, unintended and not necessarily unexpected result of therapy or other intervention (e.g., a headache following a spinal tap or intestinal bleeding associated with aspirin therapy).

Affidavit of Accuracy – a document signed by a qualified translator in which the translator who performed or verified the translation affirms that the entire document has been translated, that nothing has been omitted or added, and that the translation is true and correct. A qualified translator is an officer or employee of an official translation bureau or agency or a professor or instructor who is teaching the translated language in an accredited college or university in the United States. The type of course being taught must be included in the Affidavit of Accuracy, which must be on official school stationery and notarized.

Alternate - a person, appointed to the IRB by the EVPR, with similar qualifications who is authorized to fill the position, exercise the same duties, authority, responsibility, etc., of an IRB member who is temporarily absent.

Assent - Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Assurance – A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

Authorized Institutional Official - An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

Autonomy – Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

Belmont Report - A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

Beneficence - An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

Benefit - A valued or desired outcome; an advantage.

Biologic - Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

Certificate of Confidentiality – a document issued by the National Institutes of Health (NIH) (or other Federal Agency who may fund research) to protect the privacy of research subjects by protecting investigators and institutions from being compelled in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level to release information that could be used to identify subjects in a research project.

Chair – Chair, Co-Chair, or Vice-Chair, as designated on IRB roster submitted to OHRP, unless otherwise indicated. The person who runs the IRB meeting.

Child – In Kentucky, all research individuals less than 18 years of age unless the individual is legally emancipated, as these are the individuals who under Kentucky law meet the federal definition of a child.

Children – Plural of child.

Clinical investigation - 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. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

Clinical Trial - A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

Cognitively Impaired - Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Cohort - A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.

Compensation - Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research.

Competence - Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (*See also: Incompetence, Incapacity.*)

Confidentiality - Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

Conflict of Interest – an IRB member may not vote on a project, and is not counted towards a quorum, when s/he or an immediate family member has a conflict of interest with a project being reviewed, defined as:

- Serving as a co-investigator or other member of the research team; or
- Receiving payments in excess of \$10,000 including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts from the study sponsor over the past 12 months or anticipated for the next 12 months (excluding salary and other payments for services from the University of Louisville); or

- Having equity interest worth more than \$10,000 or more than 5% of the business entity as determined by reference to publicly listed prices (excluding mutual funds); or
- Having any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies); or
- Holding a position as director, officer, partner, trustee, employee, or any other position of management; or
- Holding patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University of Louisville.

Consent Summary – A summary of the information contained in the complete informed consent document; used with short form consent.

Continuing non-compliance - A pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, indicates a lack of understanding of the regulations or institutional requirements that may affect the rights and welfare of participants, would have been foreseen as compromising the scientific integrity of a study such that important conclusions could no longer be reached, suggests a likelihood that non-compliance will continue without intervention, or frequent instances of minor non-compliance. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

Contract - An agreement; as used here, an agreement that a specific research activity will be performed at the request, and under the direction, of the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant.

Contraindicated - Disadvantageous, perhaps dangerous; a treatment that should not be used in certain individuals or conditions due to risks (e.g., a drug may be contraindicated for pregnant women and persons with high blood pressure).

Cross-over Design - A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.

Data and Safety Monitoring Board – committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

Debriefing – Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note this usage that occurs within the behavioral sciences departs from Standard English, in which debriefing is obtaining rather than imparting information.)

Deception - in research means that the subject/respondent, at the time of the data collection, is not fully informed of the nature and purpose of the research in which she/he is involved so as to prevent potentially biased reporting of data/information.

Declaration of Helsinki – A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975, 1989, 1996, 2000 and 2002.

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

Descriptive Study - Any study that is not truly experimental (e.g., quasi-experimental studies, correlation studies, record reviews, case histories, and observational studies).

Diagnostic (Procedure) - Tests used to identify a disorder or disease in a living person.

Double-masked Design - A study design in which neither the investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as "double-blind."

Drug - Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

Emancipated Child - A legal status conferred upon persons who have not yet attained the age of legal competency (in Kentucky 18 years old) as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. A legal procedure whereby children become legally responsible for themselves and their parents are no longer responsible financially or otherwise. In Kentucky, a child is considered as emancipated when;

- a. he/she becomes self supporting,
- b. joins the armed forces,
- c. is released from the control and supervision of his or her parents or guardian by the courts, or
- d. has a valid marriage.

Pregnancy does not emancipate a female unless other conditions are met. For example, moving out of the parents' or guardian's house and into an apartment, setting up housekeeping with a partner, and having a baby can be emancipating, because the totality of the circumstances shows an intent to be free of the parents' custody, control, and support. However, the emancipation status will still be determined by the courts and is generally controlled by the contention that the female is free from the supervision and control of her parents or guardian and she has become self supporting, not that she is pregnant.

Embryo - Early stages of a developing organism broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy).

Emergency use - the use of an FDA-regulated test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

Equitable - Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.

Ethnographic Research - Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time.

Excess Human Specimens – remnants of specimens collected for routine clinical care or analysis that would otherwise be discarded. These specimens may also be called “Waste Human Specimens” or “Leftover Human Specimens.”

Existing Data – Data that existed prior to the initiation of a research project.

Expedited Review - Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

Experimental - Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness.

Family member - means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

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

FDA – Food and Drug Administration, an agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.

Fetal Material - The placenta, amniotic fluid, fetal membranes, and umbilical cord.

Fetus - The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development.

Fieldwork - Behavioral, social, or anthropological research involving the study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings).

Full-Board Review - Review of proposed research at a convened meeting at which a majority of the membership of the IRB is present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

Gatekeeper – An individual or organization that controls access to research records, documents or specimens.

Gene Therapy - Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. At present, human gene transfer is experimental and is being studied to see whether it could

treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease. Human gene transfer may help improve genetic disorders, particularly those conditions that result from inborn errors in a single gene (for example, sickle cell anemia, hemophilia, and cystic fibrosis). It may also hold promise for diseases with more complex origins, like cancer and heart disease. Gene transfer is also being studied as a possible treatment for certain infectious diseases, such as AIDS. This type of experimentation is sometimes called “gene therapy” research.

Generalizable Knowledge - conclusions, facts, or principles derived from particulars (individual subjects, records, observations, etc.) that are applicable to or affect a whole category (members of a class, kind, or group, a field of knowledge, etc.) and enhance general understanding of a topic.

Genetic Screening - Tests to identify persons who have an inherited predisposition to a certain phenotype or who are at risk of producing offspring with inherited diseases or disorders.

Genotype – The genetic constitution of an individual.

Good Clinical Practice (GCP) — Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. (International Code of Harmonization for Good Clinical Practice (ICH GCP)). The University of Louisville IRB generally supports the concept of the GCP guidelines but does not mandate that investigators at the university follow all of these guidelines.

Guardian - An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

HIPAA – Health Insurance Portability and Accountability Act of 1996. HIPAA governs the use and disclosure of protected health information (PHI) that is created or received by a covered entity that relates to:

- the physical or mental health of an individual (living or deceased)
- the provision of health care
- the payment for health care
- identifies the individual or reasonably may be used to identify the individual

Gives individuals the following rights

- right to request restrictions on use or disclosure of their PHI
- right to access medical records (including research records)
- right to amend medical records
- right to an accounting of disclosure of their PHI
- right to request alternate confidential communications
- right to lodge complaint with covered entity and / or the Department for Health and Human Services

Administrative Requirements

- Covered Entity must designate a Privacy Official

- Covered Entity must develop policies and procedures that are HIPAA compliant
- Covered Entity must provide privacy training to the workforce
- Covered Entity must implement administrative, technical and physical safeguards to protect the privacy of PHI
- Covered Entity must develop sanctions for violations of the HIPAA Privacy Rule
- Covered Entity must meet the documentation requirements
-

Human Research Protection Program (HRPP) — A system that includes all structural units, policies, and activities critical to protecting individuals studied in research and that is managed in accordance with these standards and with applicable federal, state and local laws. Some components of the HRPP may be external to the organization seeking accreditation, but the essential components of an HRPP should be identifiable in all cases.

Human subject – a living individual about whom an investigator (whether professional or student) conducting research obtains a) data through intervention or interaction with the individual, or b) identifiable private information. Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project.

Human subject (as defined by the FDA) - means an individual who is or becomes a participant in research, either as a recipient of the test article as a control or individuals on whose specimens an investigational device is used. A subject may be either a healthy human or a patient. This definition applies to all research involving drugs or devices.

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

Humanitarian Use Device (HUD) - A device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year.

Informed Consent - A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence.

Institutional Review Board (IRB) - any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical or behavioral/social science research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.

Interaction - includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Intervention - includes communication or inter-personal contact between investigator and subject.

Investigational Device Exemption (IDE) - Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations

Investigational New Drug or Device - A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

Investigator - An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

IRB Committee Member (Member) – An individual appointed by the Executive Vice President for Research or designee to serve on the IRB.

IRB approval - the determination of the IRB that the research study has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

Justice - An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

Key Personnel – Participants in a research team who contribute in a substantive way to the scientific development or execution of a project, including the [principal investigator](#)

Leftover Human Specimens– remnants of specimens collected for routine clinical care or analysis that would otherwise be discarded. These specimens may also be called “Waste Human Specimens” or “Excess Human Specimens.”

Legally Authorized Representative - An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Longitudinal Study - A study designed to follow subjects forward through time.

Major modifications – Modifications to a research project and/or consent documents that present additional risk to subjects such as dosage escalation, additional procedures or tests, significant increases in time commitment by subject, etc. Substantive protocol revisions also are considered major modifications.

Medical Device - A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

Mentally Disabled – See cognitively impaired.

Minimal risk – The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research that involves prisoners, minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303(d)).

Minor (in reference to a person) – In Kentucky, means any person who has not reached the age of eighteen (18). In the Kentucky Revised Statutes, the definition of a “minor” and a “child” are identical.

Minor - Lesser in seriousness or danger

Minor modifications – modifications to a research project and/or consent documents that pose no additional risk to subjects such as changes in title, co-investigator (s), funding sources; addition or modification of procedures that fall into one of the categories eligible for expedited review; or modifications that maintain similar or increased safeguards to protect the subject.

Monitoring - The act of overseeing the progress of a research study to ensure that the rights and well-being of participants are protected, that the data are accurate, complete and verifiable, and that the conduct of the research is in compliance with the protocol, with applicable regulatory requirements and with standards of the field.

Negligence - Failure to exercise the degree of care considered reasonable under the circumstances, resulting in an unintended injury to another party.

New Drug Application (NDA) - Request for FDA approval to market a new drug.

Non-affiliated Member - Member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (e.g., minister, business person, attorney, teacher, homemaker).

Non-compliance - Any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations or institutional policies governing such research. Non-compliance actions may range from minor to serious, be unintentional or willful, and may occur once or several times. The degree of non-compliance is evaluated on a case-by-case basis and will take into account such considerations as to what degree subjects were harmed or placed at an increased risk and willfulness of the non-compliance. Examples include, but are not limited to:

1. Failure to obtain IRB approval;
2. Inadequate or non-existent procedures for the informed consent process;
3. Inadequate supervision;
4. Failure to follow recommendations made by the IRB;
5. Failure to report unanticipated problems, serious adverse events, or protocol changes; and
6. Failure to provide ongoing progress reports.

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

Normal Volunteers - Volunteer subjects used to study normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease.

Null Hypothesis - The proposition, to be tested statistically, that the experimental intervention has "no effect," meaning that the treatment and control groups will not differ as a result of the intervention.

Investigators usually hope that the data will demonstrate some effect from the intervention, thereby allowing the investigator to reject the null hypothesis.

Nuremberg Code - A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

Office of Human Research Protections (OHRP) – The office within the Department of Human and Human Services responsible for implementing DHHS regulations governing research involving human subjects.

Open Design - An experimental design in which both the investigator (s) and the subjects know the treatment group(s) to which subjects are assigned.

Paternalism - Making decisions for others against or apart from their wishes with the intent of doing them good.

Phase 1, 2, 3, 4 Drug Trials - Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to post marketing studies (Phase 4).

- Phase 1 Drug Trial - Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.
- Phase 2 Drug Trial - Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.
- Phase 3 Drug Trial - Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

- Phase 4 Drug Trial - Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain post marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR §312.85].

Phenotype - The physical manifestation of a gene function.

PHS - Public Health Service. Part of the U.S. Department of Health and Human Services, it includes FDA, NIH, CDC, SAMHSA, and HRSA.

Placebo - A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.

Principal Investigator - A qualified person who directs a research project or program, may write the protocol, and oversees the scientific, technical and day-to-day management of the research.

Prisoner - Means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c)).

Privacy - Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

Private Information - includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Protected Health Information (PHI) – Individually identifiable health information including demographic data that relates to:

- the individual's past, present or future physical or mental health or condition,
- the provision of health care to the individual, or
- the past, present, or future payment for the provision of health care to the individual,
- and that identifies the individual or for which there is a reasonable basis to believe can be used to identify the individual. Individually identifiable health information includes many common identifiers (e.g., name, address, birth date, Social Security Number).

Protocol - The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

Quality Improvement (QI) — Periodic examination of organizational activities, policies, procedures and performance to identify best practices and target areas in need of improvement; includes implementation of corrective actions or policy changes where needed.

Quorum – a majority of voting members of an IRB, including at least one member whose primary expertise is in a nonscientific area.

Radioactive Drug - Any substance defined as a drug in §201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons [21 CFR 310.3(n)]. Included are any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and "radioactive biological products," as defined in 21 CFR 600.3(e). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

Randomization - Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

Recombinant DNA Technology - "The ability to chop up DNA, the stuff of which genes are made, and move the pieces, [which] permits the direct examination of the human genome," and the identification of the genetic components of a wide variety of disorders. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components.

Remission - A period in which the signs and symptoms of a disease are diminished or in abeyance. The term "remission" is used when one cannot say with confidence that the disease has been cured.

Research - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research even if they are a component of a larger non-research activity (e.g., instruction, demonstration).

Retrospective Studies - Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

Risk – the probability of harm or injury (physical, psychological, social, legal, or economic) occurring as a result of participation in a research study. Both the probability and magnitude may vary from minimal to significant.

Sequestration – segregating, holding separate.

Serious adverse experience (SAE) – Any adverse experience associated with the use of the drug/device that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result

in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Non-compliance - An action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of participants, increases risks to participants, decreases potential benefits or compromises the integrity or validity of the research. Examples of serious non-compliance include, but are not limited to:

1. Conducting non-exempt research without IRB approval;
2. Enrollment of subjects that fail to meet the inclusion or exclusion criteria of the protocol, that in the opinion of the IRB Chair or convened IRB increase the risk to the subject; or
3. Enrollment of research subjects while study approval has lapsed.

Short Form Consent - A short form written consent is a document stating that the elements of informed consent required by Sec. 50. 25 have been presented orally to the subject or the subject's LAR. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Significant Financial Interest - means anything of economic or monetary value that to an independent observer would be or reasonably appear to be affected by research. Please refer to the University of Louisville [Policy and Procedures For Oversight of Individual Financial Interests in Research](#) for a more comprehensive definition of significant financial interest.

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

Single-masked Design - Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally the subject, but not the investigator, knows the assignment. Sometimes called "single-blind design."

Site Visit - A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

Sponsor - a person or other entity that initiates a research study, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Sponsor-investigator - means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Statistical Significance - A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion.

Sub-investigator - The FDA regulations [21 CFR 312.3(b)] specify that in the event an investigation is conducted by a team of individuals, a sub-investigator is any other individual member of the study team.

Substantially Equivalent Language - Language though different, is interpreted to have the same intended meaning. Used in reference when comparing consent form language to executed contract language in areas such as research related injury, expectation of researchers and subjects, subject payment, or other aspects of a human study where a subject is provide information at a language level the subject understands.

Surveys - Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

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

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

Termination – the ending of all activities related to a human research project or an investigator's or key personnel's privilege to conduct or to participate in the conduct of human research at the University of Louisville except the continuation of follow-up activities necessary to protect subject safety.

Test article - means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

Therapy - Treatment intended and expected to alleviate a disease or disorder.

Unanticipated problem involving risks to subjects or others – any problem that was an unexpected event, related or possibly related to participation in the research, and suggesting that the research places subjects or others at a greater risk of harm than was previously known or suspected. Previously unforeseeable based on the information provided to the IRB.

For the purposes of this guide unanticipated problem involving risks to subjects or others, UPIRTSO, and unanticipated problem are considered to have the same meaning as described in the definition of unanticipated problem involving risks to subjects or others.

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

Vaccine - A biologic product generally made from an infectious agent or its components — a virus, bacterium, or other microorganism — that is killed (inactive) or live attenuated (active, although weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

Vulnerable Subjects/Participants — Individuals who lack the capacity to provide informed consent or whose willingness to participate in research may be unduly influenced by others. Vulnerable subjects include, for example, children, prisoners, individuals with emotional or cognitive disorders/impairments, and economically or educationally disadvantaged persons. (45 CFR 46.111 (a)(3); 45 CFR 46.111 (b); 45 CFR 46 Subparts B, C and D).

Waste Human Specimens – remnants of specimens collected for routine clinical care or analysis that would otherwise be discarded. These specimens may also be called “Waste Human Specimens” or “Excess Human Specimens.”

Witness – Impartial, non-involved observer of the consent process for enrollment into a research study.

APPENDIX A: REPORTING SUSPECTED CHILD ABUSE, SPOUSE ABUSE, AND/OR ELDER ABUSE

Under Kentucky law, health practitioners and educators are required to report to appropriate authorities when there is good reason to believe that a child or an adult has been abused. They are required to also report an injury that indicates possible abuse of an adult or dependent child or if they have personally seen a child or adult with injuries from an apparent assault.

Investigators are reminded that state law periodically changes, and does vary from state to state. Investigators conducting research outside of Kentucky should be familiar with the applicable reporting requirements of the state or country where the research is to take place.

Child Abuse

“Any person, including but not limited to a physician, osteopathic physician, nurse, teacher, school personnel, social worker, coroner, medical examiner, child-caring personnel, resident, intern, chiropractor, dentist, optometrist, emergency medical technician, paramedic, health professional, mental health professional, peace officer or any organization or agency for any of the above, who knows or has reasonable cause to believe that a child is dependent, neglected or abused, regardless of whether the person believed to have caused the dependency, neglect or abuse is a parent, guardian, person exercising custodial control or supervision or another person, or who has attended such child as a part of his professional duties shall, if requested, in addition to the report required in subsection (1) of this section, file with the local law enforcement agency or the Kentucky State Police or the Commonwealth’s or county attorney, the cabinet or its designated representative within forty-eight (48) hours of the original report a written report containing:

1. The names and addresses of the child and his parents or other persons exercising custodial control or supervision;
2. The child's age;
3. The nature and extent of the child's alleged dependency, neglect or abuse (including any previous charges of dependency, neglect or abuse) to this child or his siblings;
4. The name and address of the person allegedly responsible for the abuse or neglect; and
5. Any other information that the person making the report believes may be helpful in the furtherance of the purpose of this section.”⁶⁵

Spouse Abuse

“Any person, including, but not limited to, physician, law enforcement officer, nurse, social worker, cabinet personnel, coroner, medical examiner, alternate care facility employee, or caretaker, having reasonable cause to suspect that an adult has suffered abuse, neglect, or exploitation, shall report or cause reports to be made in accordance with the provisions of this chapter. Death of the adult does not relieve one of the responsibility for reporting the circumstances surrounding the death. An oral or written report shall be made immediately to the cabinet [Cabinet for Families and Children] upon knowledge of the occurrence of suspected abuse, neglect, or exploitation of an adult. Any person making such a report shall provide the following information, if known: The name and address of the adult, or of any other person responsible for his care; the age of the adult; the nature and extent of the abuse, neglect, or exploitation, including any evidence of previous abuse, neglect, or exploitation; the identity of the perpetrator, if known; the identity of the complainant, if possible; and any other information that the person believes might be helpful in establishing the cause of abuse, neglect, or exploitation. Neither the psychiatrist-patient privilege nor the husband-wife privilege shall be a ground

⁶⁵ KRS 620.030

for excluding evidence regarding the abuse, neglect, or exploitation of an adult or the cause thereof in any judicial proceeding resulting from a report pursuant to this chapter.⁶⁶

Elder Abuse

“Any person, including, but not limited to, physician, law enforcement officer, nurse, social worker, cabinet personnel, coroner, medical examiner, alternate care facility employee, or caretaker, having reasonable cause to suspect that an adult has suffered abuse, neglect, or exploitation, shall report or cause reports to be made in accordance with the provisions of this chapter. Death of the adult does not relieve one of the responsibility for reporting the circumstances surrounding the death. An oral or written report shall be made immediately to the cabinet [Cabinet for Families and Children] upon knowledge of the occurrence of suspected abuse, neglect, or exploitation of an adult. Any person making such a report shall provide the following information, if known: The name and address of the adult, or of any other person responsible for his care; the age of the adult; the nature and extent of the abuse, neglect, or exploitation, including any evidence of previous abuse, neglect, or exploitation; the identity of the perpetrator, if known; the identity of the complainant, if possible; and any other information that the person believes might be helpful in establishing the cause of abuse, neglect, or exploitation.” “Neither the psychiatrist-patient privilege nor the husband-wife privilege shall be a ground for excluding evidence regarding the abuse, neglect, or exploitation of an adult or the cause thereof in any judicial proceeding resulting from a report pursuant to this chapter.”⁶⁷

Definitions for this Chapter

Adult means:

1. A person eighteen (18) years of age or older, who because of mental or physical dysfunction, is unable to manage his own resources or carry out the activity of daily living or protect himself from neglect, or a hazardous or abusive situation without assistance from others, and who may be in need of protective services; or
2. A person without regard to age who is the victim of abuse and neglect inflicted by a spouse;

Protective services means agency services undertaken with or on behalf of an adult in need of protective services who is being abused, neglected, or exploited. These services may include, but are not limited to conducting investigations of complaints of possible abuse, neglect, or exploitation to ascertain whether or not the situation and condition of the adult in need of protective services warrants further action; social services aimed at preventing and remedying abuse, neglect, and exploitation; and services directed toward seeking legal determination of whether or not the adult in need of protective services has been abused, neglected, or exploited and to ensure that he obtains suitable care in or out of his home;

Caretaker means an individual or institution who has the responsibility for the care of the adult as a result of family relationship, or who has assumed the responsibility for the care of the adult person voluntarily, or by contract, or agreement;

Abuse means the infliction of physical pain, mental injury, or injury of an adult;

Exploitation means the improper use of an adult or an adult's resources by a caretaker or other person for the profit or advantage of the caretaker or other person;

⁶⁶ KRS 209.030; KRS 209.060

⁶⁷ KRS 209.030; KRS 209.060

Investigation shall include, but is not limited to, a personal interview with the individual reported to be abused, neglected, or exploited. When abuse, or neglect is allegedly the cause of death, a coroner's or doctor's report shall be examined as part of the investigation;

Emergency means that an adult is living in conditions that present a substantial risk of death or immediate and serious physical harm to himself or others;

Emergency protective services are protective services furnished an adult in an emergency;

Protective placement means the transfer of an adult from his present living arrangement to another;

Court means the Circuit Court or the District Court if no judge of that Circuit Court is present in the county;

Access to records means that any representative of the Cabinet for Families and Children actively involved in the conduct of an abuse, neglect, or exploitation investigation under this chapter shall be allowed access to the medical, mental, health, and financial records of the adult that are in the possession of any individual, hospital, firm, corporation or other facility, if necessary to complete the investigation mandated in this chapter; and

Neglect means a situation in which an adult is unable to perform or obtain for himself the services which are necessary to maintain his health or welfare, or the deprivation of services by a caretaker which are necessary to maintain the health and welfare of an adult, or a situation in which a person deprives his spouse of reasonable services to maintain health and welfare.

Abused or neglected child means a child whose health or welfare is harmed or threatened with harm when his parent, guardian, or other person exercising custodial control or supervision of the child:

- (b) Inflicts or allows to be inflicted upon the child physical or emotional injury as defined in this section by other than accidental means;
- (c) Creates or allows to be created a risk of physical or emotional injury as defined in this section to the child by other than accidental means;
- (d) Engages in a pattern of conduct that renders the parent incapable of caring for the immediate and ongoing needs of the child including, but not limited to, parental incapacity due to alcohol and other drug abuse as defined in KRS 222.005(12);
- (e) Continuously or repeatedly fails or refuses to provide essential parental care and protection for the child, considering the age of the child;
- (f) Commits or allows to be committed an act of sexual abuse, sexual exploitation, or prostitution upon the child;
- (g) Creates or allows to be created a risk that an act of sexual abuse, sexual exploitation, or prostitution will be committed upon the child;
- (h) Abandons or exploits the child; or

- (i) Does not provide the child with adequate care, supervision, food, clothing, shelter, and education or medical care necessary for the child's well-being. A parent or other person exercising custodial control or supervision of the child legitimately practicing the person's religious beliefs shall not be considered a negligent parent solely because of failure to provide specified medical treatment for a child for that reason alone. This exception shall not preclude a court from ordering necessary medical services for a child; or
- (j) Fails to make sufficient progress toward identified goals as set forth in the court-approved case plan to allow for the safe return of the child to the parent that results in the child remaining committed to the cabinet and remaining in foster care for fifteen (15) of the most recent twenty-two (22) months;

Child means any person who has not reached his eighteenth birthday, unless otherwise provided.

Emotional injury means an injury to the mental or psychological capacity or emotional stability of a child as evidenced by a substantial and observable impairment in the child's ability to function within a normal range of performance and behavior with due regard to his age, development, culture, and environment as testified to by a qualified mental health professional;

Dependent child means any child, other than an abused or neglected child, who is under improper care, custody, control, or guardianship that is not due to an intentional act of the parent, guardian, or person exercising custodial control or supervision of the child.

APPENDIX B: FETAL TISSUE RESEARCH

Fetuses and Human In Vitro Fertilization

Research involving the human fetus poses special concerns for the IRB. The fetus is unique and yet has an inextricable relationship to the mother. A fetus cannot consent to participate as a research subject. In the early 1970's Congress required that the National Commission for the Protection of Human Subjects study the subject of fetal research. The Commission in its findings did not define the "personhood" of the fetus; however, it did recognize the genetic heritage and the vulnerability of the fetus and affirmed that it should be treated respectfully and with dignity, regardless of its life prospects. The Commission also affirmed the legitimacy and importance of fetal research for improving the health of fetuses both in the present and the future. The Department of Health and Human Services has fully implemented the recommendations of the National Commission⁶⁸.

In addition to the general requirements for review of research by the IRB, prior research with animal subjects and, if reasonable, research with non-pregnant persons should form the basis of the risk/benefit assessment for fetal research. Investigators who propose research involving human fetuses are required to assure the IRB that they are seeking information not obtainable in any other fashion. Types of fetal research are categorized in the following manner:

Research Directed Toward the Fetus In Utero

Three circumstances may affect *in utero* research. In the first, the study is directed toward pregnant women, in which the fetus is indirectly involved in the research. In the second, the study is directed toward the fetus, that is, the fetus is the research subject. Finally, there are situations where both the pregnant woman and the fetus are the subjects of the research. The IRB may only approve *in utero* research when one of the following two criteria are met in addition to all other applicable institutional, Federal, State and local requirements.

1. The purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (for example a new technique for fetal transfusion for Rh incompatibility); or
2. The research poses no more than minimal risk to the fetus and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

Research Involving the Fetus Ex Utero

The Federal regulations indicate that an *ex utero* (delivered) fetus is viable if, in the judgment of the physician, it is likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. If the expelled or delivered fetus is viable, the regulations for research involving children will apply.

A non-viable fetus is defined by the Federal regulation as "an expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered fetus is non-viable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance." Research involving a non-viable fetus that would either artificially maintain vital functions or hasten their failure is forbidden by

⁶⁸ 45 CFR 46 Subpart B

Federal regulations. Ethical considerations require respect for the dignity of the dying human subject and an avoidance of unseemly intrusions into the process of dying for research purposes.

Consent for Research Involving In Utero and In Vitro Fertilization

Because of the father's continuing responsibility for his offspring, the consent of both parents is generally required for research involving a fetus. The consent of the father is not required, however, in the following circumstances:

1. The research is designed to meet the health needs of the pregnant woman; or
2. The father is not competent; or
3. The father's identity or whereabouts cannot reasonably be ascertained; or
4. The father is not reasonably available; or
5. The pregnancy resulted from rape.

Research involving the products of human *in vitro* fertilization requires the consent of the donors of both the sperm and the ova to be used in the specific research that is planned.

Research Involving Human In Vitro Fertilization

The Federal regulations require that all investigators proposing research involving human *in vitro* fertilization with or without embryo transfer must submit a full protocol to the IRB for review. In order to obtain Federal funding for the research, the project must receive review by a national Ethics Advisory Board⁶⁹. The IRB may consult with the American College of Obstetricians and Gynecologists (ACOG) and/or the American Fertility Society (AFS) when reviewing protocols involving human *in vitro* fertilization.

The greatest problem regarding *in vitro* fertilization for the IRB involves the use of "spare" embryos. Consent forms for all *in vitro* fertilization procedures should address what will happen to embryos that are not used in the particular embryo transfer procedure for which they were created (e.g., will they be used for research purposes, will they be implanted in other women, will they be destroyed, etc.)

Research with Dead Fetuses, Fetal Material, and the Placenta

The use of dead fetuses, fetal material, and the placenta is gaining considerable attention due to the lifting of a moratorium on Federally-funded research involving the therapeutic transplantation into humans of fetal tissue obtained from induced abortions. This moratorium, issued by the Assistant Secretary of Health in 1998, was lifted by a Presidential memorandum published in the Federal Register 58:7457. Interim guidelines for the support and conduct of therapeutic human fetal transplantation research were published in the NIH Guide for Grants and Contracts.

Investigators are required to conduct research involving human fetuses, fetal material, and the placenta according to the following regulatory requirements:

Separating Abortion from Research

The decision to terminate a pregnancy and procedures of abortion must be kept independent from the retrieval and use of fetal tissue. The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

⁶⁹ 45 CFR 46.204(d)

Prohibiting Payments and Other Inducements

Payments and other forms of remuneration with the procurement of fetal tissue are prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissue.

Informed Consent

- a. Potential recipients of fetal tissue, as well as research and health care participants should be informed about the source of the tissues in question. This information should be provided to prospective subjects in the informed consent form.
- b. The decision and consent to terminate pregnancy must precede discussion of the possible use of the fetal tissue in research and any request for such consent that might be required for that use.
- c. Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. Her consent to donate fetal remains is sufficient for the use of fetal tissue.
- d. Consent should be obtained in compliance with Federal and State law.

Prohibiting Direct Donations

- a. The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue.
- b. Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team.
- c. Experimental transplants performed with fetal tissue from induced abortions by a family member, friend, or acquaintance should be prohibited.

Compliance with State and Local Laws

Research utilizing fetal tissue should comply with all applicable state laws and local ordinances. Currently, Kentucky statutes do not address research utilizing fetal tissue. Investigators are reminded that state law periodically changes, and does vary from state to state. Investigators conducting research outside of Kentucky should be familiar with the applicable requirements of the state or country where the research is to take place.

State/Jurisdiction Statute Section	Specifically permits research on fetus/embryo	Restricts research on aborted fetus/ embryo	Consent provisions to conduct research on fetus/embryo	Restricts research on fetus or embryo resulting from from sources other than abortion	Restrictions of purchase/sale human tissue for research
Kentucky 436.026 311.165	No	No	No	No	Yes, prohibits sale of fetus/ fetal tissue

Research in Anticipation Of Abortion

After lengthy review, the National Commission determined that there is no difference between the moral status of a fetus destined for abortion and that of a fetus that is expected to be carried to term. Therefore, only those research procedures that are acceptable for a fetus going to term may be

performed in anticipation of abortion, to preserve the mother's right to change her mind about ending the pregnancy.

APPENDIX C: PRISONERS IN RESEARCH

Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for making choices, earning money, communicating with outsiders, or obtaining medical care. The National Commission for the Protection of Human Subjects found that prisoners often volunteer for medical research as a means of access to competent medical, social service or psychological care.

Because their autonomy is limited, prisoners may participate only in certain categories of research, and special precautions are needed to assure that their consent to participate in the research is both knowing and voluntary⁷⁰. KRS 441.055 requires the Department of Corrections to promulgate administrative regulations establishing minimum health standards for jails, which elect to house state prisoners and for jails, which do not elect to hold state prisoners. This administrative regulation sets forth procedures for the proper delivery of medical services in both types of jails. The administrative regulation 501 KAR 3:090. states Medical services; Section 1. Procedure Services. (13) Medical research shall not be permitted on any prisoner in the jail. Therefore, medical research, (behavioral research is not mentioned in the statutes or regulations), is not permitted in Kentucky jails. However, Kentucky Corrections Policies and Procedures [RESEARCH AND SURVEY PROJECTS](#) does allow for prisoner research in Kentucky's state prisons if the investigator follows the standards as set forth in this policy and obtains proper approval from the Kentucky Department of Corrections and the appropriate University of Louisville IRB.

Definition of a Prisoner

"Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46). If Subpart C does not apply, the organization may use an equivalent definition of prisoners.

"Minimal risk" for prisoners is defined by the regulations as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45CFR46.303(d)). Furthermore, the regulations state that the IRB must find that the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (45 CFR 46.305(a)(3)). If Subpart C does not apply the organization may use an equivalent definition of minimal risk for prisoners

Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

Common examples of the application of the regulatory definition of prisoner are as follows:

1. Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners; however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.
2. Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals

⁷⁰ 45 CFR 46.302

- who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
3. Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
 4. Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise about research involving these populations.

The prisoner representative serving on the UofL IRBs will be a voting member of the IRB. The prisoner representative will review, as a primary or secondary reviewer, all research conducted by UofL investigators involving prisoners. The prisoner reviewer will focus on the requirements in Subpart C or equivalent protections. If no prisoner representative is available to review the research, the UofL IRB may engage an appropriately qualified prisoner consultant to assist in the review. The prisoner consultant must meet the same requirements as any other consultant.

The prisoner representative must:

1. receive all review materials pertaining to the research the same as primary reviewer.
2. must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
3. present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed. Due to circumstance, if the prisoner representative cannot be physically present, the prisoner representative may attend the meeting by phone, videoconference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

Modifications involving more than a minor change reviewed by the convened IRB must use the same procedures as used for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

Minor modifications to the research may be reviewed using the expedited procedure.

Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. The prisoner representative must concur with the determination that the research involves no greater than minimal risk. The prisoner representative must review the research as a primary or secondary reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.

Review of modifications and continuing review, expedited or full board, must use the same procedures as for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above). If no subjects have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

Research that does not involve interaction with prisoners (e.g. existing data, record review) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater

than minimal risk for the prison population being studied. Review by a prisoner representative is not required.

If Subpart C is applicable either by funding requirement or voluntarily (e.g. Subpart C box is checked on the federal wide assurance) research that involves prisoners cannot be deemed exempt.

If Subpart C is not applicable, research using data, samples, or materials that involves prisoners or that may involve prisoners but qualifies for an exemption might be granted an exemption. It must be determined that an exemption is appropriate for the prison population being studied. The prisoner representative may be consulted for exempt determinations involving prisoners but is not required. An exemption may not be granted if the research involves interaction with prisoners (including obtaining consent).

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, when Subpart C applies, the IRB will confirm that the subject meets the definition of a prisoner. The IRB will either terminate the enrollment OR review the research study under Subpart C if it feasible for the subject to remain in the study. Before terminating the enrollment of the incarcerated subject, the IRB should consider the risks associated with terminating participation in the study. If the subject cannot be terminated for health or safety reasons, the subject may continue enrollment in the study and the IRB will review the research under Subpart C.

If some the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, the subject may continue enrollment. OHRP will be informed of the decision along with the justification.

If adequate justification is not determined but the IRB believes it is in the subject's best interest to be followed, the subject may be remove from the study and kept on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

If a subject is incarcerated temporarily while enrolled in a study and the temporary incarceration has no effect on the study, the IRB may allow the subject to remain enrolled. If the temporary incarceration has an effect on the study, handle according to the above guidance.

When Subpart C does not apply, the UofL IRB will utilize the same guidance as used for review of prisoner research as when Subpart C does apply.

Categories of Research in Which Prisoners May Participate

Prisoners may participate in the following kinds of research:

1. Studies of the possible causes, effects, and processes of incarceration and criminal behavior, if those studies present no more than minimal risk⁷¹ or inconvenience to the subjects.
2. Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects.
3. Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the secretary of the Department of Health and Human Services has

⁷¹ For research that involves prisoners, minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303(d)).

consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register.

4. Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by the secretary of the Department of Health and Human Services, after consultation with appropriate experts as described above.
5. The Secretary of DHHS waived the applicability⁷² of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:
 - a. In which the sole purposes are to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease, and
 - b. Where the institution responsible for the conduct of the research certifies to the Office for Human Research Protections, DHHS, acting on behalf of the Secretary, that the IRB approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and prisoners are not a particular focus of the research.

Additional Duties of the IRB

When the IRB reviews research that will involve prisoners they are required to first confirm that the proposed study fits within the permissible categories of research described above. Then, it must determine:

1. Any advantages that prisoners will realize as a result of participation in the research, when compared to general living conditions within the prison, are not so great as to impair the prisoner's ability to weigh the risks and benefits of participation and freely choose.
2. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (usually demonstrated by enrolling non-prisoner subjects from the community, as well).
3. Procedures for selecting subjects within the prison are fair, and free from arbitrary manipulation by prison authorities or other prisoners.
4. Control subjects will be selected randomly from among the group of eligible volunteers, unless the principal investigator justifies a different procedure.
5. The information presented during recruitment and consent procedures is in a language, and level of complexity, understandable to the subject population.
6. The IRB is assured that the parole board will not take research participation into account in making decisions about parole, and each prisoner is informed in advance that participation will have no effect on the possibility of parole.

⁷² Federal Register: June 20, 2003, Volume 68, Number 119, Page 36929-36931.

7. If medical follow-up is necessary to protect the health and welfare of the subjects, adequate provision is made for such care, taking into account the varying length of prisoners' sentences.
8. Finally, an IRB that reviews research involving prisoners is required to have at least one member who is either a prisoner, or a prisoner representative; and a majority of the IRB members cannot be in any way associated with the prison(s) involved. (This requirement may be waived if two or more IRBs are involved in reviewing the same protocol, and at least one of the IRBs meets this condition.)

Requirements for Studies Funded or Supported by the Department of Justice (DoJ)

All DoJ award recipients must be cognizant of the importance of protecting the rights and welfare of human subject research participants. All research conducted at DoJ or supported with DoJ funds must comply with all Federal (28 CFR Part 46), U.S. Department of Justice (DOJ), Office of Justice Programs, Bureau of Prisons (BoP) and National Institute of Justice (NIJ) regulations and policies concerning the protection of human subjects and the DOJ confidentiality requirements.

National Institute of Justice

Applicants for NIJ funding must submit a Privacy Certificate and have it approved by the NIJ Human Subjects Protection Officer as a condition of approval of a grant application or contract proposal regardless of whether the project involves the collection of identifiable data. In cases where no personally identifiable information will be collected, the Privacy Certificate should contain a statement to this effect and a brief project description.

The [Privacy Certificate](#) assures that the applicant understands his responsibilities to protect the confidentiality of research and statistical information and has developed specific procedures to ensure that this information is only used or revealed in accordance with the requirements of 42 USC §3789g and 28 CFR Part 22.

For NIJ sponsored research, all investigators and key personnel are required to sign Employee Confidentiality Statements. These forms are maintained by the responsible investigator.

The confidentiality statement on the consent form must state that confidentiality can only be broken if the participant reports immediate harm to participants or others. Under a privacy certificate, investigators and key personnel do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting. This is in direct conflict with Kentucky law and may require that a second consent form be signed by the participant stating that child, elder, or spouse abuse will be reported.

For NIJ-funded research, a copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

Bureau of Prisons

Investigators who wish to conduct research within the Bureau of Prisons must have academic preparation or experience in the area of study of the proposed research.

When submitting a research proposal, the investigator must provide a summary statement, which includes the names and current affiliations of the investigators, title of the study, purpose of the study, location of the study, methods to be employed, anticipated results, duration of the

study, number of subjects (staff or inmates) required, amount of time required from each, and indication of risk or discomfort involved as a result of participation.

The investigator must provide a comprehensive statement, which includes a review of related literature, a detailed description of the research method, the significance of anticipated results and their contribution to the advancement of knowledge, the specific resources required from the bureau of prisons, a description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, a discussion of the likelihood that the risks and discomforts will actually occur, and a description of steps taken to minimize any risks.

The investigator must provide a description of physical or administrative procedures to be followed to, ensure the security of any individually identifiable data that are being collected for the study, destroy research records or remove individual identifiers from those records when the research has been completed, provide a description of any anticipated effects of the research study on organizational programs and operations, provide relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules, and provide a statement regarding assurances and certification required by 28 CFR 46, if applicable.

For research conducted within the Bureau of Prisons, the Organization, IRB or EC, investigators, and key personnel must follow the requirements of 28 CFR 512, including:

- a. the project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- b. the project must have an adequate research design and contribute to the advancement of knowledge about corrections.
- c. the research design must be compatible with both the operation of prison facilities and protection of human participants.
- d. the investigator must observe the rules of the institution or office in which the research is conducted.
- e. any investigator who is a non-employee of the Bureau must sign a statement in which the investigator agrees to adhere to the provisions of 28 CFR 512.
- f. all research proposals will be reviewed by the Bureau Research Review Board.
- g. the selection of participants within any one organization must be equitable.
- h. incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered.
- i. reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both:
 1. no longer in Bureau of Prisons custody, and
 2. participating in authorized research being conducted by Bureau employees or contractors.
- j. a statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility.
- k. additional required elements of informed consent include:
 1. identification of the investigators.
 2. anticipated uses of the results of the research.
 3. a statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or

- prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
4. a statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a Investigator may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization. This applies when following Department of Justice regulations.
 - l. except as noted in the consent statement to the participant, the investigator must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information.
 - m. a non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
 - n. except for computerized data records maintained at an official DoJ site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
 - o. if the investigator is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the investigator may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
 - p. at least once a year, the Investigator shall provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
 - q. at least 12 working days before any report of findings is to be released, the Investigator shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The Investigator shall include an abstract in the report of findings.
 - r. in any publication of results, the Investigator shall acknowledge the Bureau's participation in the research project. the Investigator shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
 - s. prior to submitting for publication the results of a research project conducted under this subpart, the Investigator shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

Department of Justice Specific Language Requirements in Informed Consents

Due to the varying requirements of DoJ (NIJ, BoP) sponsored human subjects research, additional, appropriate required language in the informed consent document will be determined at the time of IRB review due to the difficulty in composing wording that will ensure that subjects are protected and agency requirements are followed in all situations that may be encountered. Information in this guidance will be utilized to ensure that subjects are provided information required by the sponsoring agency.

Additional information about prisoner research may be found on the [OHRP](#) website.

APPENDIX D: CHILDREN IN RESEARCH

The legal mandate of the IRB is to protect the rights and welfare of human subjects. This task becomes more difficult when considering children as research subjects. The Federal regulations provide for “Additional Protections for Children Involved as Subjects of Research”⁷³. In Kentucky, Subpart D of [45 CFR 46](#) and [21 CFR 50](#) applies to all research involving individuals under the age of 18 unless the individual is emancipated. In Kentucky these are the individuals who meet the Subpart D definition of a child. In most circumstances Subpart D requires parental permission.

Parental Permission and Research of Minimal Risk

Investigators are required to gain parental permission from at least one of the child’s parents or legal guardians if the research involves only minimal risk.

Parental Permission and Research of More Than Minimal Risk

The following guidelines pertain to research of more than minimal risk in which it is proposed that children participate as research subjects:

- a) If the research poses more than minimal risk and has no direct benefit to the child, the investigator is required to gain permission from both parents or the child’s legal guardian in order for the child to participate in the research.
- b) If the research poses more than minimal risk but may directly benefit the child, only one of the child’s parents or legal guardians need give permission.
- c) The investigator is not required to gain permission from both parents if one of the parents is not reasonably available, deceased, unknown, legally incompetent, or from a parent who does not have legal responsibility for the care and custody of the child. This caveat does not exempt the investigator from obtaining the permission from at least one parent who has legal responsibility for the child.

Subpart D of the Federal regulations requires the IRB to classify research involving children into one of four categories relating to the risks and benefits of the proposed research:

1. Research involving no greater than minimal risk (Category I -45CFR46.404 or 21CFR50.51).
2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual subjects. Research in this category is approvable by the IRB provided: (a) the risk is justified by the anticipated benefit to the subjects; (b) the relationship of risk to benefit is at least as favorable as any alternative approach; and (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians (Category II - 45CFR46.405 or 21CFR50.52).
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield important generalizable knowledge about the subject’s disorder or condition. Research in this category is approvable by the IRB provided (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; (c) the intervention or procedure

⁷³ 45 CFR 46 Subpart D and 21 CFR 50 Subpart D

is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and (d) adequate provisions are made for soliciting, assent of the child and permission of their parents or guardians (Category III-45CFR46.406 or 21CFR50.53) .

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. This section provides a mechanism for approval of research not falling under categories 1-3 above. The research must be approved by the secretary of the Department of Health and Human Services if it is to be funded by the DHHS, after consultation with a panel of experts, and the panel must find that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children (Category IV - 45CFR46.407 or 21CFR50.54).

Children who are foster children⁷⁴ or wards of the state or any other agency, institution, or entity can be included in research approved under §46.406, 50.53 or §46.407, 50.54 only if such research is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a foster child or ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

For additional information on Category III and IV (45CFR46.406 and 407 or 21CFR50.53 or 54) research in children see the guidance document [Special Protections for Children as Research Subjects](#)

When assessing the risk to children and evaluating a research project proposing to involve children the IRB will consider the following issues:

1. Is the participation of children as research subjects justified in this particular instance?
2. If this research question can be addressed initially in adults, has this research been conducted?
3. Have results from any adult research indicated that the proposed research would benefit, or at least not be harmful, to children?
4. Has every effort been made to ensure that a parent is present when the research intervention is conducted? This will not only comfort the child but will enable the parent to exercise the right to end the child's participation in the research project at any time. Investigators should note that in some cases (e.g., research into sensitive personal matters, physical examinations of adolescents, research into abuse, etc.) it may not be appropriate to have a parent present. If a parent will not be present during the course of the project, has the investigator clearly stated why in the protocol form?

⁷⁴ Foster children and wards are considered to have equal protection under Kentucky law by the Cabinet for Health and Families.

5. Are the personnel involved in the research, and the facility in which the research will be conducted, knowledgeable about and sensitive to the physical and psychological needs of the children and their families?
6. Have the investigators taken into account the child's previous experience with illness and medical interventions? Some children may be able to cope with the stress of research better than others as a result of previous experience with medicine. Younger, "less experienced" children may be unprepared for participation in medical research.
7. How has the investigator determined the number of children to be enrolled for the study? Investigators should justify the number of subjects they propose to study. Investigators should always plan to involve the fewest number of children necessary to obtain statistically significant data from which valid conclusions can be drawn.
8. Whether the proposed techniques are the least invasive (physically and psychologically) in order to obtain the research information.
9. Have the investigators clearly defined how the assent of the child-subjects will be obtained?
10. For research involving medical interventions, the IRB will consider previous research with animals. The investigator should indicate whether the animal research is completed and the results to date.

An IRB must have present at its meeting an advocate for children in order to review projects involving the use of these populations in research. All personnel working with children should be familiar with the State laws requiring the reporting of suspected abuse. The IRB cannot approve research that exposes children as subjects to more than minimal risk and does not satisfy the conditions outlined above. The Federal regulations, however, provide a process for seeking approval for such research from the DHHS secretary.

Additional information related to research with children may be found on the [OHRP](#) website.

APPENDIX E: MONITORS FOR FDA CLINICAL STUDIES

Selection and Qualifications of Monitors

- a. Monitors should be appointed by the sponsor.
- b. Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.
- c. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOP's, and the applicable regulatory requirement(s).

Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

Monitor's Responsibilities

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- a. Acting as the main line of communication between the sponsor and the investigator.
- b. Verifying that the investigator has adequate qualifications and resources and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.
- c. Verifying, for the investigational product(s):
 1. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
 2. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
 3. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
 4. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
 5. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorized procedures.
- d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- e. Verifying that written informed consent was obtained before each subject's participation in the trial.
- f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- g. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

-
- h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
 - i. Verifying that the investigator is enrolling only eligible subjects.
 - j. Reporting the subject recruitment rate.
 - k. Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.
 - l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
 - m. Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:
 - 1. The data required by the protocol are reported accurately on the CRF's and are consistent with the source data/documents.
 - 2. Any dose and/or therapy modifications are well documented for each of the trial subjects.
 - 3. Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRF's.
 - 4. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRF's.
 - 5. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRF's.
 - n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
 - o. Determining whether all adverse events (AE's) are appropriately reported within the time periods required by the protocol, the IRB/IEC, the sponsor, the applicable regulatory requirement(s).
 - p. Determining whether the investigator is maintaining the essential documents.
 - q. Communicating deviations from the protocol, SOP's, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOP's as well as those procedures that are specified by the sponsor for monitoring a specific trial.

Monitoring Report

- a. The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
- b. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.
- c. Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.
- d. The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

Audit

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOP's, and the applicable regulatory requirements.

Selection and Qualification of Auditors

- a. The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.
- b. The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

Auditing Procedures

- a. The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
- b. The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type, and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).
- c. The observations and findings of the auditor(s) should be documented.
- d. To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious noncompliance exists, or in the course of legal proceedings or investigations.
- e. Where required by applicable law or regulation, the sponsor should provide an audit certificate.

Noncompliance

Noncompliance with the protocol, SOP's, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

If the monitoring and/or auditing identify serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

APPENDIX F: INTERNATIONAL RESEARCH

The following information is to provide guidance to researchers who wish to conduct or participate in international research. The University of Louisville (UofL) IRBs recognize the importance of international research projects and wish to alert investigators to the additional review requirements for such activities.

All international research conducted by researchers affiliated with the University of Louisville will follow federal guidelines, be reviewed by the UofL IRBs, and follow requirements of the location where the research is conducted. All UofL policies and procedures which are applied to research conducted domestically will be applied to research conducted in other countries, as appropriate.

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

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

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

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

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

The UofL IRB will not take action to approve an application without either written documentation that local review and approval has been granted in the host country, or the consult requested by the IRB has been received and accepted.

The protocol will be submitted following the same procedures utilized to submit any other protocol.

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

- a. Proposed payments (if any) to participants: The remuneration should be described in terms of both US and local currency. Include a description of payment in relative terms (i.e. payment equates to a day's work, hourly salary, or another local reference).
- b. Local contact information: Include a local phone contact number for co-investigators or the local IRB/EC who could answer research related questions. If the project is a clinical trial, include local emergency contact phone numbers for participants.
- c. Treatment options: For clinical trials, explain if any treatment(s) will be available to participants after study completion. If a placebo arm is included in the trial, explain whether participants will be able to receive the study drug/intervention after study completion.
- d. Recruitment materials to be used locally in both the language of the host country and in English.
- e. If study team members are U.S. citizens and plan to travel to the site of the research, include the U. S. Department of State [International Travel](#) Safety and Security assessment of the conditions in the research site.

HIPAA Considerations in International Research

UofL international researchers are strongly encouraged to only transmit or receive de-identified research data from areas outside the United States. This eliminates the need to meet HIPAA requirements for the data transmitted.

HIPAA does not apply to international research as long as no protected health information (PHI) is transmitted back to a covered entity or employee of a covered entity in the United States. However, once identifiable health information is received by a covered entity, that information becomes PHI (with a narrow exception for overseas foreign nationals receiving health care from US agencies). As UofL is a hybrid covered entity, this means that when a researcher employed in a part of UofL considered inside the covered entity sends identified health information collected internationally across a UofL network or stores such information on a UofL computer or server, the information becomes PHI.

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

Additional Guidance

OHRP [International Compilation of Human Research Protections](#)

[International Conference on Harmonization Guidelines Good Clinical Practices](#)

APPENDIX G: GUIDANCE FOR ADDITIONAL COMPLIANCE REQUIREMENTS FOR FEDERAL AGENCIES OTHER THAN OHRP OR FDA WHO MAY SPONSOR, FUND, OR OVERSEE HUMAN SUBJECTS RESEARCH

Most of the sponsored research conducted by UofL researchers is subject only to DHHS (OHRP) or FDA oversight and requirements given forth in 45 CFR 46 or 21 CFR 50, 56, 312 and 812. However when research is sponsored by another federal department, agency or office, those entities may have additional human subjects protection requirements with which investigators are expected to comply.

The following is a listing of some of those additional requirements.

Compliance with this Procedure

All UofL affiliated human subjects investigators and key personnel, University of Louisville IRBs, and the Human Subjects Protection Program are expected to comply with the requirements of the federal, state, and local requirements to conduct human subjects research in schools.

Department of Defense (DoD)

The following applies to research involving human subjects conducted by the DoD or a DoD Component (all other organizational entities in the Department of Defense) and other research that is supported by the DoD or a DoD Component through a contract, grant, cooperative agreement, or other arrangement.

Research sponsored or funded by the DoD must be reviewed by the IRB under an additional set of federal regulations (32CFR219). The Principal Investigator must meet additional DoD research requirements prior to initiation of the research. The DoD follows the DHHS and FDA regulations on human subjects research, but also applies DoD Directive (DoDD) 3216.02 "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research." DoD Directive 3216.02 contains additional requirements that include, but are not limited to the items below.

The Organization/IRB will:

- a. comply with DoD limitation on exceptions from informed consent (e.g., 10 USC 980, 45 CFR 46, and 21 CFR 50).
- b. not waive the consent process without permission from the Secretary of Defense when the research meets the DoD definition of "Research Involving a Human Being as an Experimental Subject."⁷⁵
- c. ensure that an exception from consent in emergency medicine research is not approved unless a waiver from the Secretary of Defense is obtained.
- d. address and report allegations of non-compliance with human research protections.
- e. Ensure that when research involves U.S. military personnel policies and procedures include additional protections for military research participants to minimize undue influence such that:

⁷⁵ The definition is found in DoDD 3216.02, Enclosure 2. Definitions. Paragraph E2.1.3: "An activity, for research purposes, where there is an intervention or interaction with a human subject for the primary purpose of obtaining the effect of the intervention or interaction (32 CFR 219.102(f))." Examples include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose.

⁷⁶ If the research participant does not meet the definition of "experimental subject," policies and procedures may allow the IRB to waive the consent process.

1. officers are not permitted to influence the decision of their subordinates.
 2. officers and senior non-commissioned officers may not be present at the time of recruitment.
 3. officers and senior non-commissioned officers have a separate opportunity to participate.
 4. when recruitment involves a percentage of a unit, an independent ombudsman is present.
 5. when research involves U.S. military personnel, policies and procedures require limitations on dual compensation that prohibit an individual from receiving pay from more than one position for more than 40 hours of work in one calendar week.
 6. the policy includes temporary, part-time, and intermittent appointments.
- f. Address and report allegations of research misconduct.
 - g. protect pregnant women, prisoners,⁷⁷ and children.
 - h. support oversight by the sponsoring DoD Component (which may include DoD Component review of the research and site visits).
 - i. follow DoD requirements for additional review for DoD-sponsored survey research or survey research within DoD. Additional requirements for survey research of DoD personnel may be found at: http://fhp.osd.mil/pdfs/1100.13_Surveys_of_DoD_Personnel_Instruction.pdf
 - j. comply with DoD limitations on research where consent by legally authorized representatives is proposed.
 - k. ensure that when conducting DoD multi-site research, a formal agreement between the organizations is completed to specify the roles and responsibilities of each party.
 - l. ensure safeguard for research conducted with international populations.
 - m. conduct initial and continuing research ethics education for personnel who are engaged in human subject research (e.g., who review, approve, oversee, or manage research).
 - n. ensure new research and substantive scientific amendments to approved research shall undergo scientific review and that the review is considered by the IRB.
 - o. document determination by a designated Institutional Official (other than investigators) whether research meets criteria for exemption.
 - p. appoint a medical monitor for all research that is greater than minimal risk to participants.⁷⁸

The IRB/Investigator will:

- a. will ensure that, when appropriate, the research protocol will be reviewed and approved by the IRB prior to DoD approval.
- b. comply with consent form language requirements.
- c. explain to subjects any provisions for medical care for research-related injury.
- d. report unanticipated problems, adverse events, research-related injury, and suspensions or terminations of research.
- e. comply with limitations on dual compensation for U. S. military personnel.
- f. follow procedures for addressing financial and other conflicts of interest.

⁷⁷ DoD regulations prohibit research with prisoners of war (POW).

⁷⁸The definition of a medical monitor within the DoD directive differs from the industry definition and may be found in DoDD 3126.02, Section 4.4.3 "For research involving more than minimal risk (as defined in 31 CFR 219.102(i), reference (c)) to subjects, an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate." The research monitor has the authority to stop a research study in progress, remove individuals from the study, or take any steps to protect the safety and well being of subjects until the IRB can assess.

- g. comply with all provisions for research with human subjects using investigational test articles (drugs, device, and biologics).
- h. follow DoD limitations on use of humans as experimental subjects.

- a. follow DoD limitations or restrictions on some Federal employees (both uniformed and civilian) regarding payment for research participation.

- b. follow human subjects research recordkeeping requirements which may include submitting records to the DoD for archiving if required by the agency.

Department of Defense Specific Language Requirements in Informed Consents

Due to the varying requirements of DoD sponsored human subjects research, additional, appropriate required language in the informed consent document will be determined at the time of IRB review due to the difficulty in composing wording that will ensure that subjects are protected and agency requirements are followed in all situations that may be encountered. Information in this guidance will be utilized to ensure that subjects are provided information required by the sponsoring agency.

Staff in the Human Subjects Protection Program office (HSPPO) is aware of the DoD language requirements in the research application and informed consent document(s) and are available to assist UofL investigators who may have questions about the additional requirements. Any project that involves military personnel as part of the participant population additional privacy and confidentiality provisions must be addressed in the research application and consent form. Please call or e-mail the HSPPO to discuss the requirements.

While the DoD requires documented retraining in human subjects research every three years, investigators and key personnel utilizing the UofL IRB must update their human subjects in research training every two years. As with the DoD, the retraining requirement applies to all members of the study team of a research protocol that will receive DoD funding. To meet the DoD/UofL retraining requirement, UofL research team members may take the refresher human subjects course on the [CITI website](#).

The UofL has a Department of Defense Assurance Document, which is an [addendum](#) (Attachment 2) to the UofL Federal Wide Assurance on file with DHHS. This addendum outlines specific requirements of the investigator, the IRB, and statements that may be required in the consent document. If a copy of the DoD Amendment to the UofL FWA is required, it is located on the HSPPO website.

Investigators should review the requirements of [3216.02](#) "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research" prior to submitting an application for funding support from DoD.

DoD policies and links to the DoD Components policies may be found at: <http://www.dtic.mil/whs/directives/>.

Department of Education (DE)

School officials and/or teachers do not have the authority to give consent for the participation of children in research. Only a parent or legally authorized representative may allow a child, with the child's assent, to participate in research.

The IRB requires documentation of approval of the school prior to allowing investigators to contact, recruit, or enroll children into a study. Investigators should contact the appropriate school officials in the district in which they wish to conduct the research regarding the procedures for obtaining permission to conduct the research in individual schools.

The Family Educational Rights and Privacy Act (FERPA)⁷⁹, the Protection of Pupil Rights Amendment (PPRA)⁸⁰, and the No Child Left Behind Act of 2001 (NCLB)⁸¹ protect the privacy of student education records, parental access to information, administration of certain physical or mental examinations, and human subjects research involving children in the public and some private school systems.

Under FERPA, Generally, schools must have written permission from the parent or eligible student in order to release any information from a student's education record. However, FERPA allows schools to disclose those records, without consent, to the following parties or under the following conditions (34 CFR § 99.31):

- a. School officials with legitimate educational interest;
- b. Other schools to which a student is transferring;
- c. Specified officials for audit or evaluation purposes;
- d. Appropriate parties in connection with financial aid to a student;
- e. Organizations conducting certain studies for or on behalf of the school;
- f. Accrediting organizations;
- g. To comply with a judicial order or lawfully issued subpoena;
- h. Appropriate officials in cases of health and safety emergencies; and
- i. State and local authorities, within a juvenile justice system, pursuant to specific State law.

Schools may disclose, without consent, "directory" information such as a student's name, address, telephone number, date and place of birth, honors and awards, and dates of attendance. However, schools must tell parents and eligible students about directory information and allow parents and eligible students a reasonable amount of time to request that the school not disclose directory information about them. Schools must notify parents and eligible students annually of their rights under FERPA. The actual means of notification (special letter, inclusion in a PTA bulletin, student handbook, or newspaper article) is left to the discretion of each school.

Kentucky Revised Statutes (KRS) mirror the requirements of the federal regulations and are applicable to all Kentucky public schools.

Jefferson County Public Schools (JCPS), UofL's most closely affiliated school system, utilize their [Code of Acceptable Behavior and Discipline](#) which includes their *Student Bill of Rights* (p.29) (Attachment 1) to notify parents and guardians of their and their children's rights.

PPRA, as amended, has two sets of requirements for surveys :

- a. Requirements that apply to "protected information" surveys that are funded in whole or in part by the U.S. Department of Education.
- b. Requirements that apply to "protected information" surveys that are funded by sources other than the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any Department of Education program (i.e. public elementary and secondary schools and some private schools).

⁷⁹ <http://www2.ed.gov/policy/gen/guid/fpco/ferpa/index.html>

⁸⁰ <http://www2.ed.gov/policy/gen/guid/fpco/ppra/index.html>

⁸¹ <http://www.ed.gov/policy/elsec/leg/esea02/pg122.html>

PPRA, updated by NCLB in 2001, lists 8 categories of protected information for survey responses. If a student or parent is surveyed and the survey contains questions related to any one of the following eight categories, provisions must be made to solicit the active consent of the parent or guardian and the assent of the student:

- a. political affiliations or beliefs of the student or the student's parent;
- b. mental or psychological problems of the student or the student's family;
- c. sex behavior or attitudes;
- d. illegal, anti-social, self-incriminating, or demeaning behavior;
- e. critical appraisals of other individuals with whom respondents have close family relationships;
- f. legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers;
- g. religious practices, affiliations, or beliefs of the student or student's parent; or
- h. income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

PPRA has implications for IRBs in applying the Common Rule criteria for waiving informed consent (in section 116(d) of the Common Rule). Specifically the second IRB criterion: "research does not adversely affect the rights and welfare of subjects" is impacted because of the "rights" that PPRA gives parents.

Practical Implications in Applying the Common Rule Waiver Requirement pertaining to rights and welfare:

First Set of Requirements: US Department of Education Funded Protected Information Surveys

- a. Does the research involve "protected information" surveys?
- b. Are the surveys U.S. Department of Education- funded in whole or part?
- c. Are the surveys "required"?

If the answer is yes to the three questions, PPRA affords parents the right to provide active consent.

Under the circumstances, it would be difficult for an IRB to determine that the "rights and welfare" criterion for waiving informed consent entirely could be met; therefore, prior written parental consent would be required, even if the IRB determined that some of the basic elements of informed consent specified in section 116(a) could be waived as inappropriate to the activity.

Second Set of Requirements: Surveys that are funded by sources other than the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any U.S. Department of Education administered program (i.e., public schools and some private schools)

- a. Do the surveys include protected information?
- b. Are the surveys being administered or distributed by schools that receive any U.S. Department Education funds?

If the answer is yes to both questions, PPRA affords parents the right to inspect the surveys before they are administered or distributed and to opt the student out of the surveys.

PPRA requires schools to develop and adopt policies, in conjunction with parents, regarding 6 areas, some of which are relevant to surveys:

- a. Right to inspect a survey before administered or distributed;
- b. Arrangements to protect student privacy in the administration of a survey;
- c. Right to inspect any instructional material used as part of educational curriculum;
- d. Administration of physical examinations or screenings;
- e. Collection, disclosure or use of personal information for purposes of marketing or selling;
- f. Right to inspect any instrument in the collection of information for marketing or selling the surveys.

PPRA also requires schools to notify parents of the policies and to offer parents the opportunity to opt out of (remove child from) participation in third-party surveys involving protected information.

For research funded by the National Institute on Disability and Rehabilitation Research, when the UofL IRB reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB will include at least one person primarily concerned with the welfare of these research participants.

Exception (Exemption) from Written Informed Consent

A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the university or investigator conducting the research that specifies the determination of the exception.

The University of Louisville has in policies and procedures, a process to grant exceptions to parental/student consent to release student records for research. This responsibility is delegated to the Chair and Vice-Chairs of the IRB.

An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

- a. Develop, validate, or administer predictive tests.
- b. Administer student aid programs.
- c. Improve instruction.

Definitions

Child - person enrolled in research not above the elementary or secondary education level, who has not reached the age or majority as determined under state law. A student is a child for the purposes of this definition.

Eligible student - a student, or a former student, who has reached the age of eighteen (18) or is pursuing an education beyond high school and therefore the permission or consent required of, and the rights accorded to the parents of the student shall thereafter be required of, and accorded to the student.

Prior - preceding in time or in order as in obtaining written informed consent before any activities related to the research are initiated.

School official - personnel employed in instructive and administrative positions with a school board or educational institution. Parents and other non-educational persons who are elected or appointed to school-based decision-making councils or committees thereof, or other voluntary boards or committees shall not be considered school officials.

Department of Education Specific Language Requirements in Informed Consents

If a study receives funding from the Department of Education, the investigator may need to include the following associated paragraph(s) in the informed consent document or consult with the IRB/HSPPO to formulate appropriate language for the proposed research.

“We must tell you the following because the Department of Education (DOE) paid for this study or your child’s school receives money from the DOE.

The data we collect about you or your child may only be used to complete the study as stated in this consent. We will conduct this study in a way that protects the identity of you and your child. Only study team members or others who may have a legal reason to know will see your data. If you ask, you can see all the materials used for the research before the study begins. This may include teachers’ manuals, surveys, films, tapes, or other teaching material. If you want to look at any of this, please call (person’s name, phone number including area code) and (he/she) will tell you where and when it will be available for you to see. In addition to the surveys or questions we may ask you and your child to complete or answer, we want to collect the following data from your child’s school records:

When all of this study is done, we will destroy or return to the school all data that could identify you or your child. We think this study will last for (length of study) years and we will destroy or return the information to the school by (date).”

Department of Energy (DoE)

The protection of human subjects in all the research performed under Department of Energy (DOE) authorities is of prime importance to the Department. All research conducted at DOE institutions, supported with DOE funds, or performed by DOE employees, including research that is classified (UofL does not conduct classified research by policy) and proprietary, whether done domestically or in an international environment, must comply with all federal regulations and DOE requirements that address the protection of human subjects.

The Secretary of Energy is responsible for the conduct of DOE-related human subjects research. The requirements for implementing this policy are described in [DOE Order 443.1A, Protection of Human Subjects](#) to ensure that the research program keeps pace with the changing and complex nature of human subjects research, develops and implements comprehensive educational programs, and performs program compliance reviews.

Regulations and directives that specifically address the protection of human subjects include CFR Part 745; 45 CFR Part 46, Subparts B, C, and D; Department of Health and Human Services Regulation on Protection of Human Subjects; and DOE O 443.1A, Protection of Human Subjects, dated 12-20-07. The requirements of all applicable regulations and directives must be met before any research involving human subjects is initiated.

Policies and procedures require the IRB or EC to review and approve the “Checklist for IRBs to Use in Verifying That HS Research Protocols Are in Compliance with DOE Requirements” submitted by the Researchers to verify compliance with the DOE requirements for the protection of Personally Identifiable Information.

Researchers must promptly report the following to the human subject research program manager:

- a. any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken.
- b. any suspension or termination of IRB approval of research.
- c. any significant non-compliance with HRPP procedures or other requirements.
- d. the time frame for “promptly” is defined.
- e. any compromise of personally identifiable information must be reported immediately.
- f. the time frame for “immediately” is defined.

The Organization must periodically conduct self assessments to ensure compliance with the HRPP procedures and other requirements.

In addition to traditional biomedical and clinical studies, the DOE considers human subjects research to include but is not limited to studies that:

- a. use humans to examine devices, products, or materials with the express purpose of investigating human-machine interfaces or evaluating environmental alterations when humans are the subjects being tested.
- b. use personally identifiable bodily materials such as cells, blood, tissues, urine, or hair, even if the materials were collected previously for a purpose other than the current research.
- c. collect and use personally identifiable information such as genetic information or medical and exposure records, even if the information was collected previously for a purpose other than the current research.
- d. collect personally identifiable data, surveys, or questionnaires through direct intervention or interaction with individuals; and search for generalizable knowledge about categories or classes of subjects (e.g., linking job conditions of worker populations to hazardous or adverse health outcomes).

The DOE does not consider the following human subject research:

- a. studies to improve the safety or execution of procedures that apply to routine occupational activities;
- b. occupational health surveillance of DOE Federal and contractor employees to determine apparent departures from typical health status and not for the purpose of obtaining generalizable knowledge; and
- c. employee surveys used as management tools to improve worker or contractor performance as long as the identity of the participant is protected.

Research protocols must include a description of processes for:

- a. keeping (Personally Identifiable Information) PII confidential
- b. releasing PII only under a procedure approved by the IRB and DOE, where required;
- c. using PPII only for purposes of the DOE-approved research and/or EEOICPA;
- d. handling and marking documents containing PII
- e. establishing reasonable administrative, technical, and physical safeguards to prevent unauthorized use or disclose of PII;
- f. marking no further use or disclose of the PII except when approved by the IRB and DOE, where applicable, and then only:
- g. in an emergency affecting the health or safety of any individual;
- h. for use in another research project under these same conditions and with (Department of Energy) DOE written authorization;

- i. for disclosure to a person authorized by the DOE program office for the purpose of an audit related to the project; or
- j. when required by law.
- k. protecting PII data stored on removable media (CD, DVD, Flash Drives, etc.) using encryption products that are Federal Information Processing Standards (FIPS) 140-2 certified;
- l. using FIPS certified encryption that meet the current DOE password requirements cited in DOE Guide 205.3-1;
- m. shipping removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped via express overnight service;
- n. encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products;
- o. sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e. separate e-mail, telephone call, separate letter;
- p. using FIPS certified encryption methods for web sites established for the submission of information containing PII;
- q. using two-factor authentication for logon access control for remote access to systems and database that contain PII (http://csrc.nist.gov/publications/nistpubs/800-63/SP800-63V1_0_2.pdf);
- r. reporting the loss or suspected loss of PII immediately upon discovery to:
 1. the DOE Project Officer; and
 2. iRB

DOE Order 443.1A requires prompt reporting to the DOE HSR Program Manager, and coordination with and approval from the HSR Program Managers in determining plans to correct the unanticipated problem. While DOE 443.1A does not define “prompt,” they request that the HSR Program Manager(s) be notified within 48 hours of learning of any unanticipated problem that does not involve personally identifiable information (PII). However, if potential loss or compromise of personally identifiable information is involved, the incident should be reported immediately (as soon as you learn about the incident) to the Departmental Element; the DOE Cyber Incident Response Capability a doecirc@doecirc.energy.gov or 8660941-2472 and to the DOE HSR Program Manager(s).

References:

10 CFR 745 – “Protection of Human Subjects”

Checklist for IRBs to Use in Verifying that HS Research Protocols are in Compliance with DOE Requirements

The following items must be addressed in all protocols:

- a. Keeping Personally Identifiable Information (PII) confidential;
- b. Releasing PII, where required, only under a procedure approved by the responsible IRB(s) and DOE;
- c. Using PII only for purposes of this project;
- d. Handling and marking documents containing PII as “containing PII or PHI;”
- e. Establishing reasonable administrative, technical, and physical safeguards to prevent unauthorized use or disclosure of PII;
- f. Making no further use or disclosure of the PII except when approved by the responsible IRB(s) and DOE, where applicable, and then only under the following circumstances: (a) in an emergency affecting the health or safety of any individual; (b) for use in another research

- project under these same conditions and with DOE written authorization; (c) for disclosure to a person authorized by the DOE program office for the purpose of an audit related to the project; (d) when required by law; or (e) with the consent of the participant/guardian;
- g. Protecting PII data stored on removable media (CD, DVD, USB Flash Drives, etc.) using encryption products that are Federal Information Processing Standards (FIPS) 140-2 certified;
 - h. Using passwords to protect PII used in conjunction with FIPS 140-2 certified encryption that meet the current DOE password requirements cited in DOE Guide 205.3-1;
 - i. Sending removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped;
 - j. Encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products;
 - k. Sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e. separate e-mail, telephone call, separate letter;
 - l. Using FIPS 140-2 certified encryption methods for websites established for the submission of information that includes PII;
 - m. Using two-factor authentication for logon access control for remote access to systems and databases that contain PII. (Two-factor authentication is contained in the National Institute of Standards and Technology (NIST) Special Publication 800-63 Version 1.0.2 found at: [http://csrc.nist.gov/publication/nistpubs/800-63/SP800-63V 1 0 2.pdf](http://csrc.nist.gov/publication/nistpubs/800-63/SP800-63V102.pdf));
 - n. Reporting the loss or suspected loss of PII immediately upon discovery to: 1) the DOE funding office Program Manager; and 2) the applicable IRBs (as designated by the DOE Program Manager). If the DOE Program Manager is unreachable, immediately notify the DOE-CIRC (1-866-941-2472, www.doecirc.energy.gov).
 - o. Classified projects that use PII must also comply with all requirements for conducting classified research.

HQ Expectations of DOE Site IRBs - "Reporting Unanticipated Problems and Review/Approval of Projects that Use Personally Identifiable Information" - May 7, 2009

DOE Order 443.1A

Department of Justice (DoJ)

See APPENDIX C: PRISONERS IN RESEARCH

APPENDIX H: HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 (HIPAA)

The Common Rule is a set of standards common to Federal Agencies that fund research involving human subjects. These standards attempt to minimize the risks to which human subjects are exposed and assure continuing oversight by the IRB. The FDA regulations govern clinical trials of new drugs and medical devices. The University of Louisville of Louisville Biomedical IRB will utilize FDA guidance (21 CFR 50 & 56) when reviewing research involving FDA regulated test articles. DHHS regulations acknowledge the importance of confidentiality, but the HIPAA regulations are a separate set of regulations that protect the privacy and security of the individual protected health information (PHI), regardless of funding source. The HIPAA regulations builds upon existing Federal protections and creates equal standards of privacy and security protection for research governed by existing Federal human subject regulations and research that is not.

The HIPAA regulations, govern the use and disclosure of PHI that is created or received by a covered entity that relates to the physical or mental health of an individual (living or deceased), the provision of health care, the payment for health care, and identifies the individual or reasonably may be used to identify the individual. A covered entity is an institution that transmits any health information in electronic form in connection with a transaction covered by HIPAA regulations. The University of Louisville is considered a hybrid entity⁸², which means some but not all parts of the institution must comply with HIPAA.

Because of the HIPAA regulations, individuals now have more rights over their personal health information and can prevent it from being used by a covered entity or disclosed to third parties. The HIPAA Privacy regulations are premised on the idea that the use or disclosure of PHI must either fit a regulatory exception or the individual's permission must be obtained before the use or disclosure of the PHI. The regulations provide an exception for the use or disclosure of PHI for treatment, to obtain payment for treatment services, as part of the normal operations of the healthcare facility, or by law. HIPAA has several exceptions for using and disclosing PHI for research that will be discussed in this section.

HIPAA gives individuals the following rights: to request restrictions on use or disclosure of their PHI, right to access medical records (including research information that might be part of their medical records), right to amend medical records, right to an accounting of disclosure of their PHI, right to request alternate confidential communications, and right to lodge complaint with covered entity and / or DHHS.

The Privacy and Security Rules places administrative requirements on the covered entity. The covered entity must designate a Privacy Official and a Security Official, develop policies and procedures that are HIPAA compliant, provide privacy and security training to the workforce, implement administrative, technical and physical safeguards to protect the privacy and security of PHI, develop sanctions for violations of the HIPAA regulations, and meet the documentation requirements. Violations of privacy and/or security are covered under HIPAA.

The HIPAA permits the use and/or disclosure of PHI for research in the following ways:

1. a clinical trial with the subjects authorization
2. recruitment within the researcher's covered entity

⁸² **Hybrid Covered Entity-** A single legal entity that is a covered entity whose business activities include both covered and non-covered functions and that designates health care components in accordance with HIPAA regulatory requirements.

3. recruitment by obtaining PHI from another covered entity through a partial waiver of the requirement to obtain an authorization from the subject
4. retrospective records reviews with a complete waiver of the requirement to obtain an authorization from the subject
5. research on decedent information
6. research using a limited data set
7. preparing a research protocol
8. research using a de-identified data set

If a subject refuses to authorize the use and disclosure of PHI, the individual cannot participate in the research study, although refusal to authorize the research cannot impact medical treatment.

HIPAA Authorization for Research Overview

A Privacy Rule Authorization is an individual's signed permission to allow a covered entity to use or disclose the individual's protected health information (PHI) that is described in the Authorization. The Authorization used for research must describe the PHI to be used and/or disclosed, the person or entities that can use the information for the research project and the covered entity that can rely on the Authorization to disclose information to others; the persons or organizations to whom the covered entity can disclose the PHI to; and the specific purpose for which the PHI is needed in the study. The authorization must also inform the subject that once the data is disclosed to a person or organization not covered by HIPAA the researcher cannot control what the third party might do with the information

In contrast, an informed consent document is an individual's agreement to participate in the research study and includes a description of the study, anticipated risks and/or benefits, and how the confidentiality of records will be protected, among other things. If a covered entity obtains or receives a valid Authorization for its use or disclosure of PHI for research, it may use or disclose the PHI for the research, but the use or disclosure must be consistent with the Authorization.

The Authorization must be written in plain language. A copy of the signed Authorization must be provided to the individual signing it. The Privacy Rule does not specify who must draft the Authorization, so a researcher may draft one. The Privacy Rule specifies core elements and required statements that must be included in an Authorization. An Authorization is not valid unless it contains all of the required elements and statements. An Authorization form may also, but is not required to, include additional, optional elements as defined by the regulations, so long as they are not inconsistent with the required elements. The optional statements, if included may not be contrary to the other authorization requirements of the Privacy Rule. An Authorization, whether prepared by a covered entity or by a person requesting PHI from a covered entity, must include the following core elements and required statements:

The intent of the Authorization is to provide a document to be presented to a covered entity so that the covered entity knows it has the individual's permission to let the researcher use the individual's PHI for research (when the researcher is an employee of the covered entity) or to disclose the information to the researcher (when the researcher is not an employee of the covered entity) and others.

Authorization Core Elements (see Privacy Rule, 45 C.F.R. §164.508(c)(1))

1. Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner). This means the PHI that is discussed in the protocol should be described in the Authorization. A researcher who uses the same language to meet this requirement in all Authorization is unlikely to meet the specificity requirements of the regulations. If the requirements are not meet the authorization is not valid.
2. The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure. This means that any covered entity the researcher is getting data from should be listed, including the researcher's practice plan if the medical records of that practice plan will be used for the study. Because the researcher might be using information from his/her practice plan for the research, even information they might already know because they provide clinical care to the patient, they must have the subject's permission to do so. If a covered entity such as a practice plan allows its employed physician to use PHI for a research project without the subject's permission (and they do not fit another HIPAA exception) this would be a violation of HIPAA.
3. The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure. This would include any person or entity who will or may have access to the research data, including but not limited to the researcher and his/her staff.
4. Description of each purpose of the requested use or disclosure. Researchers should note that this element must be research study specific. This means that for all the PHI data elements that have been listed there should be a corresponding purpose identified. Because of this requirement for specificity a purpose cannot be for future unspecified research.
5. Authorization expiration date or event that relates to the individual or to the purpose of the use or disclosure. NOTE: For Research Authorizations UofL has identified one of the following two expiration dates as appropriate depending on the nature of the research. "The time period when information can be used or disclosed under this authorization ends when all activities related to this study are completed." or "There is no expiration date for this research authorization." .
6. Signature of the individual and date. If the Authorization is signed by an individual's personal representative, a description of the representative's authority to act for the individual.

Authorization Required Statements (see Privacy Rule, 45 C.F.R. § 164.508(c)(2))

1. The individual's right to revoke his/her Authorization in writing and the exceptions to the right to revoke and a description of how the individual may revoke Authorization.
2. Notice of the covered entity's ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the Authorization, including research-related treatment, and, if applicable, consequences of refusing to sign the Authorization. Note: in most research authorizations the subject will be required to sign an Authorization before the individual is permitted to participate in the study. If the individual does not sign the Authorization, participation in the study is denied.
3. The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information. If an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source of the research), the Privacy Rule does not continue to protect the PHI disclosed to the non-covered entity. However, other applicable Federal and State laws as well as agreements between the disclosing covered entity and the PHI recipient may establish continuing protections for the disclosed information

A research subject may revoke his/her Authorization at any time. However, a covered entity may continue to use and disclose PHI that was obtained before the individual revoked Authorization to the extent that the entity has taken action in reliance on the Authorization. In cases where the research is conducted by the covered entity, this would permit the covered entity to continue using or disclosing the PHI as necessary to maintain the integrity of the research, as, for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report unanticipated problems or adverse events.

Waiver or Alteration of Authorization (Complete Waiver or Partial Waiver)

Under the Privacy Rule at section 164.512(i), a covered entity may use or disclose PHI for a research study without Authorization (or with an altered Authorization) from the research participant if the covered entity obtains proper documentation that an IRB or Privacy Board has granted a waiver (or alteration) of the Authorization requirements. Among other requirements under section 164.512(i), a covered entity must obtain a statement that an IRB or a Privacy Board has determined that the alteration or waiver, in whole or in part, of Authorization satisfies the following three criteria in the Privacy Rule:

1. the use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - a. an adequate plan to protect the identifiers from improper use and disclosure;
 - b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law;
 - c. adequate written assurances that the PHI will not be reused or disclosed except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted by the Privacy Rule;
2. the research could not practicably be conducted without the waiver or alteration; and
3. the research could not practicably be conducted without access to and use of the PHI.

Clinical research will not generally qualify for a waiver of the Authorization if a clinical research participant will be asked to sign an informed consent before entering the study. Waiver of Authorization is more common in research that involves, for example, retrospective medical chart reviews. Additionally, when Authorization is waived for research access to medical records or other PHI, the covered entity must take reasonable steps to limit the information disclosed to that which is the minimum necessary for the research purpose. If appropriate documentation of an IRB or Privacy Board waiver or alteration of Authorization is presented to the covered entity, the covered entity may rely, if reliance is reasonable under the circumstances, upon documentation of such waiver that the request represents the minimum necessary amount of PHI for the research.

It should be noted that the IRB or Privacy Board, in make a determine if the criteria for waiver have been met must evaluate the PHI needed by the researcher to determine if it is necessary to conduct the research project.

Research Uses and Disclosures Under Permissions Obtained Prior to The Privacy Rule's Compliance Date

Sections 164.532(a) and (c) of the Privacy Rule provide that, after the compliance date of April 14, 2003, a covered entity may use or disclose an individual's PHI without an Authorization, or waiver or alteration of the Authorization requirement, in connection with research, if specific conditions are met. For many such uses and disclosures of PHI in connection with research, a covered entity may rely on any one of the following that was obtained prior to the compliance date:

1. an Authorization or other express legal permission from an individual to use or disclose PHI for research,
2. the informed consent of the individual to participate in the research, or
3. a waiver by an IRB of informed consent in accordance with applicable laws and regulations governing informed consent, unless a new informed consent document is sought after the compliance date.

These transition provisions do not apply if any change is made after the compliance date, to an informed consent, express legal permission, or IRB waiver for the research obtained before the compliance date that would invalidate these prior permissions. In such cases, an Authorization that complies with section 164.508 of the Privacy Rule is required unless the activity is permitted by another exception in the Privacy Rule (e.g., through a waiver of Authorization).

In some instances, express legal permissions, informed consents, or IRB-approved waivers of informed consents are not study specific. These permissions for research and waivers, if obtained before the compliance date, are grandfathered by the transition provisions even if provided for future unspecified research, subject to the conditions described above. The use or disclosure governed by a document obtained before the compliance date will be limited to the language of such document. To use or disclose information in a manner that goes beyond such permission document may require compliance with an HIPAA exception or obtaining an Authorization.

Discussion of Enrollment in Research without an Authorization

These types of conversations may arise under a variety of circumstances. For example, a physician may discuss treatment alternatives and other options with the individual, which may include the option of enrolling in a clinical trial. In addition, a physician may speak to the individual about a clinical trial as part of asking the individual to sign an Authorization to permit the covered provider to use or disclose the individual's PHI for the research study. Also, the Privacy Rule generally permits a covered entity to communicate with individuals and to disclose their PHI to them.. While this type of recruitment activity is permitted under the Privacy regulations, the covered health care provider must obtain the individual's Authorization or an IRB or Privacy Board waiver of Authorization, or meet certain other conditions, before using or disclosing the individual's PHI as part of the research study.

Similarly, if a physician knows of a study in which his or her patient might enroll that is being conducted by others, the physician may discuss such a trial with the patient and give the patient the researcher's contact information so the patient may contact the researcher directly. However, the physician may only contact the researchers about the patient so long as de-identified information is disclosed, the individual's Authorization or IRB or Privacy Board waiver of Authorization is obtained, or other conditions that satisfy the Privacy Rule are met. For example, it is acceptable to give a clinical summary of a patient to a researcher to determine if the patient might meet enrollment criteria, if such

discussions omit the patient's name, address, medical record number, and any other identifying information set forth in section 164.514(a)-(c) of the Privacy Rule.

Call Centers

Call centers in many cases may not be part of a covered entity. Thus, they are not required to comply with the Privacy Rule. A call center for research is an entity established to receive and answer calls from interested individuals about research project(s). Commonly, a call center will collect identifiable information about a caller who may be interested in a research study and then transmit such information to researchers involved in the study or send information about a study directly to callers.

If a call center is part of a covered entity, e.g., part of a covered health care provider that is also a researcher, it may speak with an individual without Authorization for purposes of communicating about a research study or obtaining the individual's Authorization to use or disclose his or her PHI for the study. A partial waiver of the authorization requirement should be obtained from the Privacy Board if the employees of the call center will be maintaining any identifiable information about callers. Further use or disclosure of the individual's PHI for a research study itself or other purposes is subject to the conditions set forth in the Privacy Rule.

Research Databases

There are two separate activities to consider: (1) The use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research protocol.

The Privacy Rule permits a covered entity to include an individual's PHI in a clinical research recruitment database and permit researchers access to the recruitment database, provided the individual has given permission through a valid written Authorization. The Authorization must inform the individual of the purpose for which (e.g., for the pre-screening log for one or more clinical trials) and what PHI will be used and meet the other requirements at section 164.508 of the Privacy Rule. Alternatively, a covered entity may provide a researcher access to the PHI for reviews preparatory to research, provided the required representations are obtained. See section 164.512(i) of the Privacy Rule. Unless otherwise permitted by the Privacy Rule, a subsequent Authorization must be obtained from the individual before a covered entity may use or disclose the individual's PHI for the clinical trial itself.

A covered entity's use or disclosure of PHI to create a research database or repository, and use or disclosure of PHI from the database or repository for a future research purpose, are each considered a separate research activity under the Privacy Rule. In general, the Privacy Rule requires Authorization for each activity, unless, for example, an IRB or Privacy Board waives or alters the Authorization requirement.

Documentation of a waiver or an alteration of Authorization to use or disclose PHI to create a research database requires, among other things, a statement that an IRB or Privacy Board has determined that the researcher has provided adequate written assurances that PHI in the database will not be further used or disclosed except as permitted by the Privacy Rule (e.g., for research uses and disclosures with an Authorization or waiver). A covered entity also could use or disclose a limited data set to create a research repository or database under conditions set forth in a data use agreement.

For subsequent use or disclosure of PHI for research purposes from a repository or database maintained by the covered entity, the covered entity may:

1. Obtain the individual's Authorization for the research use or disclosure of PHI as specified under section 164.508;
2. Obtain documentation of an IRB or Privacy Board's waiver of the Authorization requirement that satisfies section 164.512(i);
3. Obtain satisfactory documentation of an IRB or Privacy Board's alteration of the Authorization requirement as well as the altered Authorization from the individual;
4. Use or disclose PHI for reviews preparatory to research with representations that satisfy section 164.512(i)(1)(ii) of the Privacy Rule;
5. Use or disclose PHI for research on decedents' PHI with representations that satisfy section 164.512(i)(1)(iii) of the Privacy Rule; or
6. Provide a limited data set and enter into a data use agreement with the recipient as specified under section 164.514(e).

A covered entity may also use or disclose PHI from databases and repositories for other purposes without Authorization as permitted by the Privacy Rule, such as if required by law or to a public health authority for a public health activity (e.g., disclosures to public, including state, cancer registries). Covered entities may also de-identify PHI according to standards set forth in the Privacy Rule so that its use and disclosure is not protected by the Privacy Rule.

De-Identification of Data

The Privacy Rule provides two ways to de-identify PHI. One way is to remove the following identifiers of the individual and of the individual's relatives, employers, or household members:

(1) Names; (2) all geographic subdivisions smaller than a state, except for the initial three digits of the zip code if the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; (3) all elements of dates except year and all ages over 89; (4) telephone numbers; (5) fax numbers; (6) email addresses; (7) social security numbers; (8) medical record numbers; (9) health plan beneficiary numbers; (10) account numbers; (11) certificate or license numbers; (12) vehicle identifiers and license plate numbers; (13) device identifiers and serial numbers; (14) URLs; (15) IP addresses; (16) biometric identifiers; (17) full-face photographs and any comparable images; (18) any other unique, identifying characteristic or code, except as permitted for re-identification in the Privacy Rule.

In addition to removing these identifiers, the covered entity must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual.

Covered entities may also use statistical methods to establish de-identification instead of removing all 18 identifiers. The covered entity may obtain certification by "a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable" that there is a "very small" risk that the information could be used by the recipient to identify the individual who is the subject of the information, alone or in combination with other reasonably available information. The person certifying statistical de-identification must document the methods used as well as the result of the analysis that justifies the determination. A covered entity is required to keep such certification, in written or electronic format, for at least 6 years from the date of its creation or the date when it was last in effect, whichever is later.

Permitted Disclosures of Phi

The Privacy Rule permits PHI to be used or disclosed for adverse event reporting if the use or disclosure is;

1. permitted by the individual's Authorization,
2. pursuant to a waiver or alteration of Authorization,
3. required by law, or
4. for permitted public health activities, which may include reports to persons who are subject to the jurisdiction of the FDA when the report concerns an FDA-regulated product for which the person has responsibility, e.g., sponsors or FDA-regulated IRBs.

Where the Privacy Rule requires a covered entity to meet a minimum necessary requirement, researchers should work with their IRB, institutional officials, and research sponsors to develop a process to report unanticipated problems involving risks to subjects or others (UPIRTSO) and adverse event(s) that uses as few identifiers as possible. For example, consider coding adverse event reports to de-identify data, for example, by using study numbers unrelated to the participant's name and indicating relevant dates as "day X of the study." Also note that while an Authorization need not explicitly list each of the multitude of uses and disclosures of PHI that will comprise the research study the regulations do ask that the Authorization be as specific as possible by describing the purpose of the research study and persons or classes of persons to whom the information may be disclosed. Covered entities may nonetheless wish to include specific language about UPIRTSO or adverse event reporting, if relevant, in the Authorization to more fully inform the individual.

A covered entity is permitted to use or disclose PHI to identify or locate the whereabouts of a research participant during the study as long as the use or disclosure is not limited in the individual's Authorization (or "grandfathered" prior permission, if relevant) or waiver or alteration of Authorization.

Business Associate Agreement

If the data source is a covered entity, whether a business associate contract is required depends on the services, functions, or activities that the researcher is providing to, or performing for, the covered entity. Researchers are not business associates solely by virtue of their own research activities (although they may become business associates in some other capacity, e.g., if de-identifying PHI on behalf of a covered entity). A business associate agreement will typically be a legally enforceable contract, so a researcher may wish to consult legal counsel before signing one. Business associates agreements that involve this use of a third party to conduct a component of a research study being performed by a UofL researcher must be reviewed by the UofL Privacy Office prior to being signed.

APPENDIX I: REGULATIONS AND REGULATORY GUIDANCE

Department of Health and Human Services

- [The Belmont Report](#)
- [Title 45 Code of Federal Regulations Part 46 Protection of Human Subject Research That May Be Reviewed Through an Expedited Procedure](#)

Office for Human Subject Research Protection (OHRP)

- [IRB Guidebook](#)
- [OHRP](#)
- [OHRP](#)

Food and Drug Administration (FDA)

General

- [21 CFR 50](#)
- [21 CFR 54- Financial Disclosure by Clinical Investigators](#)
- [21 CFR 56](#)
- [FDA Good Clinical Practice](#)
- [FDA Guidance Documents from FDA Centers and Commissioner](#)
- [FDA Guidance and Information Sheets on Good Clinical Practice in FDA-Regulated Clinical Trials](#)
- [Information Sheet Guidances Guidance for Institutional Review Boards, Clinical Investigators](#)

Devices

- [21 CFR 812 - Investigational Device Exemptions \(IDE's\)](#)
- [FAQs about Medical Devices in Research](#)
- [Humanitarian Use Devices](#)
- [Significant Risk and Nonsignificant Risk Medical Device Studies](#)

Drugs Products

- [FDA Regulations: 21 CFR 312 – Investigational New Drug](#)
- [FDA Information Sheet Guidance: “Off Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices](#)
- [FDA Information Sheet Guidance: Emergency Use IND](#)
- [FDA Information Sheet Guidance: Treatment IND](#)
- [FDA FAQs: Frequently Asked Questions on Drug Development and Investigational New Drug](#)
- [FDA Instructions: Information for Sponsor-Investigators](#)
- [FDA Forms: 1571 Investigational New Drug](#)
- [Frequently Asked Questions: Statement of Investigator \(Form FDA 1572\)](#)

Biological Products

- [FDA Instructions: Information on Submitting an Investigational New Drug](#)
- [FDA FAQs: Center for Biologics Evaluation and Research \(CBER\) Frequently Asked Questions](#)

Botanical Products in Research

- [FDA Guidance: Guidance for Industry, Botanical Drug Products](#)
- [FDA FAQs: Frequently Asked Questions on Botanical Drug Product Development](#)

FDA Inspections

- [FDA Information Sheet Guidance: FDA Inspections of Investigators](#)
- [FDA Institutional Review Board Inspections](#)
- [FDA Warning Letters](#)
- [Investigator Disqualification](#)

1	2	41	Biomedical IRB, 12	84	Disclosure of Data, 61, 62, 92
2	21 CFR 50, ii, 9, 12, 20,	42	C	85	Disclosure of
3	22, 28, 44, 89, 90, 91,	43	Children, 91, 92, 103,	86	Significant Financial
4	92, 94, 95, 96, 97, 104,	44	153, 159, 160, 161	87	Interest, 82, 86
5	106, 114, 115, 116,	45	Clinical Investigations,	89	E
6	124, 125, 126, 127,	46	97, 117, 118, 120, 122,	90	Ethical Principles, 11
7	159, 165	47	130	91	EVPR. See Executive
8	21 CFR 56, ii, 21, 25,	48	Coercion, 46, 47, 50, 92	92	Vice President for
9	30, 35, 55, 56, 60, 61,	49	Commission. See	93	Research
10	65, 66, 72, 81, 104,	50	National Commission	94	Executive Vice
11	115, 123, 124, 126, 129	51	for the Protection of	95	President for
12	4	52	Human Subjects in	96	Research, 9, 15, 22,
13	45 CFR 160 and 164,	53	Biomedical and	97	32, 33, 72, 73, 78, 132
14	ii, 16	54	Behavioral Research	98	EVPR, ii, 9, 15, 18,
15	45 CFR 46, ii, 9, 10, 12,	55	Committee for the	99	19, 20, 22, 23, 32,
16	20, 21, 22, 24, 25, 28,	56	Review of Individual	100	54, 76, 80, 81, 134
17	30, 32, 35, 43, 44, 51,	57	Financial Interests in	101	Exempt Research, 57,
18	55, 56, 57, 58, 59, 60,	58	Research, 17	102	58, 59, 61, 62, 63, 64,
19	61, 72, 79, 80, 81, 89,	59	Confidentiality, 4, 22,	103	65, 67, 159
20	90, 91, 92, 94, 95, 96,	60	24, 28, 29, 30, 34, 37,	104	claim of exemption,
21	104, 105, 106, 107,	61	38, 45, 47, 50, 54, 55,	105	59
22	115, 116, 152, 156,	62	62, 91, 96, 106, 107,	106	Existing Data, 63
23	157, 159	63	110, 135, 165, 166	107	"on the shelf" data,
24	Common Rule, 165	64	Continuing Review, 14,	108	63
25	A	65	25, 52, 53, 54, 67, 68,	109	Expedited Review, 55,
26	Anonymity, 62, 63	66	70, 71, 74, 75, 77, 79,	110	56, 57, 59, 67
27	anonymous, 12, 29,	67	111, 112, 113, 114, 128	111	External IRB, 13
28	58, 61, 62, 63, 66	68	D	112	Extra Material. See
29	B	69	Data and Safety	113	Extra Specimens
30	Belmont Report, ii, 10,	70	Monitoring Plan, 87	114	Extra Specimens, 65
31	11, 15, 33, 51, 131, 132	71	DSMP, 87	115	residual material, 64,
32	Beneficence, 51	72	Department of Health	116	65
33	Justice, 51	73	and Human	117	F
34	Respect, 51, 153	74	Services, 10	118	Federal-wide
35	Benefits, 13, 14, 27, 28,	75	DHHS, 11, 15, 28, 56,	119	Assurance, 11, 15, 34,
36	37, 39, 42, 49, 51, 52,	76	157, 160, 161, 165	120	131, 132
37	53, 54, 65, 69, 84, 90,	77	DHHS. See	121	Food and Drug
38	94, 95, 96, 103, 105,	78	Department of	122	Administration, 9, 10,
39	113, 114, 152, 157,	79	Health and Human	123	15, 65, 66, 112
40	158, 159, 160, 161	80	Services	124	FDA, 10, 15, 39, 40,
		81	Director, Human	125	41, 42, 48, 65, 66,
		82	Subjects Protection	126	73, 87, 88, 91, 92,
		83	Program, ii	127	97, 101, 104, 105,

128	112, 115, 116, 117,	174	114, 128, 131, 132,	220	120, 121, 122, 123,
129	118, 122, 128, 129,	175	161	221	124, 125, 126, 127,
130	130, 131, 165			222	128, 129, 130, 131,
		176	I	223	132, 134, 135, 136,
131	H	177	IDE. See	224	137, 138, 140, 141,
132	HIPAA, 64, 66, 82	178	Investigational	225	142, 144, 145, 146,
133	Disclosure of PHI,	179	Device Exemption	226	147, 152, 153, 156,
134	165	180	Informed Consent, 10,	227	157, 158, 159, 160,
135	HIPAA Privacy Rule,	181	14, 19, 28, 38, 42, 47,	228	161, 163, 165, 168,
136	69, 165	182	48, 50, 51, 59, 62, 64,	229	169, 170, 171, 172
137	Human Subject, 27, 42,	183	65, 66, 69, 74, 75, 77,	230	Investigational Device
138	43, 44, 131, 132	184	80, 88, 90, 97, 98, 100,	231	Exemption, 56, 58
139	participants, 13, 14,	185	102, 103, 104, 105,	232	IDE, 87, 88
140	49, 98	186	107, 112, 113, 114,	233	Investigator, 10, 13, 14,
141	subjects, 9, 10, 11, 12,	187	117, 127, 128, 130, 154	234	16, 18, 19, 21, 23, 25,
142	13, 14, 16, 17, 20,	188	consent form, 14, 42,	235	27, 30, 34, 37, 38, 39,
143	21, 22, 23, 24, 27,	189	89, 90, 91, 92, 94,	236	40, 41, 42, 47, 48, 50,
144	28, 30, 32, 33, 34,	190	95, 96, 97, 100, 101	237	51, 52, 53, 54, 55, 56,
145	35, 36, 37, 38, 39,	191	Injury, 92	238	59, 62, 63, 64, 67, 68,
146	40, 42, 47, 48, 52,	192	Institutional Official, 11,	239	70, 71, 72, 74, 75, 76,
147	53, 55, 57, 58, 61,	193	15	240	77, 78, 82, 84, 87, 88,
148	62, 67, 68, 69, 70,	194	Institutional Review	241	91, 95, 96, 97, 98, 100,
149	71, 72, 73, 74, 75,	195	Board, ii, 13, 33, 36,	242	101, 102, 104, 106,
150	76, 77, 78, 80, 81,	196	73, 131, 132	243	107, 108, 110, 111,
151	88, 102, 104, 105,	197	IRB, ii, iii, 4, 5, 6, 7, 8,	244	113, 114, 116, 118,
152	106, 108, 111, 112,	198	9, 10, 11, 12, 13, 14,	245	121, 122, 127, 128,
153	113, 118, 131, 132,	199	15, 16, 17, 18, 19,	246	130, 131, 132, 158,
154	159	200	20, 21, 22, 23, 24,	247	159, 161
155	Human Subjects	201	25, 26, 27, 28, 29,	248	IO. See Institutional
156	Protection Program,	202	30, 31, 32, 33, 34,	249	Official
157	9	203	35, 36, 37, 38, 39,	250	IRB. See Institutional
158	Human Subjects	204	40, 41, 42, 43, 44,	251	Review Board
159	Research, 9, 16, 23,	205	45, 46, 47, 48, 49,		M
160	33, 34, 35, 37, 71, 72,	206	50, 51, 52, 53, 54,	252	MIRA. See Multi-
161	81, 88, 111, 131	207	55, 56, 57, 58, 59,	253	Institutional
162	research, 9, 10, 11,	208	60, 61, 62, 63, 64,	254	Research Application
163	12, 13, 14, 15, 17,	209	65, 66, 67, 68, 69,	255	Modifications, 17, 18,
164	18, 19, 20, 21, 22,	210	70, 71, 72, 73, 74,	256	44, 53, 55, 79, 87, 107
165	23, 24, 27, 28, 32,	211	75, 76, 77, 78, 79,	257	Multi-Institutional
166	34, 35, 36, 37, 38,	212	80, 81, 82, 83, 84,	258	Research
167	39, 40, 41, 42, 43,	213	85, 86, 87, 88, 89,	259	Application, 83
168	44, 47, 48, 49, 54,	214	91, 94, 96, 97, 98,	260	MIRA, 86
169	55, 68, 69, 70, 71,	215	99, 101, 102, 103,	261	
170	72, 73, 75, 76, 77,	216	104, 105, 106, 107,		
171	78, 79, 80, 98, 102,	217	108, 109, 110, 111,		
172	103, 105, 106, 107,	218	112, 113, 114, 115,		
173	108, 111, 112, 113,	219	116, 117, 118, 119,		

262	N	297	Oversight Committee	330	84, 87, 90, 91, 92, 94,
		298	for the Management	331	95, 97, 100, 101, 103,
263	National Commission	299	of Institutional	332	105, 110, 152, 153,
264	for the Protection of	300	Financial Interests in	333	156, 157, 158
265	Human Subjects in	301	Research, 13	334	genetic research, 65
266	Biomedical and	302	OCMIFIR, 13, 15, 19,	335	Risks, 13, 14, 23, 27, 28,
267	Behavioral Research	303	21, 23	336	37, 38, 39, 42, 43, 44,
268	Commission, 152,			337	53, 54, 55, 56, 58, 61,
269	156	304	P	338	62, 67, 69, 73, 75, 76,
270	National Institutes of			339	87, 89, 90, 95, 100,
271	Health, 9, 18	305	Payments, 92	340	101, 103, 113, 117,
272	NIH, 87, 154	306	Pregnant Women, 152	341	157, 158, 159, 160
273	NIH. See National	307	Prisoners, 95, 156, 157,	342	Disclosure of
274	Institutes of Health	308	158	343	alternatives, 90
		309	Privacy, 10, 14, 28, 29,	344	Disclosure of risk, 89
275	O	310	30, 45, 47, 54, 55, 57,	345	minimal risk, 51, 58,
		311	60, 62, 65, 69, 76, 86,	346	62, 87, 92, 94, 152,
276	OCMIFIR. See	312	107, 110, 139, 165,	347	157, 159, 160, 161
277	Oversight Committee	313	166, 168	348	risk/benefit
278	for the Management	314	Privacy Board, ii, iii, 10,	349	assessment, 152
279	of Institutional	315	15, 16, 81	350	Risk/Benefit Ratio,
280	Financial Interests in	316	Privacy Rule, ii, 16, 81	351	85, 87
281	Research	317	Protocol, 42, 49, 52, 64,		
282	Office for Human	318	82, 83, 87, 91, 110,	352	S
283	Research	319	153, 158, 161	353	Scientific or Scholarly
284	Protections, 15, 37,			354	Merit Review, 82
285	73	320	Q	355	Survey Research, 62
286	Office of Sponsored			356	surveys, 62, 87
287	Programs Grants	321	Questionnaires, 62, 87	357	Suspension, 72, 76
288	Management, 21, 72,				
289	78, 111	322	R	358	T
290	Office of Human			359	Termination, 72
291	Research	323	Recruitment, 52, 53, 96,		
292	Protections	324	98, 158	360	U
293	OHRP, 63	325	advertisements, 46,	361	UPIRTSO, 14, 109
294	Office of Industry	326	52, 84		
295	Contracts, 21, 72, 78,	327	Research, 38, 39, 42,		
296	111	328	46, 47, 51, 52, 56, 57,		
		329	58, 59, 61, 62, 63, 82,		

362
 363
 364 [Standard Operating Procedures \(SOP Member Handbook.102.3 Information Sheets on Medical](#)
 365 [Devices.116.20.116.20.110.101\(b\)\(1-6\) Report of Findings, 21 CFR 56, 21 CFR 312, 21 CFR 812,](#)
 366 [and 45 CFR 46.303\(c\) Guidance \(listed by topic\) Compliance Oversight Procedures- Protection of](#)
 367 [Human Subjects - Institutional Review Boards, and Sponsors Application Applications Submitting IND](#)
 368 [Applications Application and 1572 Statement of Investigator Application for a Biological Product](#)