Jefferson
HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

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Jefferson Office of Human Research Protection

Policies and Procedures Manual

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Common Abbreviations	
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
APA	American Psychological Association
BAA	Business Associates Agreement
BIMO	Federal Food and Drug Administration's Bioresearch Monitoring
CAP	College of American Pathologist
CAPA	Corrective and Preventative Action
CFR	Code of Federal Regulations
CIRB	National Cancer Institute Central Institutional Review Board
CITI	Collaborative Institutional Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CO	Compliance Officer
COI	Conflict of Interest
Co-I	Co-Investigator
COIC	Conflict of Interest Committee
CPGM	Compliance Program Guidance Manual
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Sidney Kimmel Comprehensive Cancer Center Clinical Trials Office
CV	Curriculum Vitae
CVIR	Cardiovascular and Interventional Radiology
DoD	Department of Defense
DSMB	Data Safety Monitoring Board

Common Abbreviations	
DSMP	Data Safety Monitoring Plan
DUA	Data Use Agreement
EC	Ethics Committee
ECT	Electroconvulsive Therapy
EIR	Federal Food and Drug Administration Establishment Inspection Report
eMR	Electronic Medical Record
FCOI	Financial Conflict of Interest
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
FWA	Federalwide Assurance
G	Guidance
GA	General Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HDE	Humanitarian Device Exemption
HHS	Department of Health and Human Services
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HRPP	Human Research Protection Program
HUD	Humanitarian Use Device
IBC	Institutional Biosafety Committee
IC	Informed Consent
ICH	International Congress of Harmonization
IDE	Investigational Device Exemption
IDS	Investigational Drug Service
IEC	Independent Ethics Committee

Common Abbreviations	
IIA	Individual Investigator Agreement
IIT	Investigator-Initiated Trial
IITT	Investigator-Initiated Treatment Trial
IND	Investigational New Drug Application
IO	Institutional Official
IRB	Institutional Review Board
ISM	Independent Study Monitor
JCRI	Jefferson Clinical Research Institute
JOHRP	Jefferson Office of Human Research Protection (formerly, Office of Human Research)
LAR	Legally Authorized Representative
MCARE	Medical Care Availability and Reduction of Error Fund
MSP	Medicare Secondary Payor
NAI	No Action Indicated
NCD	National Coverage Determination
NCI	National Cancer Institute
NFCR	No Further Continuing Review
NIH	National Institutes of Health
NRC	U.S. Nuclear Regulatory Commission
NSR	Nonsignificant Risk
OAI	Official Action Indicated
OAR	Office of Animal Resources
OHR	Office of Human Research (currently Jefferson Office of Human Research Protection)
OHRP	Office of Human Research Protection
OLA	Enterprise Office of Legal Affairs
OP	Institutional Review Board Organization
ORCC	Office of Research Integrity, Conduct, & Compliance
ORS	Office of Radiation Safety

Common Abbreviations	
ORSS	Office of Research Support Services
PharmD	Doctor of Pharmacy
PHI	Protected Health Information
PI	Principal investigator
PRMC	Sidney Kimmel Comprehensive Cancer Center Protocol Review and Monitoring Committee
QA	Quality Assurance
QAE	Sidney Kimmel Comprehensive Cancer Center Quality Assurance and Education
QI	Quality Improvement
RAC	Research Advisory Committee
RDRC	Jefferson Radioactive Drug Research Committee
RR	Research Review
RSC	Jefferson Radiation Safety Committee
RSO	Radiation Safety Officer
SAE	Serious Adverse Event
SC	Review Requiring Special Consideration
sIRB	Single Institutional Review Board
SKCCC	Sidney Kimmel Comprehensive Cancer Center
SOP	Standard Operating Procedures
SPIND	Single Patient Investigational New Drug Application
SR	Significant Risk
TJU	Thomas Jefferson University
TJUH	Thomas Jefferson University Hospital
UAP	Unanticipated Problem
VAI	Voluntary Action Indicated

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 101: The Authority and Purpose of the Institutional Review Boards

1. Purpose

The purpose of this policy is to:

- State the institutional authority under which the Institutional Review Boards (IRBs) are established and empowered
- Define the purpose of the IRBs
- State the principles governing the IRBs to ensure that the rights and welfare of research participants are protected
- State the authority of the IRBs
- Define the relationship of the IRBs to other Jefferson committees and officials

1.1. Responsible Parties

Director of the Jefferson Office of Human Research Protection (JOHRP)
Associate Director of JOHRP
Senior Institutional Official(s)

2. Policy

2.1. Policy Statement

This policy pertains to the activities of all IRBs operating under the authority of Jefferson's Federalwide Assurance(s) (FWA) or allied organizations that operate under a separate FWA but have agreed to adopt the Jefferson policies.

2.1.1. Statement of Institutional Authority

The IRBs are established and empowered under the authority of the President of Jefferson and Jefferson's FWA(s) with the Department of Health and Human Services (HHS).

Jefferson requires that all research involving living human subjects, human specimens, or personal information from living humans, be reviewed and approved by one of Jefferson's IRBs prior to initiation of any research activities.

2.1.2. Purpose of the IRBs

The purpose of the IRBs is to protect the rights and welfare of human subjects participating in biomedical and behavioral research conducted at Jefferson. The IRBs are responsible for the review, approval, and oversight of such research to ensure that it meets the ethical principles established for human subjects research, and that it complies with federal regulations that pertain to human subjects protection at the Common Rule (45 CFR 46) and 21 CFR 56 and any other pertinent regulations and guidance.

2.1.3. Governing Principles

The IRBs will be guided by the ethical principles regarding research involving human subjects as espoused in the report of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research entitled: *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research*. The defining principles in *The Belmont Report* are:

- Beneficence - The sum of the benefit derived by the participant from participation and the importance of the knowledge to be gained from the study outweigh the risks to the participant and warrant a decision to allow the participant to accept the risks.

- Autonomy - Legally and ethically effective informed consent is obtained unless the requirements for waiver of informed consent are met by adequate and appropriate methods following the provisions of applicable regulations.

- Justice - The selection of participants is equitable and representative of the group that will benefit from the research.

2.1.4. IRB Authority

2.1.4.1. The function of Jefferson's IRBs is to review and approve biomedical and behavioral research involving human subjects that is conducted by faculty or employees of Jefferson, regardless of the source of funding and the location at which the research is performed. The authority to carry out this mandate is stated in 21 CFR 56.108(a)(1), 21 CFR 56.108(b)(3), 21 CFR

56.109(a)(f), 21 CFR 56.113, 45 CFR 160 and 45 CFR 164. Consequently, the IRBs will review all research that:

- Is sponsored by Jefferson
- Is conducted by or under the direction of faculty or employees of Jefferson in connection with their institutional responsibilities
- Is conducted by or under the direction of faculty or employees of Jefferson using any property or facility of Jefferson
- Involves the use or disclosure of protected health information (PHI)
- Does not fit any of the categories above, but is judged to be congruent with Jefferson's mission

2.1.4.2. Each Jefferson IRB has the authority to ensure that human subjects research is designed and carried out in a manner that protects the rights, welfare, and privacy of the participants. Consequently, each IRB has the authority to:

- Approve, require modifications to issue approval, or disapprove all human subjects research activities overseen and conducted by the organization (45 CFR 46.109(a))
- Suspend or terminate approval of research not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to participants (45 CFR 46.113)
- Observe, or have a third party observe, the consent process (45 CFR 46.109(g))
- Observe, or have a third party observe, the conduct of the research (45 CFR 46.109(g))

2.2. Policy Specifics

2.2.1. Federally Funded Research

If the study is part of an application to a sponsoring federal agency, the protocol involving human subjects must be reviewed by the IRB when the application is

reviewed by the Office of Research Support Services (ORSS) and prior to the submission of the application to the agency. In the case of external funding, review may be carried out on a 'just-in-time' basis. In any case, it must be done prior to the expenditure of any grant funds. (45 CFR 46.103(d))

2.2.2. Relationship of the IRBs to Jefferson Officials and Committees

2.2.2.1. Research covered by this policy and approved by an IRB may be subject to further necessary and appropriate review and approval or disapproval by officials of the institution. If research has not been approved by an IRB, officials may not approve the research. (45 CFR 46.112)

2.2.2.2. The IRBs function independently of, but in coordination with, Jefferson officials and other committees. If IRB members or IRB staff become aware of any undue influence on the IRB review process, they should notify the Director or Associate Director of JOHRP, immediately. The allegation will be referred to the Enterprise Office of Legal Affairs, which will be responsible for investigating the allegation and taking corrective actions, as necessary.

2.2.3. Use of Policies and Procedures

JOHRP maintains written policies and procedures consistent with federal regulations and the ethics of human subjects protection. The IRBs follow these policies and procedures when reviewing proposed research.

The IRB policies do not preempt any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.

The informed consent requirements in IRB policies are not intended to preempt any applicable federal, state, or local laws that require the disclosure of additional information for informed consent to be legally effective.

Nothing in IRB policies is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local law.

3. References

The Common Rule (45 CFR 46)
21 CFR 56
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research
45 CFR 160
45 CFR 164

100 General Administration (GA)

Policy GA 102: Activities Requiring Institutional Review Board Approval

1. Purpose

To describe the activities that require Institutional Review Board (IRB) review and approval. For the purposes of this policy, approval includes exempt determinations.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Principal Investigators (PIs)
Key Personnel
IRB Members

2. Policy

2.1 Definitions

- **Clinical Investigation**: Any experiment that involves a test article and one or more human subjects that must meet the requirements for prior submission to the U.S. Food and Drug Administration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic (FD&C) Act, or whose results are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms clinical investigation, research, clinical research, clinical trial, clinical study, and study are synonymous for the purposes of 21 CFR 56. (21 CFR 50.3(c), 21 CFR 56.102(c))

- **Clinical trial**: A research study in which one (1) or more human subjects are prospectively assigned to one (1) or more interventions (which may include a placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. (45 CFR 46.102(b))

- **Human subject**: A living individual about whom an investigator (whether professional or student) conducting research:

    i. Obtains information or biospecimens through intervention or interaction with, to use, study, or analyze the information or biospecimens, or

ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimen

- **Interaction:** includes communication or interpersonal contact between investigator and participant

- **Intervention:** includes physical procedures by which information or biospecimen are gathered (e.g., venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes

- **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 an individual provided for specific purposes and can reasonably expect will not be made public (e.g., a medical record)

- **Identifiable private information**: Private information for which the identity of the participant is or may readily be ascertained by the investigator or associated with the information

- **Identifiable biospecimen**: A biospecimen for which the identity of the participant is or may readily be ascertained by the investigator or associated with the biospecimen

- **Research**: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

2.2 Policy Statement

2.2.1 Research Requiring IRB Review

Research activities involving human subjects research may begin only after receiving IRB approval. A Jefferson IRB may approve the research itself or may rely upon another IRB.

Jefferson IRB refers to research categories at 45 CFR 46.104 for exemption determinations.

The OHR-36, *Quality Improvement vs Human Research Decision Tool*, is used by an investigator to delineate quality improvement activities from human research that must be submitted to the IRB for review.

The OHR-34, *Research Requiring IRB Review: A Checklist*, is used to determine and document when an activity does not meet the definition of human subjects research and IRB review is not required. The PI can use the OHR-34 to make the determination if a research activity is not IRB-regulated, but consultation with JOHRP is encouraged if there is a question of edge cases.

If an activity previously determined to not require IRB review is subsequently thought to be human subjects research, the PI must contact JOHRP immediately. If JOHRP then determines that the activity meets the definition of human subjects research, the study must be submitted to the IRB for review. JOHRP will also determine if data collected prior to IRB approval may be used for research purposes and if any compliance issues must be investigated.

All activities meeting the definition of human subjects research may begin only after receiving IRB approval or exempt determination. Some specific examples of these include but are not limited to:

- Collection of data about a series of standard procedures or treatments for dissemination or generalization

- Patient care or the assignment of normal patients to any intervention that is altered for research purposes in any way

- A diagnostic procedure for research purposes added to a standard treatment

- Systematic investigations involving innovative procedures or treatments. For example, if any investigator plans to collect information about an innovative procedure for scientific purposes or repeat the innovation with other participants to compare it to the accepted standard

- Planned research in emergency settings. See JOHRP Policy IC 708, *Planned Research in Emergency Settings*

- Data, human cell or tissue repository: this type of research repository typically involves collection, storage, and distribution of these materials for research purposes. See the OHR-19, *Research involving Coded or Anonymous Private Information and Biological Specimens*, to determine whether research involving data, human cells or tissue requires IRB review

- Investigator-initiated research

- Student conducted research: all activities conducted by students that meet the definition of human subjects research.

Case studies: when case studies are compiled in such a way as to allow generalization of knowledge from the data collected, that activity constitutes research and must be reviewed by the IRB. Three (3) or more case studies in a series are considered human subjects research by the Jefferson IRB. This research should be submitted to the IRB for review and approval. One (1) or two (2) case reviews do not require IRB review unless they meet the criterion of providing generalizable knowledge. If IRB review is not required, the case reviews must be reviewed by the Privacy Officer in the Enterprise Office of Legal Affairs.

Single-case emergency uses of an investigational drug or device may proceed without prospective IRB review. See JOHRP Policy GA 112, *Emergency Use of an Investigational Drug, Biologic, or Medical Device*

Research involving decedent tissue and an investigational FDA regulated device does require IRB review. For all other research on decedents, IRB approval is not required, however, for activities not requiring IRB approval, the Privacy Officer in the Enterprise Office of Legal Affairs should be consulted regarding protected health information (PHI) and privacy issues.

2.2.2 Tracking Active Studies

The IRB e-system is configured to automatically generate reminder notifications of approaching study expiration. Notifications are sent to investigators and/or study staff. This is a courtesy reminder, and it is the PI's responsibility to submit renewal.

Every study meeting the definition of human research to be conducted in the Jefferson enterprise that receives either Jefferson IRB approval or exemption or external IRB approval or exemption is entered as a record in the IRB e-system. Studies receiving a fixed approval period must receive a continuing review to remain active. Note, exempt studies and studies designated for no further continuing review (NFCR) do not have expiration dates. The IRB e-system is configured to automatically generate a notification that is sent to PIs of exempt and NFCR studies. The notification reminds the PI to complete an annual check-in form in the IRB e-system, updating the study status.

In addition, all human research studies conducted at Jefferson fall under the purview of the Quality Assurance Program of JOHRP, and as such, whether approved for a fixed period, exempt, or NFCR, are subject to audit at any time.

3. References

FD&C Act section 505(i)
FD&C Act section 520(g)
21 CFR 50.3(c)
21 CFR 56.102(c)
The Common Rule (45 CFR 46)
OHR-18, *Application for Exemption from IRB Review*
OHR-34, *Research Not Requiring IRB Review: A Checklist*
OHR-36, *Quality Improvement vs Human Research Decision Tool*
JOHRP Policy GA 112, *Emergent Use of an Investigational Drug, Biologic, or Medical Device*
JOHRP Policy IC 708, *Planned Research in Emergency Settings*
OHR-19, *Research Involving Coded or Anonymous Private Information and Biological Specimens*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 103: Maintenance of Policies, Procedures, and Internal Forms

1. Purpose

To state the commitment of the Jefferson Office of Human Research Protection (JOHRP) and the Institutional Review Boards (IRBs) to maintain and follow up-to-date policies and standard operating procedures (SOPs) that adhere to ethical principles, federal and other required regulations pertaining to research with human subjects.

1.1 Responsible Parties

Director/Associate Director of JOHRP
JOHRP Personnel
Institutional Official(s)
IRB Chairs/Vice Chairs

2. Policy

2.1 Policy Statement

Adherence to the regulations and guidance from the Office of Human Research Protections (OHRP) (45 CFR 46.103(b), 45 CFR 46.108), the U.S. Food and Drug Administration (FDA) (21 CFR 56.108(a)(1), 21 CFR 56.108(b)(3), and 21 CFR 56.115) and the International Congress of Harmonization (ICH), as well as institutional policies and SOPs, will ensure that the participants in human subjects research will receive consistent and robust protections in perpetuity.

Assurance of this protection is supported by having in place written policies so that IRB review ensures research is ethically and scientifically sound.

JOHRP's applications and forms apply and articulate specific policies and procedures.

3. Procedures

3.1 Review, Revision, and Approval of Policies, SOPs, and Forms

Changes to federal or state regulations/guidelines or to good research practice, as well as to the policies and SOPs of Jefferson, may require the Quality Assurance Program of JOHRP to create or revise policies, SOPs, and/or forms.

Policies, SOPs, and forms will be reviewed by the Director or Associate Director of JOHRP as needed.

The Director or Associate Director of JOHRP must approve all new or substantially revised policies, SOPs, and forms. The Director or Associate Director of JOHRP will obtain the appropriate input from the Senior Associate Provost for Research Integrity, Conduct, & Compliance and the Enterprise Office of Legal Affairs as necessary.

Changes that are not substantive may be made without the approval of the Director or Associate Director of JOHRP.

3.2 Policy Dissemination and Training

Following approval, the appropriate individuals and departments/divisions will be informed of the new or revised policies, SOPs, and forms. The announcements are intended to keep research personnel informed of new requirements related to their human subjects research. As appropriate, the announcements are sent to the research community and are also available on the JOHRP website. Feedback from research personnel is solicited and is considered when making future policy and form revisions. When IRB members are notified of changes at an IRB meeting, this will be noted in the minutes for the meeting.

4. References

The Common Rule (45 CFR 46)
21 CFR 56
JOHRP website

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 105: Use of a Single Institutional Review Board in Multi-Site Research Studies

1. Purpose

To define the procedure for use of single Institutional Review Board (sIRB) oversight in multi-site research studies.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
Investigators
Key Personnel

2. Policy

2.1 Definitions

- **sIRB**: A single Institutional Review Board (IRB), also termed "central" IRB, is an IRB that provides IRB review and oversight for two (2) or more participating sites in multi-site research. The IRB may be associated with an academic, private, non-profit, governmental, or commercial entity.

- **Multi-Site Research**: Multi-site research projects are those that involve more than one (1) institution. In the conduct of multi-site research projects, each institution is responsible for safeguarding the rights and welfare of human subjects.

- **Reliance Agreement**: A written agreement between entities participating in multi-site research. The agreement contains terms that describe what each entity is responsible for in the review, oversight, and conduct of the research including responsibilities related to local requirements, state law, and federal regulations. Previously these agreements were referred to as IRB Authorization Agreements (IAAs).

- **Reviewing IRB**: A term used in Reliance Agreements to identify the party to the agreement that acts as the sIRB in providing IRB review for all sites participating in

the conduct of the same multi-site protocol. This is sometimes also termed the IRB of Record.

- **Relying Institution**: A term used in Reliance Agreements to identify the party to the agreement that will rely on an IRB outside of its own entity. This is sometimes also termed the Relying Site or Participating Site.

- **Unaffiliated Investigator**: A non-Jefferson investigator conducting research under the oversight of Jefferson's IRB under the terms of an Individual Investigator Agreement.

- **Individual Investigator Agreement (IIA)**: A formal agreement between Jefferson and a single independent investigator not routinely "engaged" in research that allows such a single investigator to conduct collaborative human subject research under the Jefferson IRB.

3. Procedure

3.1 Introduction

As part of the Jefferson Human Research Protection Program (HRPP), the Jefferson IRB provides review and oversight of human subjects research conducted by Jefferson faculty, employees, and students. The IRB provides this oversight unless an alternate IRB has been authorized to serve as the reviewing IRB through a formal written reliance agreement between Jefferson and the alternate IRB. JOHRP executes and ensures adherence to reliance agreements.

IRB oversight for multi-site research studies may be provided via a sIRB model or with each site providing its own local IRB oversight. All research must use an sIRB if the following apply:

- Funded by the National Institutes of Health (NIH) under the *Final NIH Policy on the Use of a sIRB for Multi-Site Research* (effective January 25, 2018) and conducted in the United States as designated in the funding application

- Under the Department of Health and Human Services (HHS) regulations related to additional guidance on the *NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* (effective January 20, 2020) and is conducted in the United States. This includes other agencies that have signed onto the Common Rule (45 CFR 46)

The following research is not subject to this provision:

i. Multi-site research for which more than a single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

ii. Multi-site research for which any federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

Regardless of which IRB will be serving as the sIRB for a given study, requisite documents for research performed within Jefferson must be provided to JOHRP by submission through the IRB e-system. Also, all Jefferson investigators and key personnel must adhere to Jefferson human subjects training and conflict of interest (COI) disclosure requirements.

When serving as the reviewing IRB, Jefferson IRB will follow its policy for reporting of unanticipated problems involving risks to participants, serious or continuing non-compliance, or suspension or termination of IRB approval. When ceding review to an external IRB, Jefferson IRB will follow the policies established by the external IRB.

3.2 Reliance on Jefferson IRB

3.2.1 Jefferson Investigator is the Principal Investigator (PI) on a Multi-Site Research Study

When a Jefferson investigator is responsible for the overall conduct of a multi-site study, the investigator must:

- Upload required documents in the IRB e-system as per Jefferson sIRB standard operating procedures
- Obtain all required ancillary institutional reviews and submit all requisite documents
- Ensure that a reliance agreement between Jefferson and the external site(s) has been established and obtain study activation authorization for external site(s) from JOHRP prior to initiation of study activities at external site(s)

- Assure that external site PI and key personnel satisfy Jefferson's training and COI disclosure requirements

- Be responsible for disseminating protocol information to site(s). Such protocol information includes initial study approval, annual review approvals, protocol modifications, unanticipated problems (UAPs) involving risks to participants or others, a finding of serious or continuing non-compliance, or the suspension or termination of IRB approval

- Report to the Jefferson IRB any UAPs occurring at external site(s) that are related to the research study

3.2.2 Jefferson Investigator is the PI on a Single or Multi-Site Research Study that Utilizes an Unaffiliated Investigator

When a Jefferson investigator's study team includes an unaffiliated investigator, the Jefferson investigator must:

- Ensure that the external investigator is not affiliated with an entity that regularly conducts research, is not acting as an agent of that entity, and is not acting as an agent of Jefferson through their participation in the protocol (i.e., the investigator is not on Jefferson's payroll, not operating as an employee of Jefferson for this protocol specifically, not a student of Jefferson receiving academic or practicum credit, and not acting as an intern of Jefferson)

- Ensure that the unaffiliated investigator(s) satisfies Jefferson's training and COI disclosure requirements

- Establish an IIA prior to the initiation of any research activities by the unaffiliated investigator

3.3 External Site Utilization of Local IRB Review when Jefferson Investigator is the PI on a Multi-Site Research Study

When an external site has an IRB and does not plan to rely on Jefferson IRB, the investigator must:

- Obtain Jefferson IRB approval for research activities to occur at Jefferson

- Provide documentation of the external site's IRB initial and continuing approval of the investigator's research at that site to JOHRP

3.4 When a Jefferson Investigator is Relying on an External IRB for Regulatory Oversight on a Multi-Site Research Study

When a Jefferson investigator will utilize a non-Jefferson IRB for review of human subjects research, the investigator must:

- Upload required documents into the IRB e-system as per Jefferson sIRB SOPs
- Obtain all required ancillary institutional reviews and submit all requisite documents
- Ensure that a reliance agreement between Jefferson and the external IRB has been established prior to initiation of study activities at Jefferson
- Obtain study activation authorization from JOHRP prior to initiation of study activities at Jefferson
- Ensure all Jefferson reporting requirements are maintained throughout the life of the study

4. References

Final NIH Policy on the Use of a sIRB for Multi-Site Research (effective January 25, 2018)
NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (effective January 20, 2020)
The Common Rule (45 CFR 46)

100 General Administration (GA)

Policy GA 106: Conflicts of Interest

1. Purpose

To define the procedure for managing conflicts of interest (COI) for individuals involved with human subjects research.

1.1 Responsible Parties

Enterprise Office of Legal Affairs
Conflict of Interest Committee (COIC)
Investigators
Key Personnel
Institutional Review Board (IRB) Members
Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel

2. Procedure

2.1 Research Personnel with COIs

COIs that may interfere with an individual's ability to carry out their study related responsibilities objectively must be managed. The main source of reference for standard operating procedures related to COIs is the Jefferson Enterprise-Wide Policy 107.03 *Conflicts of Interest Policy for Employees*. All Jefferson employees must follow the Jefferson policy. In addition, individuals involved with human subjects research must follow this policy.

Non-employees involved with human subjects research must also complete a COI disclosure by sending their name, email address, institution, and role in the research to the Jefferson COI Office. They will be sent instructions on completing the disclosure.

The COI reporting system contains all the disclosures, definitions, and monetary amounts related to COI.

Investigators must also provide the COI information requested in the IRB e-system Master Application.

The COI office that supports the COIC reports COIs and management plans to JOHRP as appropriate. The IRB may approve the management plan as received or add additional requirements. The IRB cannot disapprove the management plan.

Individuals involved with human subjects research should also report non-financial COIs to JOHRP. Non-financial COIs include:

- Personal beliefs and/or relationships
- Institutional relationships
- Career advancement
- Any situation that could interfere with an individual's ability to carry out their study related responsibilities objectively

Note: Individuals who are responsible for research development and administrators with business development interests are prohibited from serving as members of the IRB.

JOHRP assures that the IRB Chairs, Vice Chairs, and/or reviewers are notified of any COI and/or management plan pertinent to studies under review.

In pre-review of a research study, the IRB personnel will check that the COI question in the application has been answered. If a financial interest is disclosed for any investigators on the study, the COIC will be notified. The COIC also learns about financial interests via the COI reporting system. IRB approval will not be issued for a given study until a significant financial interest of any investigator on the study has been reviewed by the COIC and any management plan issued by the COIC has been accepted by the investigator(s).

The IRB Chair/Vice Chair will ensure that any pertinent COI management plans are discussed during the meeting as appropriate. Subcommittee reviewers will consider management plans as part of their review. The IRB, including subcommittee reviewers, will determine if the COI must be disclosed in the consent form. The IRB will not issue the approval letter for the study before the management plan is approved per Jefferson Enterprise-Wide Policy 107.03.

2.2 IRB Members with COIs

An IRB member with a COI pertaining to a study on the meeting agenda may not be present at the IRB meeting during the discussion, deliberation, or vote for the pertinent study. The individual is recorded as absent with the reason of COI. The individual may be asked to return temporarily to the meeting to answer questions. These actions will be documented in the meeting minutes.

- Examples of IRB member conflicts in a study would be status as investigator or key personnel on the study, or significant financial interest that could be materially changed by the outcome of the study

- Examples that would not constitute a conflict for an IRB member include reviewing the protocol of their Chair or fellow faculty member in the same division, providing a research service as part of their scope of employment, such as serving as an investigational drug service pharmacist for a study

This policy is available to all IRB members on the JOHRP website.

3. References

Jefferson Enterprise-Wide Policy 107.03, *Conflicts of Interest Policy for Employees* (Internal Jefferson Link)
JOHRP Policy OP 203, *Institutional Review Board Consultants*
JOHRP website

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 109: Roles and Responsibilities of Study Personnel and Department Chairs

1. Purpose

To describe the roles and responsibilities of the principal investigator (PI), co-investigator (Co-I), key personnel, and the department chair or their designees in the responsible conduct of human subjects research.

1.1 Responsible Parties

PI
Co-I(s)
Key Personnel
Department Chair, and their designees

2. Policy

2.1 Definitions

- **Principal Investigator (PI)**: The primary responsible agent for a research study. In the event an investigation is conducted by a team of individuals, the PI is the responsible leader of the team. The PI must be approved by the IRB.

  The PI is responsible for the study's conduct and adherence to regulations. Qualified individuals are:

  - Those with a faculty appointment: an instructor or higher in one (1) of the Colleges of the University. Thomas Jefferson University (TJU) faculty are defined as TJU employees, including those employed by a TJU controlled affiliate, that have a TJU faculty appointment, or individuals holding a TJU volunteer, adjunct, or emeritus appointment

  - Jefferson Employees without a faculty appointment in one (1) of the Colleges or hospitals of Jefferson but who have appropriate training and expertise as determined by the Institutional Review Board (IRB), in general those who hold advanced degrees such as PhD, MS, MA, PharmD, MSN, MRH, etc.

In general, residents, clinical fellows, post-doctoral fellows, and students would not serve as PI as they are in a trainee role. They can, however, serve as a Co-I.

- **Co-Investigators (Co-Is)**: In general, someone who by licensure/degree can assume oversight of the study in the absence of the PI.

- **Key Personnel**: All other individuals contributing to the conduct of the study including, but not limited to, nurses, nurse practitioners, coordinators, residents, fellows, technicians, and students (see also JOHRP Policies GA 116, *Use of Students and Employees as Key Personnel and Participants in Clinical Trials*, and JOHRP Guidance G 601, *Definition of Key Personnel in Human Subject Research*). Key personnel must be listed in the IRB e-system, submit a conflict of interest (COI) statement, and take all required human subjects training. Other individuals not listed as key personnel (i.e., students and residents) may assist in protocol-related procedures only if they do so under the direct supervision of the PI or a Co-I.

2.2 Policy Statement

The responsibilities delegated by the PI to the Co-I and other key personnel must coincide with the experience and training of that particular team member. The PI should document in writing the responsibilities delegated to all members of the team in a delegation of authority log kept in the study binder. Changes in PI, Co-I, and key personnel must be reported to the IRB.

Jefferson personnel proposing to conduct human subjects research must submit a proposal to the IRB for review.

3. Procedures

Procedures for Investigators and Department Chairs (or Their Designee)

3.1 Determination of Human Subject Involvement

The Jefferson Office of Human Research Protection (JOHRP) relies on investigators and department chairs to identify activities that will involve human subjects in research as defined in the Common Rule (45 CFR 46) and/or 21 CFR 50, and as per JOHRP Policy GA 102, *Activities Requiring Institutional Review Board Approval*. When it is not clear whether the activity involves human subjects in research, the investigator should contact JOHRP for a determination.

3.2 Requirement for a Co-I

All interventional human subjects research (generally involving a drug, biologic, vaccine or device) must have at least one Co-I to assume the responsibility for care of participants if the PI is unavailable.

3.3 Preparation of Protocol

PIs shall prepare or provide a protocol giving a complete description of the proposed research. In the protocol, the PI shall make provisions for the adequate protection of the rights and welfare of prospective research participants and ensure that pertinent laws and regulations are observed. This requirement is applicable even in cases where the research is exempt under the Common Rule (45 CFR 46). Investigators shall include the protocol, any investigator brochure, proposed informed consent form(s), any advertisements to recruit participants and other pertinent information the IRB might need to make a fully considered determination. The requirement for a written protocol may be waived at the discretion of the IRB, but in general any interventional research and all greater than minimal risk studies require a free-standing written protocol.

3.4 Scientific Merit and Ethical Consideration

Department heads, through procedures established within their respective departments, centers, or institutes, are responsible for reviewing research protocols for ethical considerations and scientific merit prior to IRB submission.

3.5 Submission of a Protocol to the IRB

Once it is determined that an investigator wants to initiate a human research study, the investigator and department head shall be responsible for ensuring that the study is submitted to the IRB for review and approval prior to its initiation.

3.6 Complying with IRB Decisions

Investigators are responsible for complying with all IRB decisions, conditions, and requirements.

3.7 Obtaining Informed Consent

Investigators shall be responsible for obtaining and documenting informed consent in the manner approved by the IRB and in accordance with 45 CFR 46.116, 21 CFR 50 Subpart B, and JOHRP policies as follows:

- JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*

- JOHRP Policy IC 702, *Documentation, Waiver and Alteration of Informed Consent*

3.8 Submission of Progress Reports on the Research

Research investigators are responsible for reporting the progress of the research as often as required by the IRB, but no less than once a year (45 CFR 46.109(e); 21 CFR 56.109(f)). Jefferson IRB requires a yearly report for all studies, including exempt studies and studies designated for no further continuing review (NFCR). For these studies, an annual check-in is submitted and reviewed administratively.

3.9 Submission of Reports Concerning Adverse Events (AEs), Unanticipated Problems (UAPs), or Risks

Research investigators are responsible for promptly reporting to the IRB any serious adverse events (SAEs) or UAPs involving risk to participants or others as per JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*.

3.10 Reporting Changes in the Research

PIs are responsible for submitting proposed changes in a research protocol to the IRB. Changes to the protocol, consent form, PI, and any other supplementary materials are submitted to the IRB. PIs, Co-Is, and key personnel are added to the study in the IRB e-system.

If a PI leaves the study, an amendment must be filed and reviewed by the IRB. If a Co-I or key personnel leaves the study, this must be documented by the study team and reported to the IRB on the Continuing Review or Final Report form at the time of continuing review and/or on an annual check-in. Note that if the only change to a consent form is the addition/removal of a Co-I, a revised consent form does not need to be submitted to the IRB at that time. The addition/removal of investigators will be made to the consent form with the next required consent amendment or continuing review, whichever comes first.

Changes in research during the period for which IRB approval has already been given shall not be initiated by investigators without prior review and approval by the IRB, except where necessary to eliminate apparent immediate hazards to the participant. In these situations, an amendment should subsequently be submitted as soon as possible to the IRB for review and approval.

3.11 Reporting of Noncompliance

Investigators, department chairs, and/or study staff are responsible for promptly reporting to the IRB any serious or continuing noncompliance with JOHRP policy or the determinations of the IRB.

3.12 Attending IRB meetings

To facilitate the review of research and the protection of the rights and welfare of human subjects, investigators may be invited to attend an IRB meeting at which their study is being discussed. Investigators may not attend IRB meetings without a specific invitation.

4. References

The Common Rule (45 CFR 46)
21 CFR 50
21 CFR 56
JOHRP Policy GA 102, *Activities Requiring Institutional Review Board Approval*
JOHRP Policy GA 116, *Use of Students and Employees as Key Personnel and Participants in Clinical Trials*
JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*
JOHRP Guidance G 601, *Definition of Key Personnel in Human Subjects Research*
JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*
JOHRP Policy IC 702, *Documentation, Waiver and Alteration of Informed Consent*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 110: Signatory Authority

1. Purpose

To describe the signatory authority given to personnel of the Jefferson Office of Human Research Protection (JOHRP), for all actions of the Institutional Review Boards (IRBs).

1.1 Responsible Parties

Senior Associate Provost for Research Integrity, Conduct, & Compliance
Director/Associate Director of JOHRP
JOHRP Personnel

2. Policy

2.1 Policy Statement

The Director and Associate Director of JOHRP, are authorized to sign all documents in connection with the review and approval of research involving human subjects. This signatory authority can also be designated to appropriate individuals such as Chairs, as necessary.

In all cases, individuals signing documents pertaining to the business of JOHRP and/or the IRBs, must sign their own name only, indicating their title.

3. Procedures

3.1 Authorization for Signatory Authority

Authorization to sign documents not described in this policy may be determined by the Director of JOHRP and provided in writing to the delegated individual.

3.2 Routine Internal Correspondence

Routine internal correspondence is any written communication between JOHRP staff and Jefferson personnel that does not imply or appear to imply IRB approval. This correspondence may be issued without the signature of the Director or Associate Director of JOHRP.

3.3 Correspondence with External Agencies

Any letter(s), memo(s), or email(s) sent to any agency of the federal government, as well as to other funding agencies, whether public or private or their agents will be signed by the Director or Associate Director of JOHRP.

3.4 Decisions Made by the IRBs

Any letter(s), memo(s), or email(s) representing the decisions or opinions of the IRBs or their respective designees, may be signed by the appropriate designated IRB staff, provided that the correspondence does not imply review and approval of a research study.

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 112: Emergent Use of an Investigational Drug, Biologic, or Medical Device

1. Purpose

To define the procedure for emergent use of a test article (drug, biologic, or device) under U.S. Food and Drug Administration's (FDA's) expanded access program.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Investigators
Key Personnel
Practicing Physicians

2. Policy

2.1 Definitions

- **Emergency Use**: "The use of a test article on a human subject in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain prospective Institutional Review Board (IRB) approval" (21 CFR 56.102(d)). Also known as emergency expanded access use. For the purposes of this policy, emergency and emergent are used interchangeably. Emergency use is a situation that occurs under FDA's Expanded Access program.

- **Expanded Access**: The use of an investigational test article with the primary purpose of diagnosing, monitoring, or treating a patient's disease or condition.

- **Life Threatening**: "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" (21 CFR 312.81(a)(1-2)). The disease need not be immediately life threatening.

- **Severely Debilitating**: "Diseases or conditions that cause major irreversible morbidity" (21 CFR 312.81(b)). Examples include blindness, loss of arm, leg, hand or foot, loss of hearing, and stroke.

3. Procedure

FDA regulations allow for emergency use of a test article without prior IRB approval, provided that such emergency use is reported to the IRB within five (5) working days. Any subsequent use of the test article at the institution is subject to IRB review (21 CFR 56.104(c)) or waiver of IRB review (21 CFR 56.105). Under FDA regulations, emergency use of a test article is research, the patient is a participant, and the data obtained must be reported to the manufacturer and the FDA.

The physician, or designee, should contact the Director or Associate Director of JOHRP as soon as possible when considering emergent use.

3.1 Investigational Drugs and Biologicals

3.1.1 Procedures to follow

Determine if the proposed use of an investigational drug or biologic meets the regulatory definition for emergency use. Emergency uses must meet all of the following criteria (see JOHRP Policy IC 708, *Planned Research in Emergency Settings*):

- The participant has a disease or condition that is life threatening or severely debilitating
- No generally acceptable alternative for treating the patient is available
- The participant's disease or condition requires intervention with the investigational drug or biologic before review at a convened IRB meeting is feasible

The physician is expected to adhere to the following procedures:

- Obtain written documentation from an uninvolved physician confirming the opinion of the treating physician
- Obtaining informed consent from the participant or participant's legally authorized representative (LAR) and appropriately documenting consent or determining that use meets the exception to the requirement for consent

(see Section 3.4) all in accordance with and to the extent required by FDA regulations

3.1.2 Obtaining the drug/biologic

The principal investigator (PI) should contact the manufacturer of the drug/biologic to determine if it can be provided under an existing Investigational New Drug application (IND) or, if an IND is not available through the manufacturer, the investigator should contact the FDA for an individual patient expanded access IND, also known as a single patient IND (SPIND).

If there is insufficient time for an IND, the FDA may authorize shipment of the test article in advance of the IND application. Requests for authorization can be made by telephone or other rapid communication means.

In general, the FDA concludes that a waiver of prospective IRB review is appropriate for an individual patient expanded access IND when the physician obtains concurrence by the IRB Chair or other designated IRB member before treatment use begins.

3.2 Investigational Medical Devices

Requirements for emergency use of an investigational medical device are similar to those for emergency use of investigational drugs and biologics.

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

- The patient is in a life-threatening or severely debilitating condition that needs immediate treatment
- No generally acceptable alternative for treating the patient is available
- The patient's condition requires the immediate use of the investigational medical device which prevents the feasible use of existing procedures to obtain FDA approval

The physician is expected to follow as many participant protection procedures as possible. These include:

- Obtain written documentation from an uninvolved physician confirming the opinion of the treating physician

- Obtaining informed consent from the participant or participant's LAR or surrogate and appropriately documenting consent, both in accordance with and to the extent required by FDA regulations, or determining that use meets the exception to the requirement for consent (see Section 3.4)

- Notifying JOHRP

- Obtaining authorization from the Investigational Device Exemption (IDE) holder, if an approved IDE for the device exists

3.3 After the Emergent Use of an Investigational Test Article

Following the emergent use of an investigational test article, the physician is expected to complete any of the following tasks that have not already been addressed:

- Report the emergent use to JOHRP in writing within five (5) working days of use, providing copies of all paperwork related to the emergent use and a synopsis of patient outcome if applicable. The letter should address the following:

    1. Sex and age of patient

    2. A brief medical history of the patient regarding emergency use of the test article, including why the condition is considered life threatening or severely debilitating and what other options, if any, have been previously employed

    3. Any information on the outcome of the emergent use

- Provide JOHRP with a copy of the independent physician assessment

- Provide a copy of the signed consent form. If obtaining informed consent from the participant, an LAR, or surrogate is not possible, certify that the conditions for an exception to the informed consent requirements are met (see Section 3.4)

- Provide a copy of the protocol and drug/biologic/device brochure, if available

- Provide pertinent documentation from the manufacturer and FDA of authorization for emergent use

- Evaluate the likelihood of a similar need for recurring use of the test article. If likely, consider initiating efforts to establish an IRB-approved protocol and an approved IND or IDE for subsequent use

Upon receipt of these documents, JOHRP will issue a letter of concurrence.

JOHRP will maintain an archive of each emergent use situation.

3.4 Exceptions to the Informed Consent Requirement in the Emergent Use Setting

Every effort should be made to obtain informed consent from the participant, or their LAR or surrogate. Obtaining informed consent shall be deemed feasible unless, before the use of the test article, both the investigator and an uninvolved physician certify in writing all of the following:

- The participant is confronted by a life-threatening or severely debilitating situation necessitating the use of the test article
- Informed consent cannot be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from, the participant
- Time is not sufficient to obtain consent from the participant's LAR or surrogate
- There is no cleared or approved available alternative method that provides an equal or greater likelihood of saving the life of the participant (21 CFR 50.23(e)(1))

If all the above conditions apply, the physician may proceed to administer the test article without consent. When and if the participant is able to provide consent, or when and if an individual is located who can act as an LAR or surrogate, consent should be obtained.

If immediate use of the test article is necessary and time is not sufficient to obtain the independent determination from an uninvolved physician, the physician may proceed to administer test article and, within five (5) working days after the use of the article, the situation should be reviewed and evaluated in writing by an uninvolved physician.

The documentation required in this section shall be submitted to JOHRP within five (5) working days after the use of the test article.

3.5 Subsequent Emergent Use of an Investigational Test Article

After an initial emergent use, FDA regulations state that any subsequent use of the test article at the institution is subject to IRB review. However, the FDA has also acknowledged that the emergency use exception to IRB approval should not be so narrowly construed as to deny emergency treatment to a second patient, and that it would be inappropriate to deny such treatment to a patient if the only obstacle is that the IRB has not had sufficient time to convene and review the issue.

3.5.1 Additional Doses: The term "use" should be interpreted as "course of treatment" rather than "a single dose" of a drug. This interpretation provides for those instances where more than one (1) dose of a drug/biologic is required (e.g., daily or twice daily doses, or a course of chemotherapy) to treat the participant.

3.5.2 Emergency Treatment of a Second Patient: Should a situation arise, which would require the emergency use of the same test article for a second patient, either by the same or another physician, subsequent use should not be withheld solely for the purpose of obtaining IRB approval provided all the above-stated procedures are followed and all conditions for emergency use are met.

3.5.3 Recurrent Use of a Test Article under Emergent Conditions: While FDA regulation indicates that a test article should not be used repeatedly without subsequent IRB review, the FDA draft guidance document *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers* (November 2022) provides for an alternate regulatory review route whereby an IRB chair or other designated IRB member can issue a concurrence that an emergent use situation may proceed without prospective IRB approval.

The matter may also be referred to the convened IRB for resolution.

Thus, the physician/investigator must select one (1) of the following actions before any additional uses of the test article will be permitted:

- Follow previously stated procedures and seek concurrence from designated IRB member

- When there is an existing protocol covering the intended use of the test article, amend the protocol to include a rescue arm. The rescue arm should list all possible providers who will likely administer the test article as co-investigators, and the existing consent form should be amended to include details of the rescue protocol

- When there is no existing protocol covering the intended use of the test article, submit a study protocol to obtain IRB approval

4. References

21 CFR 56
21 CFR 312.81
21 CFR 50.23(e)(1)
JOHRP Policy IC 708, *Planned Research in Emergency Settings*
Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers (November 2022)

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 113: Institutional Review Board Reporting of Findings and Actions to Investigators

1. Purpose

To describe how the findings and actions concerning all research submitted to the Institutional Review Board (IRB) are to be communicated to investigators.

1.1 Responsible Parties

Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
IRB Chairs/Vice Chairs

2. Policy

2.1 Policy Statement

It is imperative that JOHRP maintains open and frequent communication with the investigators and their research staff.

The IRB's findings and actions are reported in writing to the investigator (and others within Jefferson enterprise when appropriate) including its decision to approve or disapprove the proposed research activity and any modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond to the IRB and others within Jefferson.

3. Procedures

3.1 Investigator Notifications

3.1.1 Initial Submission: The IRB will notify the principal investigator (PI) of the IRB's review comments and study approval status. The correspondence will specify requirements to secure IRB approval and whether the study has been approved or not, as described in JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*.

For a study reviewed by an expedited procedure, the process is the same.

If the PI's responses and/or revisions reviewed by the IRB Analyst are satisfactory, an approval letter and stamped materials (if applicable) will be issued.

3.1.2 Renewals and Revisions: The PI and study contact(s) will be notified through the IRB e-system and by email.

3.1.3 Notification of Study Approval: The approval letter, specifying the approval and expiration dates, and any other relevant stamped study materials are available in the IRB e-system.

3.1.4 Final Reports: Final reports are reviewed by the IRB Chair, Vice Chair, or designated IRB member. If the final report is satisfactory, a closure letter will be issued through the IRB e-system.

3.1.5 Administrative Termination: Studies which have expired without submission of a continuing report, annual check in verification, or Final Report may be administratively terminated at the discretion of JOHRP. The PI and study contact(s) will be notified through the IRB e-system and by email.

3.1.6 Administrative Withdrawal: The IRB allows the PI a 90-day window to reply to any stipulations. If 90 days elapse without communication from the PI, the study may be withdrawn.

3.2 Other Notifications

At the discretion of the IRB, the Senior Research Compliance Officer may be notified of studies that the IRB feels may pose significant risk to the participants or Jefferson. See also JOHRP Policy GA 101, *The Authority and Purpose of the Institutional Review Boards*, for the role of Jefferson officials in the approval or disapproval process.

If the IRB determines that conflict of interest requirements are not being met, as part of IRB requirements to approve the study, the Senior Research Compliance Officer and the Chair of the Conflicts of Interest Committee (COIC) will be notified by the Director or Associate Director of JOHRP.

4. References

JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*
JOHRP Policy GA 101, *The Authority and Purpose of the Institutional Review Boards*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 115: Management of Research Concerns

1. Purpose

To describe how the Jefferson Office of Human Research Protection (JOHRP) handles concerns or complaints about a clinical research study from a participant, their relative, advocate, and/or surrogate, a study team member, government agency, or other individual.

1.1 Responsible Parties

Director/Associate Director of JOHRP
Institutional Review Board (IRB) Chairs/Vice Chairs

2. Procedure

Once a possible concern has been identified, JOHRP management, an IRB Chair/Vice Chair, or other qualified individual will act as reviewer.

Concerns that involve non-compliance will be handled according to University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues*.

Concerns that involve unanticipated problems (UAPs) involving risks to participants or others will be handled according to JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*.

The reviewer will work with the concerned individual, making every effort to resolve the issue in a confidential manner. As needed, the reviewer will request and collect additional information and will involve the Enterprise Office of Legal Affairs and other individuals who are not affiliated with the specific study. The reviewer or other appointed person (e.g., representative from the Enterprise Office of Legal Affairs) will contact the individual to provide findings and/or a resolution. This process will continue and expand as needed until the individual is satisfied or Jefferson has determined that it has fulfilled its obligation to the individual.

3. Reference

University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues* (Internal Jefferson link)

JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 116: Use of Students and Employees as Key Personnel and Participants in Clinical Trials

1. Purpose

To provide guidance on how to avoid coercion when recruiting students or employees as research participants for human subjects research.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
Investigators
Key Personnel

2. Policy

2.1 Policy Statement

Students and employees are not usually considered a separate class of research participants from the standpoint of ethical standards or federal regulatory compliance. Students frequently act as key personnel under the direct supervision of the principal investigator (PI) on clinical trials to obtain experience and data for their advanced degree.

Some categories of research specifically target students as participants. Students are mostly involved in research conducted in established or commonly accepted educational settings, such as research on regular and special instructional strategies, instructional technique, curricula, or classroom management methods.

The principal controversy about the use of students and employees as participants in research studies involves whether the inducements to participate are considered coercive. These two (2) groups are comparatively convenient, easy to recruit and may accept less remuneration for participation. The Common Rule (45 CFR 46) states that an investigator should seek consent “only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or

undue influence." (45 CFR 46.116) Considering that students and employees may exist in a subordinate role, often to the investigators, the potential for coercion, intentional or unintentional, does exist.

In addition to coercion, another major concern regarding student and employee participants is that of confidentiality. This applies particularly to the case where students are key personnel on a study that involves other students or employees who work together.

Extra care must be taken to ensure participant confidentiality in these instances. The Institutional Review Board (IRB) must ensure that data is stored where access is restricted, and if students are involved in data collection and analysis, the IRB must ensure that the students understand the importance of maintaining the confidential nature of the information. The IRB shall also ensure that the process of data storage is acceptable so that the data is secure

3. Procedure

The IRB shall carefully review recruiting inducements for students, giving extra consideration for inducements such as:

- Requirement for participation in a course
- Course credit
- In lieu of writing a research paper
- In lieu of attendance at faculty research talks
- Direct payment for participation

The IRB shall also carefully review recruitment inducements for employees.

The IRB must only approve methods that solicit participants by less coercive means such as using sign-up sheets or general announcements, rather than direct solicitation of individuals from the classroom or workplace environment. These options reduce the likelihood of "undue coercion" by making the request less direct and by decreasing the influence inherent in the faculty-student/supervisor-employee relationship.

4. Reference

The Common Rule (45 CFR 46)

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 118: Protocol Inclusion/Exclusion Waivers

1. Purpose

To delineate the procedures whereby sponsors and principal investigators (PIs) may petition for Institutional Review Board (IRB) approval of inclusion/exclusion waivers to enroll participants on a clinical trial.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research (JOHRP) (or designee)
Sponsor
PI

2. Policy

2.1 Policy Statement

It is uncommon for a sponsor, or the PI in the case of an Investigator-Initiated Treatment Trial (IITT), to make allowances for certain participants who fall outside of the protocol's inclusion/exclusion criteria to be enrolled on the study. These allowances are referred to as protocol inclusion/exclusion waivers. Such waivers are discouraged, however, there are circumstances in which they may be granted.

Waivers may be approved by the IRB if:

- The person's inclusion would not place them at increased risk of harm
- Participation in the study would be in the person's best interest because alternatives are limited to less favorable options.
- Scientific validity of the clinical trial would not be substantially compromised by the inclusion of the research participant

Typical examples of waiver requests include:

- Required imaging studies obtained days to weeks prior to that permitted by the protocol

- The prospective participant is slightly older or younger than specified in protocol
- Blood chemistries fall slightly outside the protocol permitted levels.

3. Procedure

If the study is an IITT, and the PI feels that a protocol inclusion/exclusion waiver is appropriate, the PI must submit an OHR-31, *Waiver Request for Inclusion/Exclusion Criteria*, with the justification and risk assessment sections completed in sufficient detail to allow an informed decision.

A protocol inclusion/exclusion waiver represents a single deviation from the protocol and should not be submitted to the IRB as an amendment to the protocol.

If the sponsor provides the PI with an inclusion/exclusion waiver for a participant, the PI will forward the notice of waiver attached to the completed form OHR-31 to JOHRP for approval prior to enrolling the participant in question.

If the PI makes requests for a waiver for the same inclusion/exclusion criterion more than one (1) time, the PI must formally amend the inclusion/exclusion criteria in the protocol.

4. Reference

OHR-31, *Waiver Request for Inclusion/Exclusion Criteria*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 120: Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others

1. Purpose

To ensure prompt reporting to the Institutional Review Board (IRB) of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UAPs) by Principal Investigators (PIs). Regulatory requirements of both the Department of Health and Human Services (HHS) (45 CFR 46.108(a)(4)) and the U.S. Food and Drug Administration (FDA) (21 CFR 56.108(b)(1)) require that:

> *Each IRB shall establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections (OHRP), HHS, or any successor office, or the equivalent office within the appropriate federal department or agency of: (i) Any unanticipated problems involving risks to participants or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) Any suspension or termination of IRB approval.*

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
SAE and UAP Reviewers

2. Policy

2.1 Definitions

- **Adverse Event (AE)**: An AE is any untoward medical occurrence that occurs during the reporting period (see Section 3 Table, *Timeframes for Expedited SAE and UAP Reporting*). The occurrence does not have to be related to the study and includes clinically significant abnormal laboratory findings. An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one (1) of the outcomes listed in this definition.

- **Adverse Event Grade**: AE grade refers to severity as per the Common Terminology Criteria for Adverse Events (CTCAE) created by HHS, National Institutes of Health (NIH), depicted below. Please see the National Cancer Institute (NCI) website for more information.
  - Grade 1 = Mild
  - Grade 2 = Moderate
  - Grade 3 = Severe or medically significant
  - Grade 4 = Life-threatening or disabling
  - Grade 5 = Death
- **Related Event**: A related event is one that is judged to be possibly, probably, or definitely associated with the test article (e.g. drug, device), procedures, conduct, or some other aspect of the study.
- **Unanticipated Problem (UAP)**: A UAP is an unexpected event that involves risk to the participant(s) or others but does not by itself meet the definition of an AE.

Examples of UAPs which may involve risk to the participant or others are listed below. The risks may be physical or psychological or involve the loss of a participant's confidentiality or rights as a research participant.

- A protocol deviation/violation that is serious or recurrent and involves risk to the participant or others must be reported as a UAP. A protocol deviation and/or violation is a departure from the IRB-approved protocol. JOHRP does not make a distinction between protocol deviations and violations. Any associated SAE must be recorded and reported as specified in this policy

- Reports from other study sites which include AEs, SAEs, and Investigational New Drug (IND) safety reports that individually or collectively suggest a UAP

- Multiple occurrences of an AE that are not individually reportable but together are considered a UAP

- An interim analysis of the data suggesting or indicating additional risk associated with a study procedure or test article

- A report (e.g. journal article or abstract) that shows the risks or potential benefits of the research might now be different from those initially presented to the IRB

- A breach of confidentiality

- Change in FDA labeling or withdrawal from marketing of a drug, device, or biological used in a research protocol

- Change made to the research without prior IRB review to eliminate an apparent immediate hazard to a participant

- Incarceration of a participant in a protocol not approved to enroll prisoners

- An event that requires prompt reporting to the sponsor

- Sponsor-imposed suspension for risk

- A participant compliant indicating unexpected risks, or that which cannot be resolved by the research team
- A change to a protocol or procedure that is instituted by the site and not pre-approved by the IRB
- Any other event that may prompt action by the IRB to ensure the protection of human subjects

- **Unexpected**: Unexpected indicates that an event is not listed or is listed with a different specificity or greater severity or frequency, in the investigator's brochure, device brochure, product insert, protocol, or consent form.

2.2 Review of SAEs and UAPs

Reported SAEs and UAPs will be reviewed by JOHRP staff and/or designee with the intention of eliminating any immediate risks to the participants and others.

Actions that may be taken include:

- Modification of the protocol, consent form or consent process
- Providing additional information to or re-consenting participants
- Modification of the continuing review schedule
- Auditing of the research and/or consent process by the Quality Assurance Program of JOHRP
- Suspension or termination of the research
- Referral to other organizational entities for further investigation
- Notification and further action taken as per University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues*

3. Procedures

3.1 Reporting of AEs, SAEs, and UAPs

3.1.1 SAEs are reportable from the time the patient consents to 30 days after the last study intervention, or as specified in the protocol.

3.1.2 Logs of all AEs, SAEs, and UAPs must be maintained.

3.1.3 SAEs are reported in the SAE reporting system (i.e. eSAEy). UAPs are reported in the UAP reporting system (i.e. eazUP).

3.1.4 If an event is ongoing or unresolved when it is initially submitted, an additional report should be submitted if the event resolves.

3.1.5 If an event necessitates a change to the protocol and/or consent form, submit an amendment to JOHRP.

3.1.6 The timeframes for reporting SAEs and UAPs start when anyone on the study team becomes aware of the event. The event is not considered reported to the IRB until the investigator signs off on the event in the JOHRP reporting system.

3.1.7 AEs, SAEs, and UAPs must be recorded and reported per the agreement with other IRBs of record (e.g. commercial IRBs, other institutions IRBs).

3.1.8 Generally, reports of external events (e.g. IND safety reports) do not need to be submitted to the IRB in an expedited manner. For external events that necessitate a change to the research (e.g. protocol, consent), an amendment must be submitted to the IRB

3.1.9 If Jefferson is acting as the coordinating site for a multi-center study:

3.1.9.1 If the sponsor, Data Safety Monitoring Board (DSMB), or other entity is monitoring safety across all sites, an amendment must be submitted to the IRB in the event of a change to the research (e.g. protocol, consent).

3.1.9.2 If no other entity is monitoring safety across all sites, events at all sites must be reported to the IRB as indicated in the table below.

3.1.10 In addition to the timeframes provided in the table below, all AEs, SAEs, and UAPs are to be reported to the IRB with the next continuing review or final report (whichever comes first), including SAEs and UAPs that have already been

submitted to the IRB in an expedited manner. Please note that grade 1 and 2 AEs do not need to be reported to JOHRP.

The following events are reportable to the IRB in the timeframes indicated below:

Timeframes for Expedited SAE and UAP Reporting

Event	Timeframe (Business Days)
An AE that meets **ALL** these criteria: • Serious (Grades 3,4,5 (death)) • Unexpected (in specificity / severity / frequency) • Possibly, probably, or definitely related	**5**
A UAP that meets **ALL** these criteria: • Involves risk to the participant(s) or others • Is serious	**5**

4. References

45 CFR 46.108(a)(4)
21 CFR 56.108(b)(1)
NIH NCI *Common Terminology Criteria for Adverse Events (CTCAE)*
University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues* (Internal Jefferson Link)
OHRP Guidance: *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* (January 15, 2007)
21 CFR 312
21 CFR 812.3 (s)
21 CFR 314.80

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 121: Jefferson Office of Human Research Protection and Institutional Review Board Document Management

1. Purpose

To describe the requirements for management of all Jefferson Office of Human Research Protection (JOHRP) and Institutional Review Board (IRB) documentation including document retention, administrative documents, and archiving.

1.1 Responsible Parties

Director/Associate Director of JOHRP
JOHRP Personnel

2. Policy

2.1 Policy Statement

Each study file maintained by JOHRP must contain a complete history of IRB actions related to review and approval of the particular study. This would include: scientific reviews (if any), continuing reviews, amendments, renewals following expiration, and reports of adverse events (AEs) and unanticipated problems (UAPs). JOHRP will also maintain a list of IRB members for each IRB as per regulatory requirements (45 CFR 46.108(a)(2); 45 CFR 46.115(a)(5)). All records received by the IRB regarding a study, whether approved or not, must be retained as required by regulatory requirements (45 CFR 46.103(a)) and/or institutional policy, and should be stored in an appropriately secure manner.

Records must be accessible for inspection and copying by authorized representatives of a sponsor, funding entity, or regulatory agency (45 CFR 46.115 (b)) as well as by institutional audits at reasonable times and in a reasonable manner.

Required documents must be submitted to any appropriate requesting funding entity, as required.

2.2 Policy Specifics

2.2.1 Document Retention

The IRB and investigators must follow University Policy 102.39, *Policy on Retention of University Records*. Records must be retained longer if specified in the contract. For sponsored studies, when the retention period ends, the investigator should contact the sponsor before destroying any records. To ensure participant privacy, the investigator must consider the prompt destruction of protected health information (PHI) after the retention period ends. Records must be destroyed as specified in University Policy 102.39. Shredding or depositing records in locked confidential bins are acceptable methods. After records have been destroyed, this will be documented (e.g. in the appropriate study file or database).

IRB files approved prior to the IRB e-system launch are stored in locked rooms. Hard copies of files exceeding the three (3) year retention limit may be purged annually. The study folder and its materials will be discarded appropriately.

If the study, or an individual involved with the study, is the subject of litigation, all IRB records pertaining to the study will be retained until the issue is resolved.

2.2.1.1 Study related documents:

Adequate documentation for each study will be maintained and retained in the IRB e-system including:

- Records of initial, continuing, and amendment review activities, both full and expedited, and exempt studies, including appropriate submitted materials, reviewer determinations and determinations required by regulations and protocol-specific findings supporting those determinations for:
    - Waiver or alteration of consent process
    - Research involving pregnant persons, fetuses, and neonates
    - Research involving prisoners
    - Research involving children
- One (1) copy of the original submission
- A copy of the most recently approved Master Application

- A copy of the latest protocol
- A copy of the original approved consent form, and any approved revised consent forms
- Scientific evaluations
- Progress reports submitted by investigators
- All reported protocol deviations as submitted
- Reports of injuries to participants
- Approval period for each initial and continuing review
- Department of Health and Human Services (HHS) approved sample consent document and protocol, when applicable
- Copies of all submitted monitoring reports, site visit reports, and other continuing review activities
- Copies of all correspondence between the IRB and investigators
- Statements of significant new findings provided to participants as submitted by the investigator
- For exempt studies, the specific exemption category
- IRB records for initial and continuing review reviewed by the expedited procedure must include:
    - The specific permissible category
    - A description of the action taken by the reviewer
    - Any determination required by the regulations along with protocol-specific findings justifying those determinations

2.2.2 IRB Administration Documents:

In addition, the following IRB administrative documents will be retained:

- Rosters of regular and alternate IRB members including:
  - Name
  - Earned degrees
  - Scientist/non-scientist status
  - Representative capacity
  - Indications of experience sufficient to describe each regular and alternate member's chief anticipated contributions to the IRB's deliberations
  - Any employment or other relationship between each member and the IRB and/or Jefferson (e.g., full-time employee, part-time employee, member of a governing panel or Board, stockholder, paid or unpaid consultant), affiliation status, capacity of member (member, chair, ex officio), IRB member training records, and voting status
- CVs and Training Records for regular and alternate IRB members
- Current copies of the Standard Operating Policies and Procedures
- Agendas and minutes of all IRB meetings (JOHRP Policy OP 206, *Institutional Review Board Administration*)
- Reports of any complaints received from participants, regulatory agencies and their resolution
- Delegation of specific functions, authorities, or responsibilities by the Director or Associate Director of JOHRP, or an IRB Chairperson in writing

3. References

The Common Rule (45 CFR 46)
21 CFR 56.115
21 CFR 312.62
University Policy 102.39, *Policy on Retention of University Records* (Internal Jefferson Link)
JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 124: Good Clinical Practice for Investigators

1. Purpose

To provide guidance to investigators and key personnel on Good Clinical Practice (GCP) for human subjects research. This guidance is taken from the International Congress for Harmonization (ICH) E6: Guidelines for Good Clinical Practice.

1.1 Responsible Parties

Investigators
Key Personnel

2. Policy

Investigators and key personnel should follow the following guidance when conducting human subjects research. Although they appear below, the most current version of the ICH guidelines should be referenced.

3. Investigator Responsibilities under the Policy

3.1 Investigator's Qualifications and Agreements

3.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and/or regulatory authority.

3.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

3.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

3.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.

3.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

3.2 Adequate Resources

3.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) potential for recruiting the required number of suitable subjects within the agreed recruitment period.

3.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3.2.3 The investigator should have an adequate number of qualified staff and adequate facilities available for the foreseen duration of the trial to conduct the trial properly and safely.

3.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

3.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

3.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual, or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. While not required by GCP, per Jefferson policy, a written agreement (e.g. professional services agreement) between Jefferson and the external individual/party should be entered into that includes the services to be provided and the qualifications of the individual/party. Contact the Office of Research Support Services (ORSS) for assistance.

3.3 Medical Care of Trial Participants

3.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a co-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

3.3.2 During and following a participant's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events (AEs), including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness of which the investigator becomes aware.

3.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to inform the primary physician.

3.3.4 Although a participant is not obliged to give their reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. While not required by GCP, it is general good practice that if a participant withdraws from a trial, the investigator should take all reasonable steps to ensure the participant's safety such as appropriate discontinuation of study medications.

3.4 Communication with IRB/IEC

3.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

3.4.2 As part of the investigator/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

3.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

3.5 Compliance with Protocol

3.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by regulatory authority, which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

3.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor, prior review, and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

3.5.3 The investigator, or their designee, should document and explain any deviation from the approved protocol.

3.5.4 As soon as possible, a description of the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a) to the IRB/IEC for review and approval/favorable opinion

b) to the sponsor for agreement and, if required

c) to regulatory authority

3.6 Investigational Product(s)

3.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

3.6.2 Where allowed/required, the investigator/institution may/should assign some or all the investigator/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

3.6.3 The investigator/institution and/or pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational

product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile the quantities of all investigational product(s) received from the sponsor.

3.6.4 The investigational product(s) should be stored as specified by the sponsor (see ICH E6(R2) 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

3.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

3.6.6 The investigator, or the designee of the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

3.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, or unblinding due to a serious adverse event (SAE)) of the investigational product(s).

3.8 Informed Consent of Trial Subjects

3.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the *Declaration of Helsinki*. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

3.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form and/or written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue

participation in the trial. The communication of this information should be documented.

3.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a participant to participate in or continue to participate in a trial.

3.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally authorized representative to waive or to appear to waive any legal rights, or releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

3.8.5 The investigator, or their designee, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally authorized representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

3.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally authorized representative and the impartial witness, where applicable.

3.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally authorized representative ample time and opportunity to inquire about details of the trial and to decide whether to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally authorized representative.

3.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion.

3.8.9 If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally authorized representative, and after the subject or the subject's legally authorized representative has orally consented to the subject's participation

in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative.

3.8.10 The informed consent discussion, the written informed consent form, and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research

b) The purpose of the trial

c) The trial treatment(s) and the probability for random assignment to each treatment

d) The trial procedures to be followed, including all invasive procedures

e) The subject's responsibilities

f) Aspects of the trial that are experimental

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

j) The compensation and/or treatment available to the subject in the event of trial-related injury

k) The anticipated prorated payment, if any, to the subject for participating in the trial

l) The anticipated expenses, if any, to the subject for participating in the trial

m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled

n) That the monitor(s), the auditor(s), the IRB/IEC, and regulatory authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access

o) That trial records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential

p) That the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial

q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury

r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated

s) The expected duration of the subject's participation in the trial

t) The approximate number of subjects involved in the trial

3.8.11 Prior to participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects. While not required by GCP, per Jefferson policy, the signed and dated

informed consent form will be made part of the subject's electronic medical records along with any informed consent form updates and amendments.

3.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally authorized representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

3.8.13 Except as described in ICH E6(R2) 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

3.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally authorized representative provided the following conditions are fulfilled:

a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

c) The negative impact on the subject's well-being is minimized and low.

d) The trial is not prohibited by law.

e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

3.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally authorized representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally authorized representative is not available, enrollment of the subject should

require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally authorized representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see ICH E6(R2) 4.8.10) should be requested.

3.9 Records and Reports

3.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

3.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

3.9.2 Data reported on the case report form (CRF), that are derived from source documents, should be consistent with the source documents. Discrepancies should be explained.

3.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see ICH E6(R2) 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to ensure that changes or corrections in CRFs made by sponsor's designated representatives are documented are necessary and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

3.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see ICH E6(R2) 8, or attachment A to this policy) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

3.9.5 Essential documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see ICH E6(R2) 5.5.12). While not required by GCP, documents should be retained to ensure researchers can validate findings and defend against any research misconduct allegations. See Jefferson Policy No. 110.02 Responding to Alleged Misconduct in Research discussing the six (6) year statute of limitations.

3.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

3.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

3.10 Progress Reports

3.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

3.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see ICH E6(R2) 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

3.11 Safety Reporting

3.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the appropriate regulatory authorities and the IRB/IEC.

3.11.2 Adverse events (AEs) and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

3.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

3.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should ensure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the appropriate regulatory authorities. In addition:

3.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable. The investigator/institution should promptly inform the sponsor and the IRB/IEC, providing a detailed written explanation of the termination or suspension.

3.12.2 If the sponsor terminates or suspends a trial (see ICH E6(R2) 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

3.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see ICH E6(R2) 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

3.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the appropriate regulatory authorities with any reports required.

4. Sponsor

4.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms (CRFs), and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

4.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify processes and data that are critical to ensure human subject protection and the reliability of trial results.

4.0.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures (SOPs), computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

4.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring.

b) The extent to which such errors would be detectable.

c) The impact of such errors on human subject protection and reliability of trial results.

4.0.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or the reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

4.0.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

4.0.6 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

4.0.7 Risk Reporting

The sponsor should describe the quality management approach implemented in the trial, summarizing important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 *Data Quality Assurance*).

4.1 Quality Assurance and Quality Control

4.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted, and data is generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

4.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see ICH E6(R2) 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

4.1.3 Quality control should be applied to each stage of data handling to ensure that all data is reliable and processed correctly.

4.1.4 Agreements made by sponsor with the investigator/institution and any other parties involved with the clinical trial should be in writing, as part of the protocol or in a separate agreement.

5. References

ICH E6 Guidelines for Good Clinical Practice (R3)
University Policy 102.39, *Policy on Retention of University Records* (Internal Jefferson Link)
Declaration of Helsinki
University Policy No. 110.02, *Responding to Alleged Misconduct in Research* (Internal Jefferson Link)
ICH E3, Section 9.6 *Data Quality Assurance*

Attachment A – Regulatory Binder Index

Section	Contents
Protocol	• Study Protocol and Amendments • Protocol or Amendment Signature Pages • Non-Disclosure Agreement • Investigator's Brochure
1572 / Regulatory Forms / CV	• FDA Form 1572 (if applicable) • Curriculum Vitae of investigator(s) • Medical Licenses (US only, if applicable) • Financial Disclosure Agreement (if applicable) • Copies of IRB & HIPAA training certificates
Original IRB-Approved Consent Form(s)	• Original Informed Consent(s)
IRB Approval Letter and Correspondence	• IRB/IBC/RAC Approvals for Protocol • Copies of Amendments, Advertisements, and Continuing Reviews • Other IRB Correspondence (copies of OHR-20 for deviations/violations, etc.)
Laboratory	• Lab Certifications as applicable (CAP, CLIA) • Laboratory Normal Ranges • CV of pathologist, if applicable
Study Logs	• Printouts of SAE reports • Investigator Personnel Team Signature Page • Site Visit Logs • Site Signature Logs • Master Participants Logs • Screening Logs • Training Logs (Site Initiation Visit attendance log & training certificates)

Section	Contents
Correspondence	• Study related correspondence between the site, sponsor, CRO, etc.
Serious Adverse Events (SAEs)	• Printouts of SAE reports • IND Safety Letters
Drug / Device Accountability (if applicable)	• Receipt / packing invoices • Accountability Form • Supply Forms
Miscellaneous	• Miscellaneous (CRF transmittal logs, etc.)

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 125: Investigator Responsibility and Delegation of Responsibility

1. Purpose

To define the responsibilities of the principal investigator (PI) and the delegation of authority to members of the study team.

1.1 Responsible Parties

Investigators
Key Personnel

2. Policy

2.1 Policy Statement

This policy applies to the PI and all other designated individuals involved in supervising, managing, or conducting human subjects research at Jefferson.

3. Procedure

3.1 Investigator Responsibilities

3.1.1 Consults with and obtains approval from the Institutional Review Board (IRB) for clinical study activities prior to proceeding.

3.1.2 Ensures that site procedures and practices are in compliance with institutional standard operating procedures (SOPs), Good Clinical Practice (GCP), and all institutional recommendations/requirements (JOHRP Policy GA 124, *Good Clinical Practice for Investigators*).

3.1.3 Ensures that responsibilities and activities delegated to others in the conduct of regulated human subjects research are understood and carried out by individuals who are qualified by training and experience to do so, with appropriate documentation of that delegation (JOHRP Policy QA 304, *Study Team Training*).

3.1.4 Establishes training policies and SOPs to provide all designated individuals with the opportunity to maintain and enhance their ability to carry out their delegated

responsibilities, and ensures all individuals engaged in clinical research have met their training requirements (JOHRP Policy QA 304, *Study Team Training*).

3.1.5 Ensures that financial and professional conflicts of interest (COIs) are recognized, reported to the Enterprise Office of Legal Affairs and any other appropriate authorities, and mitigated where possible (JOHRP Policy GA 106, *Conflicts of Interest*).

3.1.6 Provides sponsor with sufficient evidence of qualification of all key personnel and a commitment to conduct the study according to the sponsor and investigator's mutual agreement.

3.1.7 Ensures that all key personnel are adequately prepared to participate in sponsor-initiated site training on the regulations, the protocol and the investigational product (JOHRP Policy QA 304, *Study Team Training*).

3.1.8 Ensures regular, timely, effective, and well-documented communication among all individuals participating in the conduct of clinical research (JOHRP Policy GA 124, *Good Clinical Practice for Investigators*).

3.1.9 Ensures the proper use, storage and accountability of investigational products (JOHRP Policy GA 124, *Good Clinical Practice for Investigators*).

3.1.10 Maintains all required documents and records in the appropriate location, for a period of time specified by Sponsor and by regulatory requirements (JOHRP Policy GA 124, *Good Clinical Practice for Investigators*).

3.1.11 Ensures compliance with the protocol and cooperation with the Sponsor's Monitors (JOHRP Policy GA 124, *Good Clinical Practice for Investigators*).

3.1.12 Terminates participation in an investigation that is determined to present an unreasonable or significant risk to participants, or for an inability to comply with the investigational plan (JOHRP Policy GA 124, *Good Clinical Practice for Investigators* and JOHRP Policy RR 407, *Suspension or Termination of Human Subjects Research*).

3.1.13 Protects the rights and welfare of study participants and ensures initial and ongoing review by the IRB and any other relevant institutional participant safety committees. (References: JOHRP Policy IC 701, *Informed Consent and HIPAA*

Authorization: General Requirements, and JOHRP Policy IC 702, *Documentation, Waiver and Alteration of Informed Consent and HIPAA Authorization*).

3.1.14 Ensures that each participant signs the current version of the Jefferson IRB-approved informed consent form and continues the process of informing participants about their ongoing participation throughout the duration of the study (JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*, and JOHRP Policy IC 702, *Documentation, Waiver and Alteration of Informed Consent and HIPAA Authorization*).

3.1.15 Safeguards the scientific, ethical, and regulatory validity of the clinical study by requiring strict adherence to participant enrollment criteria, participant identification methods (protection of confidentiality), management of participant medical care while enrolled, and biological specimen collection and handling requirements (JOHRP Policy GA 127, *Participant Screening and Enrollment*).

3.1.16 Ensures the management of participants' medical care while enrolled and that adverse events (AEs) are recorded and, if serious, are promptly investigated and reported to the sponsor, relevant institutional, and regulatory authorities (JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants and Others*).

3.1.17 Maintains a system for recording and managing data and observations from clinical studies, including required safeguards for electronic data collection systems.

3.1.18 Employs quality assurance practices that ensure scientific, ethical, and regulatory compliance by permitting the independent review and assessment of policies, procedures and records for quality improvement purposes (JOHRP Policy QA 301, *Quality Assurance/Quality Improvement Program*, and JOHRP Policy QA 303, *Inspections by the FDA and Other Regulatory Agencies*).

3.1.19 Cooperates with regulatory authorities (e.g., U.S. Food and Drug Administration (FDA), Office of Human Research Protections (OHRP)) in their assessment of the clinical research program's compliance with applicable regulations (JOHRP Policy QA 303, *Inspections by the FDA and Other Regulatory Agencies*)

3.2 General Responsibilities of the Study Team

3.2.1 Communicate effectively with participants, other study team members, the IRB, and the sponsor.

3.2.2 Support required training activities through their own professional development in relevant content areas.

3.2.3 Communicate all AEs and abnormal laboratory results to the investigator for an assessment of severity and report non-serious AEs or serious adverse events (SAEs) to the IRB and sponsor appropriately.

3.2.4 Meet regularly with the investigator and other study team members to discuss participant participation and protocol progress.

3.2.5 Prepare for and attend investigator and study start-up meetings.

3.2.6 Participate in monitoring visits and audits, as appropriate.

3.2.7 Make available to monitors, auditors, the IRB, and regulatory authorities all requested study-related records.

3.2.8 Ensure accuracy, completeness, legibility, and timeliness of case report forms (CRF).

3.2.9 Ensure that CRFs accurately reflect source documents, explain any discrepancies between source documents and CRFs and endorse changes or corrections to a CRF.

3.2.10 Ensure documentation of study-related procedures, processes, and events.

3.2.11 Comply with written procedures to document changes to data and/or CRF.

3.2.12 Maintain study documents as required by the regulations and sponsor for the appropriate timeframe and under secure conditions.

3.3 Delegation of Responsibility and Signature Authority

3.3.1 Except where noted in these policies, the investigator has the authority to delegate any study-related task and responsibility to any qualified member of the study team properly trained to carry out the designated function.

3.3.2 The investigator or their designee must identify the individual to whom significant study-related functions have been assigned by name and/or title.

3.3.3 Designated personnel may sign various documents as approved by the Investigator.

3.3.4 The Investigator may sign any document in the absence of designated personnel.

3.3.5 If a designated individual signs in place of another whose name is typed or printed near the space for signature, the signatory shall sign their name followed by the word "for" indicating they are signing for that person.

3.3.6 For instances in which the signatory is signing a totally blank space, that person shall sign their name and provide a date.

3.4 Transfer of Responsibility to Contractors

3.4.1 The investigator has the authority to delegate any study-related task and duty to a qualified contractor (e.g., consulting firm, independent consultant) properly trained to carry out the designated function.

3.4.2 The investigator or their designee must identify the individual(s) by name and/or by title, to which significant study-related functions have been assigned in a properly executed vendor agreement.

3.4.3 The investigator will maintain a file documenting the qualifications of such contractors as part of the study binder.

4. References

21 CFR 312 Subpart D, *Responsibilities of Sponsors and Investigators*
21 CFR 812 Subpart E, *Responsibilities of Investigators*
21 CFR 312.52, *Transfer of Obligations to a Contract Research Organization*
ICH E6 Guidelines for Good Clinical Practice (R3)
JOHRP Policy GA 124, *Good Clinical Practice for Investigators*
JOHRP Policy QA 304, *Study Team Training*
JOHRP Policy GA 106, *Conflicts of Interest*
JOHRP Policy RR 407, *Suspension or Termination of Human Subjects Research*
JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*
JOHRP Policy IC 702, *Documentation, Waiver and Alteration of Informed Consent*
JOHRP Policy GA 127, *Participant Screening and Enrollment*
JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*
JOHRP Policy QA 301, *Quality Assurance/Quality Improvement Program*

JOHRP Policy QA 303, *Inspections by the FDA and Other Regulatory Agencies*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 126: Sponsor Agreements

1. Purpose

To describe the requirements that must be included in written agreements with sponsors to ensure:

a) the human research protection program is applied to all sponsored research

b) timely communication of information with sponsors that might affect the ongoing oversight of a protocol by the Institutional Review Board (IRB) is arranged

c) the benefits of knowledge obtained through research are realized and the interests of the current and future research participants are protected

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
IRB Chairs/Vice Chairs
Assistant Director of Contracts, Office of Research Support Services (ORSS), or their designee
Director of Jefferson Clinical Research Institute (JCRI) Business Operations
Senior Research Compliance Officer
ORSS

2. Policy

2.1 Policy Statement

The ORSS may require the written agreements with sponsors to include necessary provisions to evidence the protection of human research subjects.

3. Procedure

3.1 JOHRP and ORSS shall ensure that both offices communicate regarding the inclusion of necessary provisions in sponsor agreements.

3.2 ORSS, Contracts shall be responsible to ensure that a written agreement is entered into with each sponsor and each agreement includes, but is not limited to, the following:

a) A provision obligating Jefferson to conduct the research according to the protocol and obligating the parties to comply with all applicable laws and regulations, including but not limited to, from the Department of Health and Human Services (HHS) (when applicable), from the U.S. Food and Drug Administration (FDA), and ethical obligations and expectations related to the research to protect human subjects.

b) A provision, if applicable, addressing the medical care for research participants with a research-related injury to include who is responsible to provide care and who is responsible to pay for the care. The informed consent language should align with the contract language.

c) In studies where the sponsor bears responsibility for monitoring the research, reporting obligations including that of the sponsor to promptly report any findings of study monitors that could:

   i. Affect the safety of participants

   ii. Affect the willingness of study participants to continue participation in the study

   iii. Influence the conduct of the study; or

   iv. Alter the IRBs' approval to continue the study

d) Plans for disseminating findings from the research and the roles that investigators and sponsors will play in publication or disclosures of results, including but not limited to, provisions:

   i. Obligating the sponsor to abide by Jefferson policies and standard operating procedures regarding the publication of findings from sponsored research; and

   ii. Addressing the communication of results from a research study from the sponsor to Jefferson, then, as appropriate, from Jefferson to participants, when those results directly affected the participants' safety or medical care.

3.3 The Enterprise Office of Legal Affairs shall coordinate with ORSS and JOHRP on an ongoing basis to provide standard form agreement provisions to be included in all sponsor agreements including provisions addressing the items in Section 3.2 above. These provisions may be amended from time to time.

4. References

ICH E6 Guidelines for Good Clinical Practice (R3)
21 CFR 56

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 127: Participant Screening and Enrollment

1. Purpose

This policy describes the process to be followed for confirming the eligibility of participants to enroll in human subjects research.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel

2. Policy

2.1 Policy Statement

Every individual who is considered for enrollment in research must have their eligibility confirmed to participate

3. Procedures

3.1 General Instructions and Responsibilities

The investigators or their designees are responsible for ensuring written confirmation of an individual's eligibility to be enrolled in a clinical study prior to their enrollment.

3.2 Preparing Participant Eligibility Documentation

- The Principal Investigator (PI) or their designee should prepare a screening and enrollment log and a participant eligibility checklist, including all of the inclusion and exclusion criteria for the study. These forms may be obtained from the sponsor or using templates on the JOHRP website

- For retrospective studies, it is not necessary to keep a list of participants screened, but an enrollment log is required

- For studies with few (e.g. one (1) or two (2)) eligibility criteria, an eligibility checklist is not required, but documentation of each participant's eligibility must be maintained

3.3 Conducting Screening Activities

As a general rule, consent must be obtained before any protocol specific screening procedures are performed on prospective participants. Proposed deviations from the rule must be brought to the attention of the Institutional Review Board (IRB) in the initial IRB submission.

3.3.1 To allow for the review of possible study candidates in the electronic medical record, waiver of authorization must be requested in the master application in the IRB e-system. The submission should also include the script/letter that will be used to contact possible study candidates. Obtaining statistics on a general number of patients from the electronic medical record with a specific condition/parameters, but without identifiers does not require IRB review. This can be performed as preparatory to research.

3.3.2 A Jefferson researcher may contact any patient in the Jefferson electronic medical records. The individual contacting the patient should use wording on the availability of the study rather than referring to the patient as having a particular diagnosis. Depending on the sensitivity of the research topic, it may benefit the researcher if they first contact the practice from which the patients are being drawn.

3.3.3 If the patient shows interest, the consent process is then followed before any study specific procedures are done.

3.3.4 When conducting screening activities, the PI or their designee should use the screening and enrollment log as a running list of all prospective participants screened and enrolled for the study. Summary statistics on the number of participants pre-screened can be kept, but the actual list with patient names should not be available to anyone other than study staff and should be secured and destroyed when no longer needed.

3.3.5 When a prospective participant is identified, the investigator or their designee should obtain all protocol-relevant medical records and information regarding the participant. This must be done in compliance with institutional requirements and Health Insurance Portability and Accountability Act (HIPAA) regulations.

3.3.6 The investigator or their designee should record the status (e.g. screen failure, enrolled, etc.) of all prospective participants on the screening and enrollment log.

3.3.7 Based on discussions with the participant and review of the medical records, the Investigator or their designee should complete a participant eligibility checklist for each prospective participant.

3.3.8 All logs, checklists, and originals or copies of appropriate supporting documentation will be maintained in each site's study file or specific participant file, as appropriate.

3.4 Participant Numbering

3.4.1 The investigator will ensure maintenance of a key to identify all screened and enrolled participants. Each screened participant should be given a unique identifier. This identifier may change if the participant is enrolled. The participant code could include a site number if applicable, and a sequential participant number. This procedure, including any other protocol-specific participant cohort assignment, should be defined in the protocol or study-specific operations manual.

3.4.2 Once a participant's eligibility to participate in the clinical study has been confirmed, the participant will be assigned a unique participant number according to the protocol.

3.4.3 All study records maintained on each participant will use the unique participant number where possible to protect the participant's confidentiality.

4. References

21 CFR 321.60 *General Responsibilities of Investigators*
21 CFR 812.110 *Specific Responsibilities of Investigators*
ICH E6 Guidelines for Good Clinical Practice (R3)
JOHRP Website

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 128: Designation of the Institutional Official Responsible for the Human Research Protection Program

1. Purpose

To designate the Senior Research Compliance Officer as the Institutional Official (IO) with overall responsibility for the Human Research Protection Program (HRPP).

The Senior Research Compliance Officer currently holds the title of Senior Associate Provost for Research Integrity, Conduct, & Compliance.

1.1 Responsible Parties

Institutional Official (IO)
Director of Jefferson Office of Human Research Protection (JOHRP)
Provost of Thomas Jefferson University
Senior Research Compliance Officer

2. Policy

2.1 Policy Statement

This policy designates the Senior Research Compliance Officer as the IO charged with responsibility for research, research integrity, and science policy. The IO is responsible for general oversight of Jefferson's HRPP and reports directly to the Provost of Thomas Jefferson University.

The Director of JOHRP reports directly to the IO, ensuring that there is direct accountability by JOHRP to the IO.

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 129: Protection of Privacy Interests of Research Participants and Confidentiality of Participant Data

1. Purpose

To state the policy and outline the procedures regarding the protection of privacy interests of research participants and confidentiality of participant data.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Institutional Review Board (IRB) Chairs/Vice Chairs
IRB Members
JOHRP Personnel
Investigators
Key Personnel

2. Policy

2.1 Definitions

- **Privacy**: For the purposes of this policy, “privacy” will be defined as an individual’s desire to control the ways in which they are approached and/or the ways in which their private information is shared with others. Privacy may or may not be linked to confidentiality of personal information collected or generated during a research study.

- **Confidentiality**: Confidentiality pertains to the accessing, handling, storage, collection, and use of an individual’s personal information. 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 in ways inconsistent with the understanding of the original disclosure and without further permission from the individual.

2.2 Policy Statement

Privacy and confidentiality are supported by "Respect for Persons" and "Beneficence"; two (2) of the principles of research ethics identified in *The Belmont Report*. As part of its review of research following 45 CFR 46.111 and 21 CFR 56.111, the IRB is required to determine that privacy is protected when appropriate.

The Health Insurance Portability and Accountability Act (HIPAA) became effective on April 14, 2003 with the publication of the Privacy Rule and its regulations for protected health information (PHI). The Privacy Rule promulgated regulations that:

a) Established a requirement for a Privacy Notice to be provided to all patients, see *Thomas Jefferson University Notice of Privacy Practices*

b) Inform the patient how their PHI may be used or disclosed for research purposes

c) Inform the patient/research participant of their rights, including, but not limited to, the right to copy and inspect their medical record, right to correct their medical record, and the right to request an accounting of certain disclosures of their PHI

2.2.1 Disclosure of PHI

Disclosures of PHI are permitted for treatment, payment, and healthcare operations without the need for authorization, however, an acknowledgement by the individual of receipt of a provider's Privacy Notice explaining how PHI will be used is required. If disclosure is permitted, PHI disclosed must be the minimum information necessary to accomplish the intended purpose of the use or disclosure. The Privacy Rule restricts disclosure of PHI for specific purposes including research and establishes civil and criminal penalties for improper disclosure and/or use.

3. Procedures

3.1 Investigators Conducting Human Subjects Research

Jefferson provides all patients with a *Notice of Privacy Practice* ("Privacy Notice") that, as a minimum:

- Describes the use and disclosure of PHI for research purposes

- Gives the participant the right to access their medical records and to receive an accounting of certain disclosures about who accessed their PHI

- Allows the participant to request a correction to their medical record

- Limits the use and disclosure of PHI to the minimum necessary to accomplish the goals of the research study, unless a written authorization is obtained from the participant

Each research participant participating in human subjects research must be provided with a HIPAA Informed Consent Form or a study informed consent form that includes the HIPAA requirements. An investigator conducting human subjects research must provide the participant with an IRB-approved copy of the consent form document that contains the HIPAA-compliant Privacy Notice approved by the Enterprise Office of Legal Affairs or the study informed consent form that includes the HIPAA requirements. At Jefferson, the HIPAA authorization to use and disclose PHI for research purposes is contained in the *Instruction Manual for the Consent Form for a Research Study*.

The investigator is permitted to access, use, and disclose PHI for research purposes under one of the following conditions:

- An authorization is obtained from the participant (HIPAA authorization section in the *Informed Consent Template*)

- The IRB has waived the authorization requirement

- A limited data set is collected and accompanied by a Data Use Agreement (DUA). Contact Jefferson's Privacy Office for a DUA

- Decedent PHI exclusively will be collected. Contact Jefferson's Privacy Office for appropriate forms

- The information to be collected will be de-identified

PHI use that meets these conditions will be documented in new study applications to the IRB, with the exception of decedent information.

3.2 Approval of a Waiver of Authorization

An investigator must satisfy the following criteria for IRB approval of a waiver:

1. The use/disclosure of the PHI involves not more than minimum risk to the privacy of the participant based on, as least, the following elements:

    - An adequate plan to protect identifiers from improper use/disclosure
    - An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless the law requires retention or there is a valid scientific rationale to retain
    - Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for research for which the use or disclosure of PHI would be permitted by the participant
    - The research cannot practicably be conducted without the waiver
    - The research cannot practicably be conducted without access to and use of PHI

2. An investigator may use and disclose PHI for research purposes pursuant to a documented waiver of authorization issued by the IRB. This document, known as a HIPAA waiver letter, includes the following information:

    - Identification of the IRB approving the waiver and the date of approval
    - A statement that the IRB has determined that the waiver satisfies the criteria in the Privacy Rule as stated above
    - A brief description of the PHI covered by the waiver
    - A statement that the waiver has been approved by a convened IRB or by expedited review

3.3 PHI and Recruitment for Research

If an investigator wishes to review medical records to identify prospective research participants, they must include a plan for doing so in the study application. Along with obtaining appropriate IRB approval, research staff should also obtain appropriate

departmental permission before searching medical records and/or databases to which they ordinarily would not have clinical access.

The U.S. Food and Drug Administration (FDA) has addressed the issue of confidentiality during the screening process (FDA Information Sheet, *Recruiting Study Subjects*), including consideration of such issues as:

- What will happen to the personal information obtained by phone if the caller ends the interview or hangs up?
- Is the data being gathered by a marketing company; if so, are identifiers and/or health information being sold?
- Are names of non-eligible individuals being maintained in case they qualify for another study?
- Are paper copies of the records shredded?

The acceptability of the procedures would depend on the sensitivity of the data gathered. For particularly sensitive information, the investigator may wish to obtain a Federal Certificate of Confidentiality (JOHRP Guidance G 607, *Certificates of Confidentiality*).

3.4 Accessing PHI through Limited Data Sets/Data Use Agreement

A limited data set represents PHI that contains limited elements that HIPAA qualifies as identifiers. An investigator planning to use a limited data set should consult the Jefferson Policy No. 134.04, *Requests for Use and Disclosure of PHI for Research Purposes*, as to what constitutes the specific direct identifiers. The investigator should also complete the waiver section of the study application.

The use of a limited data set requires the investigator to work with the Enterprise Office of Legal Affairs to secure a Data Use Agreement (DUA) which will describe the data that may be shared and how the data can be used. Contact the Privacy Officer for preparation of a DUA.

3.5 Accessing PHI through De-identification

An investigator may use or disclose PHI without authorization if the PHI has been de-identified by the removal of specific identifiers so that the individual cannot be identified. Release or use of de-identified data is exempt from HIPAA requirements. However, IRB

review is required for human subjects research even when the protocol uses de-identified data. The investigator should contact the JOHRP for consultation. In addition, the use and disclosure of de-identified data with researchers outside Jefferson requires the investigator to work with the Enterprise Office of Legal Affairs to secure a DUA, which will describe the data that may be shared and how the data can be used.

3.6 Research on PHI of Decedents

An investigator planning to use or disclose PHI of a decedent for research purposes must certify to the Privacy Officer that:

- The use or disclosure of the PHI is being sought solely for research
- The research cannot be carried out without the PHI

Research conducted exclusively with decedent data and/or tissue does not qualify as human subjects research and does not require IRB review.

The IRB may request documentation from the investigator in the form a copy of the decedent's death certificate. Under 45 CFR 46, the IRB is not required to review research to be carried out based on decedent's PHI. PHI to be collected during research that falls under those regulations should be sent to Jefferson's Privacy Office for review.

3.7 Accounting of Research Disclosures

The Privacy Rule gives the participant the right to receive an accounting of all disclosures of PHI made by the investigator that occurred during the six (6) years prior to the individual request for an accounting. The investigator must provide the accounting of research disclosures to Jefferson's Privacy Officer. This accounting does not need to be provided to the IRB.

3.8 Multi-Site Research

If PHI for a study is to be shared between separate research sites, the investigator must ensure that:

- The consent document/authorization form lists the sites and sponsor (if any) that will be involved in the research, to whom the PHI will be disclosed and for what purpose(s)

- Cooperative procedures are available for obtaining PHI from site(s) for responding to participant requests to inspect or copy their research information

- The sites are informed of any amendment(s) to PHI requested by a participant

- In the case of studies operating under a waiver of authorization, any request(s) from a participant to receive an accounting of disclosures need to be available to all the sites

If research is being conducted in states other than Pennsylvania, the Principal Investigator (PI) must provide information on any state specific regulations on privacy requirements and genetic research. The PI may consult with the Enterprise Office of Legal Affairs for advice or direction.

4. Privacy and Confidentiality Issues

The IRB members must consider privacy and confidentiality as part of their regulatory and ethical duty to protect the rights and welfare of participants. During their review of a study, they must evaluate:

1. The degree of sensitivity of the information being collected and the measures that have been established for protecting the confidentiality of the information obtained, and

2. The ways in which the participant is assessed and contacted throughout the duration of the study. The IRB will require the investigator to provide such information on the study application, the protocol and the confidentiality section of the consent document

4.1 Confidentiality Issues in the Informed Consent

The IRB is responsible for ensuring that the consent document adequately provides the participant with information concerning the extent to which confidentiality of the research and medical records will be maintained. Both 45 CFR 46.116 and 21 CFR 50.52 require that the consent document contains a statement describing the extent, if any, to which confidentiality of research records identifying participants will be maintained. FDA regulations require that participants are informed of the possibility that the FDA may inspect the records for the study.

The IRB is also responsible for ensuring that the HIPAA section of the consent document is properly completed and contains information required to protect the participant's PHI.

4.2 Privacy Issues

The IRB must also consider the protection of privacy during the participant's participation in the study. This extends from the recruitment process until the participant has completed the last study visit or has been contacted for the last time for final follow-up data collection. Issues of privacy that may be considered include:

- Appropriateness and privacy of location for recruitment and consent interview
- The manner by which the participant is approached for recruitment (e.g. mail, email, phone, in person)
- The manner by which the participant is approached and/or contacted through the duration of the study
- Setting of the research
- Who obtains consent
- Provisions to address any privacy requests and/or complaints made by the participant during the study
- Provisions to limit non-study personnel's knowledge of participant's participation in the research study

Researchers should respect an individual's desire not to be approached, or to be approached in alternate ways, if so expressed.

The IRB will also consider how screening data is handled by the investigator. Retention of this data without consent of the participant represents a potential breach of privacy that may be particularly egregious if the prospective participant declines to participate in the study or does not qualify for the research. The FDA has addressed the issue of privacy and confidentiality during the screening process (FDA Information Sheet, *Recruiting Study Subjects*).

Furthermore, the IRB must be cognizant of the potential for sponsors and contract research organizations to create databases of prospective participants based on recruitment procedure(s), and provide, where possible, regulatory oversight of the process.

4.3 The IRB and the Sponsor

The FDA requires sponsors, or research monitors hired by the sponsor, to monitor the study for accuracy of data submitted to the FDA in accordance with regulatory requirements. Sponsors and monitors will be provided with copies of medical records directly pertaining to the study-specific data and its verification, as determined by the PI. Sponsors and monitors may also secure access to Jefferson patient electronic medical record (eMR) for the relevant study when the sponsor signs Jefferson's Carelink Agreement for Monitors and the sponsor's monitors agree to the terms of use. It is important that the investigator and/or key personnel inform the participant during the consent interview of the extent to which confidential records and PHI identifying the participant will be maintained and that, under law, the FDA may inspect the records for FDA-regulated studies.

The IRB must ensure that the information required in the HIPAA Privacy Statement has been included in the investigator-submitted consent form.

5. References

The Common Rule (45 CFR 46)
21 CFR 56.111
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research
Health Insurance Portability and Accountability Act (HIPAA)
21 CFR 50.52
FDA Information Sheet, *Recruiting Study Subjects*
JOHRP Guidance G 607, *Certificates of Confidentiality*
JOHRP *Informed Consent Template*
JOHRP *Instruction Manual for the Consent Form for a Research Study*
Enterprise Policy No. 134.04, *Requests for Use and Disclosure of PHI for Research Purposes*
Policy No. 134.01, *Privacy/Confidentiality of Health Information – Corporate Policy Thomas Jefferson University Notice of Privacy Practices*

Jefferson Office of Human Research Protection Policies and Procedures Manual

100 General Administration (GA)

Policy GA 133: Human Subjects Research Training

1. Purpose

To explain training requirements for individuals involved in human subjects research.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
Investigational Review Board (IRB) Members

2. Procedure

All investigators, key personnel, and IRB Members must receive training prior to their involvement in human subjects research. This training is available through the Collaborative Institutional Training Initiative (CITI). JOHRP will maintain the training records. JOHRP will also ensure that study personnel have completed the appropriate training before issuing the approval letter for a new study or continuing review and before the addition of study personnel is approved for an existing study.

These training requirements apply whether Jefferson personnel are engaged in research reviewed by a Jefferson IRB or an external IRB.

Investigators and key personnel must complete the CITI training appropriate to their area of research. Those doing biomedical research must take the biomedical and Good Clinical Practice (GCP) courses. Those doing socio-behavioral research must take either the socio-behavioral course or both the biomedical and GCP courses.

To maintain certification, active researchers must complete the refresher modules every three (3) years following their initial certification.

JOHRP has the option of accepting certification of training that is comparable to that which is described in this policy. JOHRP staff will determine the suitability of non-CITI materials to meet training requirements.

Jefferson personnel who took CITI training elsewhere should log on to their accounts and make Jefferson an affiliate institution. This will provide JOHRP with access to your most current training and allow you to receive automated e-mail notifications of training status.

All new IRB members and alternates, who joined the IRB after 5/16/19, must complete the CITI training for IRB Members. All IRB members who joined on or before 5/16/19 are grandfathered into training by virtue of their experience as IRB members. After the initial training, no refresher CITI training is required.

3. References

CITI website

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 201: Institutional Review Board Membership

1. Purpose

To ensure that the membership of the Institutional Review Boards (IRBs) conforms to the requirements of 45 CFR 46.107 and 21 CFR 56.107(c).

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Board Analysts

2. Policy

2.1 Policy Statement

The membership of the IRB will meet or exceed the requirements of the Common Rule (45 CFR 46.107).

Each IRB shall:

- Have at least five (5) members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution

- Be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including 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

- Be able to ascertain the acceptability of proposed research in terms of institutional commitments including policies, resources, and regulations, applicable law, and standards of professional conduct and practice through the inclusion of persons knowledgeable in these areas

If an IRB regularly reviews research that involves a category of participants that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with

impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one (1) or more individuals who are knowledgeable about and experienced in working with these categories of participants.

Each IRB shall include at least one (1) member whose primary concerns are in scientific areas and at least one (1) member whose primary concerns are in nonscientific areas.

Each IRB shall include at least one (1) 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. Unaffiliated members by definition may not be affiliated with the Jefferson nor have a family member (first degree relative) who is affiliated with Jefferson.

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflict of interest (COI), except to provide information requested by the IRB. For doctors of pharmacy (PharmDs) and clinical pharmacologists, preparing and dispensing a study drug does not constitute a COI.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Each IRB shall have access to a legal representative from the Enterprise Office of Legal Affairs.

Board Analysts are appointed as voting members.

3. Procedures

After establishing an IRB per these requirements, JOHRP Leadership will ensure that these requirements continue to be met if a member leaves the IRB. JOHRP leadership is responsible for training the new members.

If the IRB Chair is not available, the Vice Chair will chair the meeting. If both the Chair and Vice Chair are not available, an interim Chair will be appointed for the meeting.

Members are expected to attend at least 75% of meetings yearly. If that expectation is not met, the Director of JOHRP or the Chair may meet with the individual to discuss ways to improve attendance.

Before an IRB meeting, there is a reviewer assignment meeting. At these meetings, the following are addressed:

- The number of protocols to be reviewed
- The distribution of the reviews
- Any IRB membership issues
- The need for consultants

A designated JOHRP staff member will report changes in IRB rosters to the Office of Human Research Protections (OHRP) as required. JOHRP staff members will prepare and maintain a current roster of the IRB members including:

- Name
- Earned degrees
- Representative capacity
- Indications of experience such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations
- Any employment or other relationship between each member and the institution.

The roster will be up to date and available should OHRP, the Association for Accreditation of Human Research Protection Programs, Inc. (AAHRPP), or the U.S. Food and Drug Administration (FDA) request to see it.

4. References

45 CFR 46.107
21 CFR 56.107(c)
AAHRPP website

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 202: Recruiting, Appointing, and Performance Evaluation of Institutional Review Board Members, Chairs, and Vice Chairs

1. Purpose

To establish an Institutional Review Board (IRB) that conforms to federal regulations for IRB membership as stated in 45 CFR 46.107, *IRB membership*, and 21 CFR 56.107.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Chairs/Vice Chairs
Senior Research Compliance Officer

2. Policy

2.1 Policy Statement

This policy stipulates the Jefferson IRB membership requirements for an IRB Chair and the following categories of IRB members:

- affiliated scientist/non-scientist members
- unaffiliated community members; and
- alternate members.

The policy delineates the procedures by which such members are recruited, appointed and evaluated in their duties on the IRB.

Appointment to each of the IRBs will be made on the basis of expertise and experience with an aim to maintain an appropriate diversity of members to allow for complete and adequate review of research activities commonly conducted at Jefferson. Qualifications for IRB membership are outlined in JOHRP Policy OP 201, *Institutional Review Board Membership*.

3. Procedures

3.1 Recruitment and Appointment of IRB Members

3.1.1 **Jefferson Scientist/Non-Scientist Members**: Potential Jefferson IRB members in this category will be solicited by the Director and/or Associate Director of JOHRP and/or the IRB Chairs. The appointment will be made, as appropriate, by the Director of JOHRP.

The expertise and experience of a prospective candidate for IRB membership will be reviewed by the Director of JOHRP, and the Chair of the IRB to which the individual will be appointed. The individual will meet with the Director of JOHRP to discuss the responsibilities of IRB membership.

Potential board members who are Jefferson employees are expected to inform their department chairs or directors of the pending appointment.

3.1.2 **Unaffiliated Community Members**: Every effort will be made by the Director and/or Associate Director of JOHRP and the IRB Chairs to recruit individuals from the community who are not affiliated with Jefferson and whose family members are not affiliated. The review of qualifications and training of community members will follow the same procedures for affiliated members.

3.1.3 **Alternate Members**: Alternate members may be recruited, reviewed, and trained as described above for primary IRB members. The alternate member is formally appointed to the board and is listed on the IRB roster. The roster will present the required information about the alternate member in the same way as for the primary member. The IRB minutes shall document when an alternate member replaces a primary member and which member they are replacing.

The Jefferson IRBs tend to have more than five (5) members. Generally, any alternate may substitute for any primary member as long as the quorum and all other membership requirements are met. This does not apply to the assignment of reviewers. If a primary member has specific experience relevant to a particular study (e.g. prisoner advocate), the alternate should have similar expertise. As such, the rosters will not indicate specific individuals for whom the alternate may substitute. When alternates substitute for a primary member, the alternate member should have access to the same material as the primary member.

3.2 Recruitment and Appointment of an IRB Chair

The IRB Chair will be selected from current or past members of an IRB who have had significant experience in IRB issues and in the operation of a convened IRB meeting. The IRB chairs will be selected and appointed by the Director of JOHRP in consultation with the Associate Director of JOHRP and the Senior Research Compliance Officer.

3.2.1 Responsibilities of an IRB Chair: The chair is expected to have an in-depth understanding of the ethical principles of *The Belmont Report*, the *Declaration of Helsinki*, and the policies and procedures employed by the Jefferson IRB. They are expected to have a working knowledge of the federal rules and regulations that govern human subjects research.

3.2.2 The IRB Chair will:

- Direct the full committee meetings and strive to keep the discussion of protocols focused on substantive issues
- Vote on protocols unless a conflict of interest (COI) exists
- Work with the Director and Associate Director of JOHRP in establishing, implementing and monitoring compliance with JOHRP policy
- Will assign, in conjunction with the Director and Associate Director of JOHRP, two (2) IRB members as principal reviewers for new protocols and at least one primary reviewer for continuing review and amendments requiring full board attention. The assignments are based on the expertise of the reviewers
- Review all protocols submitted and contribute to the evaluation of a study with respect to risk, scientific and statistical merit, and standards of medical or surgical practice
- Evaluate the performance of each member, including the vice chair, on an ongoing basis
- Communicate with members to resolve important issues prior to meetings of the convened committee
- Assist JOHRP personnel in the drafting of IRB correspondence to researchers regarding IRB decisions

- If so delegated by the Director of JOHRP, review and sign IRB correspondence in a timely fashion

- Serve as a reviewer for research that qualifies for an expedited process. The Director and Associate Director of JOHRP and other designated IRB voting members may also conduct expedited reviews as appropriate

- Represent the IRB in defending or discussing IRB decisions with researchers

- In consultation with the Director or Associate Director of JOHRP, be empowered to suspend the conduct of a research project or clinical trial, pending IRB review, if they deem that participants are placed at unacceptable risk or determine that an investigator is not following JOHRP policies or procedures

3.2.3 At the discretion of the Director of JOHRP, the Chair:

- May be asked to represent the IRB in discussions with other offices at Jefferson

- May be asked to represent the IRB in discussions with federal authorities

3.3 Recruitment and Appointment of an IRB Vice Chair

The IRB Vice Chair will be selected from current or past members of an IRB who have had significant experience in IRB issues. The IRB Vice Chairs will be selected and appointed by the Director of JOHRP in consultation with the Associate Director of JOHRP, IRB Chair, and the Senior Research Compliance Officer.

3.3.1 The Vice Chair's duties are as follows:

- Chair the board meeting in the absence of the Chair

- At the discretion of the Director/Associate Director, assume additional duties of the Chair in the absence of the Chair

- Serve as a fourth reviewer for all new protocols, in addition to two (2) Board members and the Chair

- Attend protocol review assignment meetings
- Review transactions as assigned
- Evaluate the performance of each member on an ongoing basis.

3.4 Evaluation of Member Performance

IRB Member performance and membership needs are assessed on an ongoing basis at the IRB reviewer assignment meetings of the Chairs, Vice Chairs, and Director/Associate Director. The Director, Associate Director, or Chair/Vice Chair will meet with any member who wants to discuss their own performance, the performance of a Chair or Vice Chair or any IRB-related issue upon request.

Individual IRB member performance is also formally assessed typically once every two (2) years on a rotating basis at the reviewer assignment meetings (one (1) or two (2) members at each meeting) by the following criteria:

- Meeting attendance record
- Quality of reviews
- Meeting participation and oral presentation skill

Feedback is provided to the members by the Director/Associate Director of JOHRP or Chair/Vice Chair of the relevant board and the evaluation is kept on file in the office of the Director of JOHRP.

The Chairs and Vice Chairs are also evaluated on an on-going basis at the IRB reviewer assignment meetings with the Director and Associate Director. There is ample time at these meetings to discuss any general board issues or specific issues related to the conduct of board meetings. Chairs and Vice Chairs are also evaluated by the Director and Associate Director through observation of how full Board meetings are conducted. The Director and Associate Director are voting members of all Jefferson Boards and attend meetings regularly.

To monitor effectiveness, evaluations will be periodically revisited to assess whether IRB members have taken steps to improve performance as necessary. Lack of improvement may warrant a follow-up evaluation.

4. References

45 CFR 46.107
21 CFR 56.107(c)
JOHRP Policy OP 201, *Institutional Review Board Membership*
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research
Declaration of Helsinki

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 203: Institutional Review Board Consultants

1. Purpose

To describe the procedure for utilizing consultants to assist in Institutional Review Board (IRB) review of research.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Members
Consultants

2. Procedure

Per 45 CFR 46.107(e), an IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB (and are not counted toward quorum but may participate in the discussion).

The Director/Associate Director of JOHRP may determine that a consultant is needed for the review of a research study. This will usually occur at the time of reviewer assignment with consultation with the Chair/Vice Chair. Any IRB member may recommend that a consultant may be needed.

Consultants must have a completed confidentiality agreement and conflict of interest (COI) disclosure (see JOHRP Policy GA 106, *Conflicts of Interest*). Consultants who are not affiliated with Jefferson will also provide curriculum vitae (CV). Any prospective consultant with a COI will not be engaged for such reviews.

Appropriate study-related material will be provided to the consultant for review. For full reviews, IRB members will be notified at the convened meeting that a consultant has reviewed the study. The consultant may present the review. Pertinent comments/information will be incorporated into the meeting minutes and the consultant's written review of the study will be maintained on the IRB e-system.

3. References

45 CFR 46.107(e)
JOHRP Policy GA 106, *Conflicts of Interest*

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 204: Institutional Review Board Review of Protocols

1. Purpose

To establish the authority and composition of the Institutional Review Board (IRB) and describe the procedure for review and approval of an IRB submission.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Chairs/Vice Chairs

2. Policy

2.1 Policy Statement

The IRB is a Jefferson standing committee empowered to protect the rights and welfare of human research participants recruited to participate in research activities conducted under the auspices of the institution. Jefferson has three (3) separate IRBs which for ease of reference are referred to throughout the policy manual as the IRB. The IRB has full authority to approve, require modifications in, not approve, terminate, or suspend all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy.

As specified in 45 CFR 46.107(c) and 21 CFR 56.107(c), *IRB Membership*, each IRB shall consist of one (1) or more nonscientist members, one (1) or more unaffiliated members, and one (1) or more faculty in each of the areas of medicine/basic science/behavioral science where it is anticipated that protocols will be submitted such that the IRB will qualify for an unrestricted reviewing status from the Office of Human Research Protections (OHRP). All appointed members of Jefferson IRBs are voting members.

3. Procedure

A week prior to the IRB meeting, the Director of JOHRP, the Chair, and Vice Chair will meet and assign reviewers to all new studies, amendments, and continuing reviews requiring full board review. Two (2) primary reviewers are assigned for new studies, and at least one (1)

primary reviewer is assigned to each continuing review and amendment. Reviewers are chosen based on scholarly/scientific/appropriate expertise and IRB experience. Reviewers are expected to conduct an in-depth review of the study based on completion of a reviewer questionnaire.

If appropriate expertise is not available on a board, then expertise will be sought from another board or from an appropriate consultant as stipulated in JOHRP Policy OP 203, *Institutional Review Board Consultants*.

Documents pertaining to studies requiring review by the convened IRB, including initial review, continuing review, and modification to approved studies, are available on the IRB e-system one (1) week prior to the relevant convened meeting. Members who are not able to access the materials in the IRB e-system are sent the relevant documents by e-mail one (1) week prior to the IRB meeting. Documents for studies that qualify for expedited review are also available on the IRB e-system one (1) week prior to the relevant IRB meeting.

4. References

45 CFR 46.107(c)
21 CFR 56.107(c)
JOHRP Policy OP 203, *Institutional Review Board Consultants*

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 205: Institutional Review Board Member Responsibilities

1. Purpose

To define the responsibilities of Institutional Review Board (IRB) members.

1.1 Responsible Parties

Senior Research Compliance Officer
Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Members

2. Procedure

The primary responsibility of each IRB member is to review human subjects research to determine if it is ethically and scientifically sound and to protect the rights and welfare of human subjects. Each IRB member may be assigned to be the primary reviewer for a study. IRB members must have the appropriate expertise and training per JOHRP Policy GA 133, *Human Subjects Research Training*, and must remain unbiased.

The specific responsibilities of various IRB members are as follows:

2.1 Unaffiliated Members

Each IRB shall include at least one (1) 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 (45 CFR 46.107(c)). The role of the unaffiliated member is to advocate for the interests of the community as a whole.

2.2 Non-Scientific Members

Each IRB shall include at least one (1) member whose primary concerns are in non-scientific areas (45 CFR 46.107(b)). The primary role of the non-scientific members is to review the research, especially consent, from the perspective of the participant.

2.3 Scientific Members

Each IRB shall include at least one (1) member whose primary concerns are in scientific areas (45 CFR 46.107(b)). The primary role of the scientific members is to ensure that the research is medically and scientifically sound.

2.4 Chairs/Vice Chairs

The primary role of the chair is to facilitate the IRB meetings and to participate in assigning studies to the appropriate reviewers. The chair may initiate the suspension or termination of a study per JOHRP Policy RR 407, *Suspension or Termination of Human Subjects Research*. The Vice Chair, or another delegated, qualified member, assumes these responsibilities in the chair's absence.

2.5 Primary Reviewers

The primary reviewer must review all submission materials and present the review to the IRB. The review is maintained in the IRB e-system.

3. References

JOHRP Policy GA 133, *Human Subjects Research Training*
45 CFR 46.107
JOHRP Policy RR 407, *Suspension or Termination of Human Subjects Research*

Jefferson Office of Human Research Protection Policies and Procedures Manual

200 IRB Organization (OP)

Policy OP 206: Institutional Review Board Meeting Administration

1. Purpose

To provide the framework to ensure that the Institutional Review Board (IRB) meetings are conducted and documented in a manner consistent with federal and institutional policies.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Chair/Vice Chair

2. Policy

2.1 Policy Statement

Except when using expedited or exempt review procedure, the IRB will review proposed research at a convened meeting at which a quorum is present. (45 CFR 46.103(b)(4); 45 CFR 46.108).

2.2 Policy Specifics

2.2.1 JOHRP personnel will check applications for review for inclusion of all relevant forms and IRB and the Health Insurance Portability and Accountability Act (HIPAA) training status for all participating personnel listed in the IRB e-system. Incomplete applications will not be accepted or distributed for review.

2.2.2 IRB Meetings and Materials Sent to Members Prior to the Board Meeting:

Yearly schedules for each IRB will be published and distributed to all IRB members and posted on the JOHRP website. All materials for review are available one (1) week prior to the relevant convened meeting. Members who are unable to access the materials electronically are sent the relevant documents via email one (1) week prior to the convened meeting. It is expected that all IRB members will review all provided materials in enough depth to be able to discuss the information at the convened meeting. A member wishing to obtain additional materials provided to the primary reviewer(s) may request that information from the administrative secretary of that IRB.

Documents provided to all IRB members include:

- Meeting agenda
- Master application
- Proposed informed consent document
- Continuing review/renewal material
- Any amendments
- Other pertinent documents such as questionnaires and recruiting advertisements

Primary reviewers of studies that are new requiring full convened board, that require continuing review, or require expedited review will receive the above items plus:

- The complete protocol for new/renewal applications
- A copy of the National Cancer Institute (NCI) generic consent document for central IRB (CIRB) oncology studies
- The Investigator Brochure for studies involving an investigational drug or biologic and/or any information pertaining to an investigational device

2.2.3 Primary Reviewers:

Primary reviewer(s) are assigned to provide in-depth review of new studies, continuing reviews, and amendments by completing the appropriate reviewer questionnaire and presenting the study to the committee. In general, two (2) IRB members are assigned to each new study, one (1) to each continuing review, and one (1) to each amendment. This number may be increased as necessary to add additional expertise to the review (JOHRP Policy OP 204, *Institutional Review Board Review of Protocols*).

2.2.4 Quorum:

A meeting cannot be convened until a quorum is achieved. A quorum is defined as the presence of greater than half of the total voting members of a Board. For example, if the Board's voting membership is 14, the quorum necessary to convene a meeting would be eight (8). If that same Board's voting membership is 15, the quorum would still be eight (8). The Board Analyst determines when a quorum is met, and the quorum number is documented in the meeting minutes.

Furthermore:

- An alternate member may attend in place of an absent regular member in order to fulfill the quorum requirements. The alternate member must be listed on the roster

- A quorum consists of regular and/or alternate members and must include at least one (1) member whose primary concerns are in scientific areas and one (1) non-scientist voting member who represents the general perspective of research participants. The non-scientist contributes to quorum and may be either affiliated or non-affiliated. Also see JOHRP Policy OP 201, *Institutional Review Board Membership*

- When U.S. Food and Drug Administration (FDA) regulated research is reviewed, one (1) member who is a physician must be present

- The presence of a consultant may not be added toward a quorum

- If a quorum is temporarily lost during a meeting, no further votes can be taken until it is regained

- If a quorum is permanently lost during a meeting, the meeting will be adjourned

- When the convened IRB reviews research involving prisoners, a prisoner representative will be present

- If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, one (1) or more individuals who are knowledgeable about or experienced in working with such participants must be present

2.2.5 Meeting Minutes:

The Board Analyst assigned to the IRB, or a designee, will take the minutes of each meeting. The minutes will document the following items:

- The order in which the submissions were reviewed
- Actions taken by the IRB
- Separate deliberations for each action
- Meeting attendance, including status of any attendee who is not a regular member (alternate, consultant), any conflicts of interest (COI), and when an alternate member replaces a primary member
- Status of members (scientist, non-scientist, non-affiliated)
- Votes for each protocol as numbers for, against, and abstaining
- Who is absent during the vote and explanation of any conflicts that require the absence
- The basis for requiring changes in the research
- The basis for not approving the research
- Summary of the discussion of controverted issues and their resolution
- The approval period for initial and continuing review if it is not one (1) year
- References to federal regulations that justify the determinations for:
    - Waiver or alteration of the consent process (not required for exempt studies)
    - Research involving pregnant persons, human fetuses, and neonates
    - Research involving prisoners
    - Research involving children
- Information regarding the risk determination for research involving devices

- References to the rationale for the determination that a device poses significant risk (SR) or non-significant risk (NSR)

- If the research involves persons with impaired decision-making and/or adults unable to consent, the appropriate regulatory criteria have been met

- Names of members who leave the meeting because of a COI including COI as the reason for the absence

A copy of the final minutes will be retained in the IRB e-system. In addition, the final minutes will be made available to Board members upon request. The minutes will be retained as described in JOHRP Policy GA 121, *Jefferson Office of Human Research Protection and Institutional Review Board Document Management*.

2.2.6 Voting

2.2.6.1 Conducting a Vote

IRB members vote upon the recommendation of the primary reviewers according to the established criteria for approval stated above. Members will also determine:

- The level of risk, whether minimal or greater than minimal

- The length of the approval period. Unless otherwise determined by the members, the approval period will be one (1) year. Approval periods are no greater than one (1) year. Less than one (1) year will be noted in the minutes

- The necessity of monitoring of the investigative site

A majority greater than half of the voting members present must vote in favor of a motion in order for that motion to be carried out. Only regular members or alternate members attending the meeting in place of a regular member may vote (See Section 2.2.4). Any member with a COI with the study, including any member who will be involved in the conduct of the study, must absent themselves from the room during deliberation and voting on the study. This absence must be indicated in the minutes.

2.2.6.2 Motions for Voting

The IRB evaluates each proposal to determine if the criteria at 45 CFR 46.111 and other applicable regulatory requirements have been met. The IRB makes the decision to approve or not approve based on the *Guidance for IRB Voting Criteria* document. The IRB makes the following recommendations:

- Approve

  The IRB will recommend that a proposal is approved if no changes are requested or if the changes requested are consistent with those described in the "Motion to Approve" category of the *Guidance for IRB Voting Criteria* document. When this occurs, the site response to the requested changes will be reviewed by designated IRB personnel.

- Not Approve

  The IRB will recommend that a proposal is not approved if the changes requested are consistent with those described in the "Motion to Not Approve" category of the *Guidance for IRB Voting Criteria* document. When this occurs, the proposal must be revised, re-submitted in full, and reviewed by a convened IRB.

  If the IRB does not have enough information to deliberate, the IRB may defer a vote. Once the necessary information is obtained, the study must be reviewed by a convened IRB.

  In either case, the original reviewer(s) will be invited to provide comments as consultants if the study is subsequently reviewed by a different Board.

2.2.6.3 Reporting IRB Decisions to Researchers

See Section 3 of JOHRP Policy GA 113, *Institutional Review Board Reporting of Findings and Actions to Investigators*

3. References

The Common Rule (45 CFR 45)
JOHRP Policy GA 121, *Jefferson Office of Human Research Protection and Institutional Review Board Document Management*
JOHRP Policy OP 204, *Institutional Review Board Review of Protocols*
JOHRP Policy OP 201, *Institutional Review Board Membership*

JOHRP Policy GA 113, *Institutional Review Board Reporting of Findings and Actions to Investigators*
Guidance for IRB Voting Criteria

Jefferson Office of Human Research Protection Policies and Procedures Manual

300 Quality Assurance (QA)

Policy QA 301: Quality Assurance Program

1. Purpose

To establish a program of oversight of human research activities that:

- Involves audits to assess compliance with Jefferson policy, regulations, ethical principles, and Good Clinical Practice (GCP)
- Supports and further educates investigators and study personnel regarding policy, regulations, ethical principles, and GCP
- Ensures the rights of human subjects and data integrity are protected
- Creates a culture of responsible conduct of clinical research

1.1 Responsible Parties

Quality Assurance Personnel

2. Procedures

2.1 Site Audits

Routine Audits are selected using a risk-based approach taking into account the amount of external oversight. Some criteria for selecting studies for audit may include:

- Level of IRB review
- Phase 1 studies
- Pediatric studies
- Significant risk devices
- IND/IDE held by Jefferson employees

For Cause Audits are generated based on report or request reflecting significant concern regarding study activities, such as termination or suspensions, noncompliance, or unanticipated problems (UAPs). After assessing the information provided, Quality Assurance personnel will decide if an audit or other action is appropriate.

The audit checklist contains the items which may be reviewed during an audit.

The audit report is used to document compliance with Jefferson policy, regulations, ethical principles, and GCP, to further educate investigators and study personnel. The audit report is provided to Jefferson Clinical Research Institute's (JCRI) Education and Training group and Jefferson clinical research leadership.

The audit report findings are also used to assess opportunities for improvements to the Human Research Protection Program (HRPP) as a whole. As needed, the Jefferson Office of Human Research Protection (JOHRP) will make appropriate modifications to the HRPP including the revision of policies and forms, announcements, and website changes. The improvements will be reassessed through future audits.

Quality Assurance Program Audits are conducted at the direction of legal counsel and the resultant reports are confidential and privileged. Audit reports should be securely maintained and separated from study and regulatory documents such that they are not accessible by parties external to Jefferson. An audit certificate issued by the Quality Assurance Program indicating that an audit has taken place can be viewed by external parties. If the certificate does not meet an external party's needs, please contact the Enterprise Office of Legal Affairs for assistance.

Resolution of findings provided by the investigator are approved by Quality Assurance personnel. Any findings that are serious or continuing will be communicated to senior JOHRP personnel and University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues*, will be followed.

2.2 Corrective and Preventative Action (CAPA) Plan

For repetitive, systemic, and/or severe issues, a CAPA plan will be initiated.

The form with the deficiency documented will be sent to the responsible party, e.g. in the case of a research study, the Principal Investigator (PI). The responsible party should identify the root cause of the deficiency and provide a written plan for the correction of the existing issue and the prevention of future issues.

The responsible party or their designee must submit a written plan to address current findings and to prevent recurrence of the issue in the future. When the final CAPA has been approved by both parties, it is signed by the responsible party and JOHRP and Quality Assurance personnel.

2.3 Consent Observation

Consent observations may be done on a routine or for cause basis. The consent process with a study participant or a mock consent may be observed. The Consent Observation Form contains the items which are reviewed.

2.4 Audits of IRB Processes and Documentation

The IRB internal audit forms contain the items which are reviewed during an audit. The Quality Assurance Program will audit the following on an annual basis:

- IRB roster
- IRB minutes
- Exempt study IRB files. Note: Full and expedited IRB files are reviewed during Quality Assurance site audits
- JOHRP policies and procedures as necessary and non-JOHRP policies and procedures as requested

The Director of JOHRP, has the authority to implement and/or modify existing policies or procedures to ensure efficient, transparent operations that adhere to federal regulations and Jefferson policies or can recommend new policies and procedures to the Senior Research Compliance Officer for implementation.

Audits are conducted by the Quality Assurance Program at the direction of legal counsel and should not be shared externally.

2.5 Additional Responsibilities of the Quality Assurance Program

The Quality Assurance Program for the IRB includes:

- Addressing quality and compliance-related questions from Jefferson research staff
- Participating in educational sessions for Jefferson research staff

- Health Insurance Portability and Accountability Act (HIPAA) training
- Participation in any additional quality assurance and compliance initiatives, as needed

3. References

JOHRP Internal Audit Forms
University Policy 110.15, *IRB Review of Noncompliance Issues* (Internal Jefferson Link)

Jefferson Office of Human Research Protection Policies and Procedures Manual

300 Quality Assurance (QA)

Policy QA 303: Inspections or Audits by External Entities

1. Purpose

To ensure that the correct steps are taken before, during, and after an inspection or other external audit.

1.1 Responsible Parties

Investigators
Key Personnel
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Policy

The U.S. Food and Drug Administration (FDA) and other regulatory agencies have the authority to inspect investigator sites and Institutional Review Boards (IRBs).

3. Procedures

3.1 Preparing for a Regulatory Audit

Certain regulatory and/or accrediting agencies have authority to audit the operations of research sites and IRBs. Such agencies include FDA, the Office of Human Research Protections (OHRP), and others who may be authorized by regulations or agreement with Jefferson to audit specific documents and procedures. Sponsors or funding agencies of research may also have authority to audit research sites.

For external audits involving the FDA or OHRP, the following individuals must be immediately notified by the Jefferson Principal Investigator (PI) or their designee:

- Senior Research Compliance Officer
- Director of JOHRP
- Enterprise Office of Legal Affairs and Corporate Compliance Officer
- Department Chair

- Hospital Administration, if applicable

In addition, for sponsored research, the Jefferson PI or their designee shall notify the study sponsor, consistent with the terms of the study agreement, unless the regulatory agency directs otherwise. If the regulatory agency directs Jefferson to withhold such notice, the Jefferson PI or their designee shall immediately notify the Enterprise Office of Legal Affairs.

The FDA's Bioresearch Monitoring (BIMO) manuals Compliance Program Guidance Manual (CPGM) for Clinical Investigators and CPGM for Institutional Review Boards can serve as resources during preparation for audit.

3.2 Participating in an Audit

JOHRP personnel, investigators, and key personnel are expected to follow the procedures for the conduct of external and internal audits of specific studies or study sites. Please notify JOHRP as soon as possible if there is advanced knowledge of an inspection. Prior to being granted access to study-related documentation, inspectors or auditors should be asked to provide identification and proof of their authority or authorization to conduct the audit (e.g. FDA 482, *Notice of Inspection*). Copies of the FDA 482 should be made for retention at the site and sent to JOHRP. For site audits, the research team should ensure that the consent form correctly identifies the auditing agency as a party that will have access to PHI. The research team shall also be responsible for redaction of such information from files prior to the audit, if required.

Auditors will be escorted throughout the inspection while on Jefferson campus and provided with an adequate working area to conduct the audit. Jefferson personnel shall make every reasonable effort to be available and to accommodate and expedite any auditor's request.

Documents may be copied physically or digitally to be taken off-site by authorized individuals. A file containing a copy of the requested documents should be maintained by the office or site involved in the audit.

Daily audit/inspection updates should be sent to the Quality Assurance Program of JOHRP for all studies and to the Quality Assurance & Education group of SKCCC for oncology studies. These updates should include questions asked by the auditor/inspector, who was interviewed, which documents were requested, and any other pertinent information.

3.3 Follow-up After an Audit

Reports resulting from the audit requiring an official response, either verbal or written, should be addressed by the PI, the Director of JOHRP, or other appropriate individuals, as soon as possible after the report is issued.

Designated personnel will review the results of the audit to determine if any further action is required. If the audit showed serious or continuing deviations from protocol and/or adherence with regulations the site must inform JOHRP immediately, JOHRP may find it necessary to initiate a non-compliance investigation. JOHRP will also use the audit results to evaluate the human research protection program (HRPP) to determine if any modifications are necessary.

The regulatory agency will issue the final report (e.g. FDA Establishment Inspection Report (EIR)) and may require actions similar to the following that are issued by FDA: Official Action Indicated (OAI), Voluntary Action Indicated (VAI), No Action Indicated (NAI). Possible consequences of an OAI finding include study hold, re-inspection, rejection of study data, warning letter, and/or restriction/disqualification of investigator.

All OAI reports should be submitted immediately to JOHRP for review prior to submitting response to the auditing agency.

4. References

Compliance Program Guidance Manual for Clinical Investigators
Compliance Program Guidance Manual for Institutional Review Boards

Jefferson Office of Human Research Protection Policies and Procedures Manual

300 Quality Assurance (QA)

Policy QA 304: Study Team Training

1. Purpose

To describe the process for conducting and documenting training of the Principal Investigator (PI), Co-Investigators (Co-Is), and other designated individuals who participate in the conduct of human subjects research.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
PI
Key Personnel

2. Policy

This policy pertains to all investigators, key personnel, and other designated individuals who are involved in supervising, managing, or conducting human subjects research within Jefferson.

The PI at each site assumes the responsibility for the conduct of a clinical study and the protection of human subjects and has the authority to delegate portions of that responsibility to other key personnel. They are responsible for ensuring that key personnel to whom those responsibilities are delegated also are qualified by training and experience to perform their study-related duties.

All personnel are responsible for taking the appropriate training to conduct study-related duties, document training, and demonstrate they can apply training in the conduct of their duties.

3. Procedures

3.1 PI's Employee Training Plan

Jefferson complies with federal directives to educate key research personnel by requiring those personnel to complete a formal program of training on federal and Jefferson policies and procedures pertaining to the conduct of human subjects research.

The PI will ensure that all study personnel on human subjects research studies complete mandatory initial and on-going Jefferson training programs regarding the ethically and scientifically sound conduct of human subject research.

Training of key personnel concerning a specific research study will be scheduled and supervised by the PI and/or their designee. The initial training program should familiarize key personnel with the development and specifications of the investigational products, including preclinical safety information, and pertinent regulatory requirements on conducting clinical studies in accordance with Good Clinical Practice (GCP).

Designated training staff on site or commercially sponsored courses may be used to provide this training. This training is to be distinguished from the human subjects training provided by the Collaborative Institutional Training Initiative Program (CITI). The training should consist of the following elements as appropriate to their position on the study:

- Standard operating procedures (SOPs)
- Investigational product development and specifications
- Drug chemistry and mechanism of action (or device design and development)
- Pre-clinical testing and results
- Safety profile and expected adverse events (AEs)
- Manufacturing/quality assurance process
- Investigational New Drug (IND) or Investigational Device Exemption (IDE) Process
- Applicable regulatory requirements (investigational product accountability, reporting requirements)
- Investigator Brochure
- Monitoring guidelines and procedures

- Protection of human subjects (IRB, informed consent, other internal or external regulatory groups)
- Study documentation and files
- Study design and conduct
- Protocol and case report form (CRF) development
- Entering information on the CRF
- Data collection, analysis, interpretation, and reporting

Jefferson staff who are responsible for assessing sites and investigators for inclusion in a clinical study, and for study monitoring, should receive training in the following areas:

- Investigator qualification and interviewing
- Facility and resources assessment
- Site initiation and training
- Investigational product accountability procedures
- Monitoring visit preparation
- Records inspection
- Monitoring report preparation
- Study closeout procedures

The PI should provide an appropriate period of time for new employees to cover the topics in this curriculum. New employee training must be completed before participating in the conduct of a clinical study or engage in contacts with study participants.

For continuing education purposes, the PI's designee should schedule ongoing in-house GCP and human subject protection updates, to be provided by the PI's staff or JOHRP as appropriate.

3.2 Site Team Training

Participating investigators and key personnel working on or overseeing research on human subjects should receive initial and ongoing training regarding the responsible conduct of research and SOPs.

All personnel will support required training activities by taking an active part in their own professional development in relevant content areas.

3.3 Documentation of Training

The PI will maintain copies of training program certificates of completion and all updated staff training records for all employees. The content of training should be maintained in the study records.

4. References

21 CFR 312
21 CFR 812
ICH E6 Guidelines for Good Clinical Practice (R3)
NIH Notice NOT-OD-16-148 Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials (September 16, 2016)

Jefferson Office of Human Research Protection Policies and Procedures Manual

300 Quality Assurance (QA)

Policy QA 305: Verification by Outside Sources that No Material Changes Have Been Made to an Institutional Review Board-Approved Protocol

1. Purpose

To define a policy and procedure as to how the Institutional Review Board (IRB) will make a determination whether outside verification is required to ascertain that no material changes have been made to an IRB-approved protocol without IRB notification.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Investigators
Key personnel
IRB members

2. Policy

2.1 Policy Statement

The need for outside verification could arise when a Principal Investigator (PI) is under special oversight by the IRB or a federal agency or has specific conflicts of interest (COIs) that require an increased amount of monitoring by the IRB and/or other institutional offices. There may be other situations to which this policy will apply.

3. Procedure

The Director or Associate Director of JOHRP will make a determination as to when outside verification will be required that no material changes have been made to an IRB-approved protocol.

For many situations, JOHRP's Quality Assurance Program will conduct an audit of the study in question. Quality Assurance Program will create a report for presentation to the Director or Associate Director of JOHRP.

In some situations, it may be more appropriate or expeditious for the IRB to identify an institutional or extra-institutional individual(s) who can provide verification of the status of a

particular study. The IRB may invite these individuals to a meeting to present or simply discuss the submitted report at a meeting. The IRB will also determine whether or not the PI will be notified of these reports.

The findings of the Quality Assurance Program and institutional or extra-institutional status reports may be shared with the PI who in this instance would be asked to provide to the IRB a written explanation of the discrepancies. If the discrepancies are systematic and/or substantial, the IRB may determine that a non-compliance hearing or other educational or remedial action is required. Also, if the discrepancies reveal a significant increase in risk to the participants, the IRB may require that the study be suspended or terminated.

Audits conducted by the Quality Assurance Program are at the direction of legal counsel and should not be shared externally.

4. References

21 CFR 56.10(a)(2)
45 CFR 46.108(a)(3)(ii)

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 401: Initial Review – Criteria for Institutional Review Board Review and Approval

1. Purpose

To address federal and ethical criteria that the Institutional Review Board (IRB) must apply when reviewing and approving research.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
IRB Members

2. Procedure

2.1 Review of Studies by Jefferson IRBs

The IRB Chair is responsible for providing on-going guidance during the meeting concerning the review and deliberative processes leading up to the vote on the study.

Primary reviewers must have scientific or scholarly expertise, or other knowledge that allows an in-depth initial review of the protocol submission and for making approval recommendations for consideration by the convened IRB. They should also ascertain whether any special considerations exist that may influence the review of the study, such as conflicts of interest (COIs) and whether third-party verification of the submitted information is necessary.

At the time of assignment of reviewers, if there is not at least one (1) person on the IRB with appropriate expertise or knowledge to conduct an in-depth review, the IRB defers protocol review to another meeting, another Jefferson IRB or obtains expert consultation.

The approval date is the date the IRB voted to approve with or without conditions. The expiration date of an approved protocol is one (1) day less than a year from the date of IRB approval. For approved protocols, the expiration date is the last date that the protocol is approved. The IRB may determine that an approval period of less than one (1) year is appropriate, depending on risk assessment. The approval period will be recorded in the meeting minutes and in the approval letter.

2.2 Review of Studies Involving Vulnerable Populations

When some or all the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards should be considered by the IRB to protect the rights and welfare of these participants. If research involves vulnerable participants, the IRB Chair, or the Director or Associate Director of JOHRP, will ensure that at least one (1) reviewer (or consultant if necessary) has the knowledge and scientific expertise to perform in-depth review of the protocol. The protocol may be reassigned to another board in order to ensure such expertise. If consultants are employed, even if from another Jefferson board, their comments and concerns will be noted in the minutes, but they may not vote on the protocol.

2.3 For initial review of research by a convened IRB, any additional information provided to an individual reviewer will be available to any IRB member who wishes to review it.

2.4 Criteria for Initial IRB approval for research (45 CFR 46.111 and 21 CFR 56.111)

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

- Risks to participants are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose participants to risk, and whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes

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

- Selection of participants is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children,

prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons

- Informed consent will be sought from each prospective participant or the participant's legally authorized representative (LAR), in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20

- Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.20

- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants

- When appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data

- When some or all the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these participants

The IRB will determine that researchers have the resources necessary to protect participants:

- Adequate time for the researchers to conduct and complete the research

- Adequate number of qualified staff

- Adequate facilities

- Access to a population that will allow recruitment of the necessary number of participants

- Availability of medical or psychosocial resources that participants might need as a consequence of the research

2.5 For initial review, the IRB determines:

- The Principal Investigator (PI) or their designee will obtain the legally effective consent of the participant or may obtain consent from the participant's LAR

- The circumstances of the consent process required to provide the prospective participant or their LAR sufficient opportunity to consider whether to participate

- The circumstances of the consent process required to minimize the possibility of coercion or undue influence

- Individuals communicating information to the participant or their LAR during the consent process will provide information in language understandable to the participant or their LAR

- Information being communicated to the participant or the representative during the consent process will not include exculpatory language through which the participant or their LAR is made to waive or appear to waive any of the participant's legal rights

- Whether additional disclosures are required for inclusion in the consent process

- Verifies that the consent process is appropriate for the study

2.5.1 When following Department of Health and Human Services (HHS) regulations:

- The IRB ensures that the required and appropriate additional elements of disclosure are included in the consent process

- To allow use of the long form of consent documentation, the IRB determines:

    - The consent document contains all the required elements

    - The participant or the participant's LAR will sign the consent document

    - A copy of the consent document will be given to the person signing the consent document

    - The researcher will give either the participant or their LAR adequate opportunity to read the consent document before it is signed

- To allow the use of the short form of consent documentation, the IRB determines:
    - The short form document states that the elements of disclosure required by regulations have been presented orally to the participant or their LAR
    - A written summary embodies the basic and required additional elements of disclosure
    - There will be an impartial witness to the oral presentation
    - For participants who do not speak English, the witness is conversant in both English and the language of the participant
    - The participant or their LAR will sign the short form
    - The witness will sign both the short form and a copy of the summary
    - The person obtaining consent will sign a copy of the summary
    - A copy of the signed short form will be given to the participant or their LAR
    - A copy of the signed summary will be given to the participant or their LAR

2.5.2 When following the U.S. Food and Drug Administration (FDA) regulations, the IRB determines:

- There is a statement noting the possibility that the FDA may inspect the records that will be provided to each participant
- There is a statement that the results of the research will be posted on ClinicalTrials.gov
    - A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website

will include a summary of the results. You can search this website at any time.

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

When a participant withdraws from a study, if any specimens are collected, the participant may have the option to request that specimens be destroyed on a per study basis.

A researcher may ask a participant who is withdrawing whether the participant 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 participant distinguishes 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 addresses the maintenance of privacy and confidentiality of the participant's information.

The researcher must obtain the participant's consent for this limited participation in the study, assuming such a situation was not described in the original consent document. The IRB must approve the consent document.

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

2.5.3 Waiver or alteration of the consent process/parental permission:

- The IRB may waive or alter the consent process by determining that the applicable regulatory criteria are met (45 CFR 46.116(f)(3))

- The IRB may waive parental permission by determining that the criteria for waiver are met at both 45 CFR 46.116(f)(3) and 45 CFR 46.408(c)

- The IRB may waive the requirement for written documentation of the consent process by determining that applicable criteria are met
- The IRB documents its findings in regard to the waivers or alteration
- When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information that will be provided to participants
- When granting waivers of the requirement to obtain written documentation of the consent process, the IRB considers requiring the researcher to provide participants with a written statement regarding the research

2.6 Review of Community Based Research

For review of research in which community members may be involved in research design, implementation, and dissemination of results, the IRB will:

- Include member(s) or a consultant with expertise in community-based research
- Require a description of the steering committee or other mechanism whereby community input is solicited and implemented
- Assess the quality and effectiveness of the steering committee at the time of continuing review and, if IRB, investigator/staff or member of the steering committee requests, review by the Quality Assurance Program will be initiated and feedback will be provided

The IRB reviewer conducts a demographic review at the time of continuing review and will request comments from the PI if there is concern regarding lack of diversity in enrollment.

2.7 Review of Department of Defense (DoD) Supported Research

See JOHRP Guidance G 620, *Department of Defense Requirements for the Conduct of Human Subjects Research*.

3. References

JOHRP *Consent Form for a Research Study*
JOHRP *Instruction Manual for the Consent Form for a Research Study*

JOHRP Policy GA 106, *Conflicts of Interest*
The Common Rule (45 CFR 46)
21 CFR 56.111
FDA-2018-N-2727, *Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations*
JOHRP Guidance G 620, *Department of Defense Requirements for the Conduct of Human Subjects Research*
21 CFR 50.20

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 402: Continuing Review by Convened Institutional Review Board

1. Purpose

To describe the process for the continuing review of research by convened Institutional Review Board (IRB) (i.e., "full" review).

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
IRB Members

2. Procedure

The IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to:

- The degree of risk
- The degree of uncertainty regarding the risk
- The vulnerability of the participant population
- Whether the study involves novel therapies

Continuing reviews occur at least annually, except as described in this policy. The IRB will maintain records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require it as described in this policy.

The assigned IRB reviewers(s) will present the full continuing review for discussion and vote at a convened Board meeting. The IRB will make the recommendation to approve or not approve as described in JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*.

2.1 Determination of the Need and Interval for Continuing Review

Active studies must have current IRB approval. To maintain this approval, the IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to degree of risk, not less than once per year, except as described:

Unless an IRB determines otherwise, continuing review is not required for the following research:

1. Research determined to be eligible for expedited review

2. Research that is exempt from the Common Rule (45 CFR 46)

3. Research that has progressed to the point that it involves only one (1) or both of the following, which are part of the IRB-approved study:

    a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

    b. Accessing follow-up clinical data from protocol-specific procedures that participants would otherwise undergo as part of clinical care.

2.2 Submitting Continuing Review Materials to the IRB

Research-related activities may not occur in the absence of IRB approval except where necessary to eliminate apparent immediate hazards to the human subjects. To maintain active IRB approval, an investigator must submit the Continuing Review or Final Report form with all associated materials to the IRB. This must be done until the study ends or until it is determined that continuing review is no longer required. Investigators are sent automated emails prior to the study expiring. The continuing review ideally should be submitted at least six (6) weeks before the current expiration date to avoid lapse in approval. If a Continuing Review form is not submitted before the expiration date, a termination notice ultimately will be issued.

If the continuing review is not approved prior to the expiration date, enrollment and other research related activities must cease. If the investigator, in conjunction with the IRB, determines that the participants on the study would suffer a hardship if study-related medical care were discontinued, appropriate medical care may continue beyond the expiration date for a reasonable amount of time provided that the investigator is in the process of submitting a continuing review. However, the data collected during this period of lapsed IRB approval may not be used for research purposes without IRB approval.

To re-open an expired study, a Continuing Review form with all associated materials must be submitted to the IRB and receive approval. If an expired study has been completed, a Final Report form should be submitted.

2.3 Extension of IRB Approval Period

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date will not be granted. The only way to reactivate an expired study is to submit a Continuing Review form.

2.4 Suspension of IRB Approval

IRB approval for the conduct of a study may be suspended at any time if the IRB determines that protections of human subjects have been compromised or if risks have reached an unacceptable level. Some examples of reasons for the IRB suspending a study are:

- A greater than expected number of adverse events (AEs), unexpected serious adverse events (SAEs) or unanticipated problems (UAPs)

- Evidence that the investigator is not conducting the research in compliance with federal, Jefferson, or IRB policies.

2.5 Continuing Review

The purpose of the continuing review is to review the accumulated research data from the previously approved period according to all applicable regulatory criteria. The information submitted on the Continuing Review form and associated documents are reviewed by one (1) or more IRB members with appropriate expertise.

Continuing review includes, but may not be limited to the following activities:

2.5.1 Site Visits and Third-Party Verification

The IRB has the authority to observe, or have a third party observe, the consent process and the conduct of research it has approved, verifying that the study is being conducted as per the protocol approved by the IRB and according to federal and local regulation.

2.5.2 Review of Serious Adverse Events (SAEs) and Unanticipated Problems (UAPs)

The investigator is responsible for submitting SAEs and UAPs to the IRB as described in JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*. The policy describes which

SAEs and UAPs must be submitted to the IRB for immediate review, and which are included in the continuing review. The IRB reviews the SAEs, UAPs, and other requested safety information included with the continuing review to determine if the risk profile has changed and if additional protections or actions are necessary to ensure adequate protection to research participants.

Researchers are obligated to report to participants any new findings that arise from the IRB review process that may affect their willingness to continue participation in the study.

2.5.3 Significant New Findings

During the course of an approved study, the IRB may review reports generated from data safety monitoring boards, sponsor communication, adverse events, current literature and other sources to determine if:

- The risk determination of the research has changed
- The risk/benefit ratio is still acceptable
- New information needs to be conveyed to the participants
- A segment of the population may be bearing an undue burden of research risk

2.5.4 Reports from Investigators, Key Personnel, and Employees

It is the responsibility of all employees, investigators, and key personnel to promptly report to JOHRP any findings, results, occurrence or new information about an active study involving human subjects research that could affect the rights and welfare of the participants. JOHRP will act on any such information in order to protect the research participants. Based on any new information, the IRB may determine that the informed consent form requires revisions.

2.5.5 Reports of Alleged Non-Compliance with Federal Regulations at the Common Rule (45 CFR 46)

All reports of inappropriate involvement of human subjects in research from any source will be received and reviewed by the Director or Associate Director of JOHRP. All reports of alleged non-compliance with federal human subjects

regulations deemed to be credible will be handled according to University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues*.

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with IRB policies, is not in compliance with federal regulations, or has been associated with serious harm to participants or others. Suspensions or terminations of research: 1) funded by any federal agency signed onto the Common Rule, or 2) regulated by FDA shall be reported by the Director of JOHRP, to the Office of Human Research Protections (OHRP) and/or the FDA as appropriate.

2.5.6 Verification from an External Source that No Material Changes have Occurred Since the Previous IRB Approval

If the IRB determines it needs verification from sources other than the Principal Investigator (PI) that no material changes have occurred since the previous IRB approval, the IRB may request an independent assessment of information or data provided in the continuing review. Sources could include copies of FDA or sponsor audits, site visits conducted by authorized personnel, reports from participants or study staff, or an audit requested by the IRB. If the necessity arises, the scope and extent of such an independent assessment will be determined on a case-by-case basis by the IRB.

3. References

The Common Rule (45 CFR 46)
JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*
University Policy 110.15, *Institutional Review Board Review of Noncompliance Issues* (Internal Jefferson Link)
JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 403: Exempt Studies

1. Purpose

To define the requirements for classifying a study as exempt from Institutional Review Board (IRB) review, and the procedure for making the determination and conducting the review.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
IRB Members

2. Procedure

Exempt studies do not require continuing review by the IRB. A new study may be designated as exempt from Common Rule requirements, including IRB review, provided it meets one (1) of the criteria cited in 45 CFR 46.104. The specific categories and other criteria for exemption are cited in the master application in the IRB e-system.

The investigator cannot make the final exemption determination, as this falls within the purview of the IRB. An IRB reviewer is assigned the application for review and makes the final exemption determination. The assigned reviewer cannot have a conflict of interest (COI) in the study in order to review it and make the exemption determination. The Principal Investigator (PI) is notified of the exemption determination. The exemption determination is recorded in the IRB exemption letter.

Research for which ‘limited IRB review’ is a condition of exemption is specified in the master application, and applies to exemption categories 2, 3, 7, and 8. However, Jefferson does not intend to conduct research under categories 7 and 8, nor does it intend to implement broad consent as defined in the Common Rule (45 CFR 46). Thus, categories 6, 7, and 8 are not included in the master application. Under ‘limited IRB review’ per the Common Rule, the IRB makes an additional determination that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

Amendments to exempt research as well as notification of completion of the exempt research must be submitted to the IRB. The IRB maintains oversight of exempt studies by sending automated reminders from the IRB e-system to PIs annually querying whether the exempt study is still active and whether there have been any study-related events that the IRB should be informed about. This information is obtained through the Annual Check-In form that should be submitted by the PI. The Quality Assurance Program of JOHRP also performs annual internal audits of select exempt studies.

Exempt studies, while not within the purview of the Common Rule regulations, are held to Jefferson's ethical standards. The following standards are evaluated by the JOHRP reviewer based on review of the pertinent submission documents.

- The activity involves research
- The research poses no more than minimal risk to participants
- Selection of participants is equitable
- Privacy of participants is maintained
- Adequate provisions are in place to maintain confidentiality of identifiable information (Jefferson's Privacy Officer may be consulted as needed concerning adequacy of plans to protect the identifiers from improper use or disclosure)
- If there are interactions with participants, the IRB will determine that:
    - Consent process is adequate
    - Participation is voluntary
    - Name and contact information for the researcher is provided
    - There is a description of procedures

3. References

The Common Rule (45 CFR 46)

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 404: Expedited Review of New and Continuing Research

1. Purpose

To define the expedited review procedure for new studies and continuing reviews.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
Institutional Review Board (IRB) Members

2. Procedure

2.1 Determination and Processing of Expedited Review

JOHRP personnel use the Office of Human Research Protection (OHRP) guidance document *Categories of Research that may be Reviewed by the Institutional Review Board through an Expedited Review Procedure* (November 1998) to determine if a study meets the criteria for expedited review. The rationale for designating a study as expedited is that all study procedures fall within these categories and the study qualifies as minimal risk. Minimal risk means that 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.

An IRB may use the expedited review procedure to review the following:

- Research encompassed in the categories in the OHRP guidance, unless the reviewer determines that the study involves greater than minimal risk

- Minor changes in previously approved research during the period for which approval is authorized

- Research for which limited IRB review is a condition of exemption (JOHRP Policy RR 403, *Exempt Studies*). Under limited IRB review, the IRB makes an additional

determination that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data

- Studies determined to meet the criteria for expedited review will be reviewed by the Director, Associate Director of JOHRP, Chair, Vice Chair and/or designated IRB members as appropriate. All expedited reviewers will be trained by senior JOHRP personnel. The reviewers will receive the same materials that a primary reviewer receives (see JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*).

- In reviewing the application, the expedited reviewer will make the recommendation to approve or not approve the study. The reviewers may exercise all the authorities of the IRB except they cannot disapprove of the research. The comments are provided to the investigator/study personnel.

  Note: “Disapprove,” as used in the Common Rule, is to be distinguished from “Not Approve”, a Jefferson-specific term. Disapprove indicates a final decision, whereas Not Approve is a temporary action accompanied by reviewer comments provided to the investigator, who can resubmit a revised submission.

  A research activity may be disapproved only after full board review. If, in the opinion of the reviewer, the study should be disapproved (as the term is used in 45 CFR 46.110), the study must be re-submitted in full, and reviewed by a convened Board.

All expedited transactions are documented in the minutes of each meeting. The Board is not required to vote on these items. They are documented for information, auditing and record-keeping purposes only. When an expedited study is approved, an approval letter and stamped materials are released to the Principal Investigator (PI), and the study may begin.

At the time of initial review and approval of an expedited study, the study may be designated for no further continuing review (NFCR) as per 45 CFR 46.109(f)(1)(i), unless the IRB reviewer feels there is a reason to require a continuing review. If this is the case, the reviewer should document the reasons on the IRB reviewer questionnaire. The approval letter will indicate that the expedited study has been approved for a defined period of time and will include the expiration date.

The IRB maintains oversight of NFCR studies by sending automated email reminders to PIs for the purpose of prompting the PI to submit an annual check-in that obtains

information about whether the study is still active and whether there have been any study-related events that the IRB should be informed about. The Quality Assurance Program of JOHRP also includes NFCR studies in their site audits.

3. References

Categories of Research that may be Reviewed by the Institutional Review Board through an Expedited Review Procedure (November 1998)
JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*
The Common Rule (45 CFR 46)
JOHRP Policy RR 403, *Exempt Studies*

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 407: Suspension or Termination of Human Subjects Research

1. Purpose

To define the process for suspending or terminating an approved research study.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Institutional Review Board (IRB) Members

2. Policy

2.1 Definitions

- **Suspension of IRB Approval**: A temporary halt in IRB approval of some or all research activities of a given study.

- **Termination of IRB Approval**: A permanent halt in IRB approval of all research activities of a given study.

3. Procedure

Per 45 CFR 46.113, *Suspension or Termination of IRB Approval of Research*, an IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator and appropriate institutional authorities within five (5) business days. For studies under the Department of Health and Human Services (HHS) and/or U.S. Food and Drug Administration (FDA) requirements, suspension or termination of approval shall be reported to the Office of Human Research Protections (OHRP) and/or FDA within 30 days.

Reasons for suspension or termination include, but are not limited to:

- Research is not being conducted as approved by the IRB

- Research is not being conducted according to regulations or IRB policy
- Unexpected harm to research participants
- Research misconduct issues

If there is a suspected reason for suspending or terminating a study, additional information may have to be collected. This may include an audit by the Quality Assurance Program of JOHRP.

Suspensions and terminations may be determined by a convened IRB, the Director or Associate Director of JOHRP, or an IRB Chair or Vice Chair in consultation with the Director or Associate Director. JOHRP will notify the investigator in writing of the decision and rationale, as well as any study-related processes that may continue. The investigator will have the opportunity to respond in writing or at the IRB meeting when the issue is reviewed. If a convened IRB did not make the determination to suspend or terminate a study that originally received full review, the action must be reported to a convened IRB for review.

When a study is suspended or terminated, the Principal Investigator (PI) must submit a plan to JOHRP. The plan must address the following:

- The method and timeframe for notifying participants
- Plans to protect the rights and welfare of participants which may include:
    - Transferring participants to another site/investigator
    - Clinical care outside of the research setting
    - If permitted by JOHRP, continuing necessary research activities
    - Follow-up of participants
    - Withdrawal from the trial in an orderly fashion, including any appropriate safety testing or procedures
    - Notifying participants of adverse events (AEs) or new safety information as appropriate

4. References

45 CFR 46.113

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 408: Review of Amendments

1. Purpose

To define the review procedure for amendments to an approved research study.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
Institutional Review Board (IRB) Members
Investigators

2. Procedure

Changes in a study may not be initiated without prior IRB approval of an amendment to the protocol, consent form, and/or other study materials except where necessary to eliminate immediate apparent hazards to participants. If such an exception to the rule is utilized, an amendment must be submitted to the IRB as soon as possible.

2.1 Submission of Amendments

An amendment to a study is to be submitted to JOHRP as a completed Amendment to Research Protocol form, containing a summary of pertinent changes. If protocol modification is initiated without prospective IRB review to eliminate apparent immediate hazards to a participant, it must be reported to JOHRP within three (3) working days.

2.1.1 Amendments include, but are not limited to, changes in:

- Aims that affect the design of the study or a sub-study
- Study design
- Randomization methods
- Recruitment sample size

- Recruitment practices
- Eligibility/exclusion criteria
- Data collection methods or instruments
- Data collection or visit schedule
- Interventions or treatments
- Risk or Benefit to the participant

2.2 Receipt of Amendments

Amendments for studies are submitted to the IRB e-system where JOHRP personnel will preview the amendment and determine the level of review.

2.3 Convened Review of Amendments

Amendments requiring convened Board review will be assigned a primary reviewer by the reviewer assignment committee for review at the next Board meeting. If possible, the chosen reviewer will be one (1) of the original reviewers of the study. If both original reviewers are no longer IRB members, the reviewer chosen for the amendment will be a current Board member.

All members of the reviewing Board will receive the Amendment to Research Protocol form and all modified materials. All materials and documents submitted for review are posted on the e-system one (1) week prior to the IRB meeting. The assigned reviewers and all Board members have access to all materials posted.

The Primary Reviewer(s) will be present and discuss the amendment at the convened meeting of the Board.

The following categories of amendment must receive convened IRB review:

- Amendment changes risk/benefit ratio of study
- Amendment substantially alters science of study
- Amendment provides new information that may affect a participant's decision to continue participation

The following can also be considered when making the determination:

- Is enrollment open or closed?
- Are participants currently receiving treatment?
- Is the amendment to be implemented at Jefferson, or is it being submitted for administrative purposes only?

Minor modifications do NOT include the addition of procedures that:

- Involve more than minimal risk, or
- Do not fall into categories 1-7 of research that can be reviewed using the expedited procedure.

2.4 Approval of Amendments

The recommendation to approve or not approve will be made as described in JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*. A formal approval letter for the amendment will be released to the investigator along with an IRB-approved revised consent form, if consent form changes were required.

2.5 Expedited Review of Amendments

As cited in 45 CFR 46.110, an IRB may use the expedited review procedure to review certain types of research involving no more than minimal risk and for minor changes in previously approved research during the period for which approval is authorized. In conducting the review, the reviewer(s) may exercise all the authorities of the IRB except that the reviewer(s) may not disapprove an expedited amendment as the term is used at 45 CFR 46.110(b). In this case, the proposal must be re-submitted in full and reviewed by a convened Board.

Examples of minor amendments that can be reviewed using an expedited review include but are not limited to:

- The addition of research activities that qualify for exemption or fall under an expedited review category
- Advertising

- Reasonable increase or decrease in the number of participants
- Narrowing the inclusion criteria
- Broadening the exclusion criteria
- Changes to the dosage form (e.g., tablet to capsule or liquid) of an administered drug when the dose and route of administration remain constant
- An increase in the number of safety visits for the purpose of increase safety monitoring
- A decrease in the number of study visits, provided the decrease does not affect the collection of information related to safety evaluations
- Changes in remuneration
- Changes to improve the clarity of statements or to correct typographical errors, provided that the change does not significantly alter the content or intent of the statement
- The addition or deletion of qualified investigators
- The addition or deletion of study sites
- Minor changes specifically requested by other Jefferson committees with jurisdiction over research

All expedited amendments will be entered onto the agenda and minutes of the appropriate Board meeting for information, auditing, and record-keeping purposes only. As soon as an expedited amendment is approved, an approval letter and stamped materials are released to the Principal Investigator (PI), and the amendment may be implemented.

3. References

45 CFR 46.110
JOHRP Policy OP 206, *Institutional Review Board Meeting Administration*
JOHRP Policy RR 401, *Initial Review – Criteria for Institutional Review Board Review and Approval*

JOHRP Policy RR 402, *Continuing Review by Convened Institutional Review Board*

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 409: Study Completion

1. Purpose

To provide information to individuals conducting human subjects research regarding how to close out a study after completion of all aspects of the study.

1.1 Responsible Parties

Principal Investigator (PI)
Study Personnel
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Policy

2.1 Policy Statement

This policy describes the procedure whereby an investigator must notify the Institutional Review Board (IRB) when a human subjects research study has been completed.

3. Procedures

3.1 Studies Involving Participants

Study completion means that all activities involving study procedures, participant follow-up, and/or analysis of identifiable patient information, including any access to patient records for data confirmation, have been completed. Upon study completion, the PI must submit, in a timely manner, a final report to the IRB using the Final Report form. The investigator must complete the progress report section covering the entire period of the study so that the IRB will be able to determine the success of the study relative to the initial IRB approval. The final progress report should include a brief summary of the success/outcomes of the trial, success or failure of enrollment, retention problems, unanticipated problems (UAPs), impact of the research on standard of care, and potential future directions for the research.

If all requested documentation has been submitted, JOHRP personnel will review the IRB file for completeness and place the Final Report on the agenda for the next appropriate meeting of the convened IRB. The Final Report will be assigned to the Vice Chair of that IRB and be given expedited review. If the Final Report is considered to be complete and

approved by the Vice Chair, an acknowledgement of study closure will be issued to the PI. Approval of final reports are recorded in the minutes of the meeting.

3.2 Studies Declared Exempt

For completed exempt studies, submit a Final Report in the IRB e-system.

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 410: Review of Advertisements

1. Purpose

To provide directions for the review and approval of advertisements.

1.1 Responsible Parties

Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Institutional Review Board (IRB) Chair/Vice Chair
IRB Members

2. Procedures

The IRB will review advertising materials intended to be seen or heard by a prospective participant to solicit their participation, or to solicit interest from other healthcare workers in referring participants to the study.

The IRB need not review and approve listing of clinical trials on a web site or in a booklet when the system format limits the information presented to basic trial information such as:

- Title
- Purpose of the Study
- Protocol Summary
- Basic Eligibility Criteria
- Study Site Location
- How to Contact the Site for Further Information

The IRB or primary reviewer must review the information contained in the advertisement, and the mode of communication. No advertising may be used until the IRB or primary reviewer has approved it.

Any review of an advertisement should assure that the advertisement does not:

- State or imply a favorable outcome or other benefit beyond what is stated in the consent form and the protocol
- Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation
- Make claims, either explicitly or implicitly, that the drug, biologic or device is known to be equivalent or superior to any other drug, biologic or device
- Use terms such as “new treatment”, “new medication” or “new drug”
- Promise “free medical treatment” when the intent is only to say that the participants will not be charged for taking part in the investigation
- Inappropriately emphasize payment for participation (e.g., inappropriate use of dollar symbols, large font, etc.)
- Include any exculpatory language

These criteria apply to review of advertising materials at initial review, continuing review, and amendments.

Advertisements to recruit participants should be limited to the information necessary for prospective participants to determine their interest or eligibility. When appropriately worded, the following items may be included in the advertisement:

- The name and address of the investigator and/or the research facility
- The condition under study and/or the purpose of the research
- A summary of the criteria that will be used to determine eligibility for the study
- A brief list of benefits, if any, and any significant risks
- The time or other commitment required of the participant

- Total potential amount of payment, payment by visit, or other pertinent payment information

- The location of study and the person or office to contact to volunteer or for further information

Final copies of all advertising materials including print, audio copy or transcript and digital video or transcript must be reviewed by JOHRP before they are implemented.

3. References

Information Sheet: Recruiting Study Subjects, Guidance for Institutional Review Boards and Clinical Investigators (January, 1998)

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 412: Recruitment, Enrollment, and Payment

1. Purpose

To define the criteria the Institutional Review Board (IRB) will use to assess participant recruitment, enrollment incentives, and participant payment. The criteria support equitable selection, unbiased study personnel, and a non-coercive informed consent process by ensuring proper participant recruitment, advertising, and study related payments.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
IRB Members
Investigators
Key Personnel

2. Procedure

The IRB will use the following criteria to determine adequacy and acceptability of recruitment procedures, enrollment, and payment to participants.

2.1 Criteria applicable to recruitment:

- The inclusion/exclusion criteria
- The content, mode, and location of advertising about the study
- The setting in which the prospective participant is approached for recruitment
- The intended populations of prospective participants to be approached for recruitment
- Whether prospective participants are vulnerable to coercion or undue influence, by nature of their situation, social status, level of education, health status, cognitive ability, and other demographic categories of vulnerability

- Whether any payment or non-monetary incentive to participants seems reasonable and proportionate for the procedures the participant will undergo and the length of the study

- Whether the payment information is clearly explained in the consent form

Note: It is prohibited for a sponsor to compensate participants by offering a coupon for discount on the purchase price of investigational product once it receives marketing approval.

2.2 Criteria Applicable to Jefferson Investigators and Key Personnel

The following are not permitted:

- Enrollment incentive provision in a study contract

- Acceptance of or request for enrollment incentive by Jefferson, its investigators, or subcontractors

- Fees paid to the researcher or Jefferson that exceed the actual costs for recruiting human subjects

- Bonuses, milestones, or similar forms of additional payments to the researcher or Jefferson for timely, early, or over-enrollment of human subjects, for retention of human subjects, or for timely or early IRB approval

- Use by the sponsor of per participant payment rates that vary based only upon the number of human subjects enrolled, including increased per participant rates paid for over-enrollment of participants

- Extra-contractual benefits acquired by the researcher or Jefferson such as unrestricted research gifts, medical or office equipment, authorship rights, journal subscriptions, educational stipends, payment of conference fees, software, personal gifts, favors, or similar inducements provided in exchange for enrolling human subjects

- Payment of referral or finder's fees in exchange for the referral of patients or clients as prospective participants in human subjects' research

- Obtaining human subjects through recruitment firms and/or persons whose practices are not consistent with this policy

2.3 Criteria Applicable to Study Advertisements

The advertisement must not:

- State or imply an outcome or other benefits beyond what is outlined in the consent document and the protocol
- Include exculpatory language
- Overemphasize the payment amount by such means as larger or bold type or use of '$$' or other symbols
- Promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation
- Make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with labeling
- Use terms, such as "new treatment," "new medication," or "new drug," without explaining that the test article is investigational

The advertisement should be limited to the following information:

- The name and address of the investigator or research facility
- The purpose of the research or the condition under study
- A summary of the eligibility criteria
- A brief list of potential benefits to participants, if any
- Amount and frequency of payment
- The time or other commitment required of the participants
- The location of the research and the person or office to contact for further information

- Appropriate graphics

2.4 Participant Payment

The IRB should ensure that all payment to participants, including amounts and schedule, is described in the payment section of the consent form. Payment cannot be considered a benefit and reference to payments should not be made in the benefits section of the consent form.

The IRB will review payment information to ensure that it does not create undue influence on an individual to enroll or continue participation in the study and that it is appropriate to the study duration and procedures. This is especially important for pediatric studies where the payment is made to the parent and not the child-participant.

Payment should be prorated for visits/test completed. In general, payment should not be contingent on completion of the study and should not be excessively delayed.

2.4.1 Lotteries and Raffles

The IRB will review research involving the use of lotteries and raffles as incentive to participate.

The Commonwealth of Pennsylvania considers all forms of gambling to be illegal unless specifically accepted by law. Lotteries or raffles used in the context of providing incentives to research participants may be permitted under some circumstances. The IRB will determine, on a case-by-case basis, whether lotteries or raffles may be used to recruit research participants.

Research participant compensation should be equitable across all participants experiencing the same level of risk and/or inconvenience. In the case of lotteries or raffles, all participants may have an equal chance of receiving an incentive, but the resulting compensation for research participation is arbitrarily different. There is also concern that most people overvalue their likelihood of winning, and therefore, offering a large prize may present undue influence or coercion, undermining the process of informed consent. For these reasons, the use of lotteries and raffles in research is discouraged.

Researchers should explore all other options for distributing incentives equitably among research participants before proposing the use of lotteries or raffles. The IRB will always give preference to incentive structures providing small incentives

to all participants over those providing one (1) or several larger incentives to fewer participants.

The IRB will consider use of lotteries or raffles where the following criteria apply:

1. The study is no more than minimal risk. Lotteries and raffles as an incentive for participants should only be used in minimal risk studies.

2. Participation is limited to individuals 18 years of age or older

3. Incentive amounts and proposed method and timing of disbursement cannot be coercive or present undue influence. Incentive values should not be so high as to unduly induce individuals to participate in or stay enrolled in the study when they would have otherwise withdrawn. The dollar value of incentives must be low and proportionate to study involvement.

4. Compensation must be appropriate to the study population and commensurate to the level of effort and amount of time spent on the research tasks. For example, it is not appropriate to provide a chance of receiving a $1,000 bookstore credit to an undergraduate student in return for completing a 10-minute survey.

5. Cash cannot be distributed.

6. The study protocol, the informed consent, and all advertisements and recruitment materials must clearly define the incentives, the timing of distribution, the process for selecting recipients, and the definitive odds for receiving an incentive, e.g.

   There will be 100 participants recruited for this study. There will be 20 thank-you gifts randomly distributed. Each individual has a one-in-five chance of being randomly selected to receive a thank-you gift.

7. Eligibility for receipt of an incentive must not be contingent upon completing the study. All enrolled participants must be eligible.

8. The process for distributing incentives must not compromise the privacy of participants or the confidentiality of their data.

The IRB shall consult with the Enterprise Office of Legal Affairs as needed.

3. References

Jefferson Policy No. 200.39 *Solicitation* (Internal Jefferson Link)
Privacy/Confidentiality of Health Information - Corporate Policy, 134.01

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 413: Review of Research Involving Investigational Drugs and Devices

1. Purpose

To define the Institutional Review Board (IRB) submission and review criteria for human subjects research involving drugs and devices.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
IRB Members
Investigators
Key Personnel

2. Procedure

The investigator must complete and submit all required forms and documents to ensure that the IRB receives all pertinent information about the investigational drug/device.

These forms may include but are limited to:

- Summary of Interventional Human Subjects Research in the Master Application
- Drug/Device sections of the Master Application
- U.S. Food and Drug Administration (FDA), Investigational New Drug (IND), and Investigational Device Exemption (IDE) correspondence and documentation

If the research is being conducted under an IND/IDE, the investigator must provide the sponsor protocol or sponsor or FDA correspondence documenting the IND/IDE number.

If a study involves an FDA-regulated product, but no IND or IDE number is provided by the sponsor, the Principal Investigator (PI) must confirm that the research meets one (1) of the exemptions below. If none of these are met, then the sponsor must obtain an IND/IDE number.

Note that per 21 CFR 312.2(b)(6), a clinical investigation involving an exception from informed consent under 21 CRF 50.24 is not exempt from the requirements of 21 CRF 312.

2.1 IND Exemptions

2.1.1 Exemption 1

Per 21 CFR 312.2(b)(1), the clinical investigation of a drug product that is lawfully marketed in the United States is exempt if all the following apply:

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

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

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

iv. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in part 21 CFR 50

v. The investigation is conducted in compliance with the requirements of 21 CFR 312.7

Note: Per 21 CFR 312.2(b)(4), the FDA will not accept an application for an investigation that is exempt under this exemption category 1.

2.1.2 Exemption 2

Per 21 CFR 312(b)(2), A clinical investigation involving one (1) of the following in vitro diagnostic biological products:

- Blood grouping serum
- Reagent red blood cells

- Anti-human globulin

Is exempt if all the following apply:

a) It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure

b) It is shipped in compliance with 21 CFR 312.160

2.1.3 Exemption 3

Per 21 CFR 312(b)(3), a drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 21 CFR 312.160.

2.1.4 Exemption 4

Per 21 CFR 312(b)(5), a clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

2.2 IDE Determinations

The IRB reviews the Device Section of the Master Application to determine if the FDA regulations governing device research apply and if device is non-significant risk and meets the requirements for an abbreviated IDE.

Also, see JOHRP Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Non-Significant Risk*.

3. References

21 CFR 312
21 CFR 56
21 CFR 50
JOHRP Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Non-Significant Risk*

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 414: Institutional Conflicts of Interest

1. Purpose

To describe circumstances in which a research study must be reviewed by an external Institutional Review Board (IRB) due to an institutional conflict of interest (COI) in the study.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Principal Investigator (PI)
Conflict of Interest Committee

2. Policy

2.1 Background

There may be situations where Jefferson has a financial interest in a research study determined to be greater than minimal risk and to be conducted at Jefferson. In order to eliminate any real or apparent bias in the regulatory review and oversight for a study under these circumstances, the Jefferson IRB must divest itself of primary regulatory oversight for the study. This necessitates that the study be reviewed by an external IRB that will assume regulatory responsibility and oversight for the study for its duration. This IRB is deemed the “IRB of record”.

3. Procedures

The Conflict of Interest Committee makes all determinations regarding the existence of institutional financial conflicts of interest (FCOI) in human research studies. When the Committee makes this determination in regards to a specific study, the PI must first submit the study for IRB pre-review by an unaffiliated IRB member who will determine the risk designation of the study. An unaffiliated IRB member is an individual who holds a member position on a Jefferson IRB but does not have a relationship with Jefferson (i.e., is not an employee of Jefferson, is not affiliated with Jefferson, and does not have a family member (first degree relative) who is affiliated with Jefferson (See JOHRP Policy OP 201, *Institutional Review Board Membership)*. If the study is deemed minimal risk by an unaffiliated IRB member, it may be reviewed by an IRB at Jefferson. If the study is deemed greater than

minimal risk by the unaffiliated IRB member, it must be submitted to an external IRB that will serve as the IRB of record for the duration of the study. The external IRB will be one with which Jefferson has an established service agreement.

Jefferson will rely on the external IRB for the duration of the research study. The IRB Reliance agreement stipulates the allocation of responsibilities between Jefferson and the external IRB in regard to ensuring the study is compliant with all applicable regulations.

The IRB of record will communicate to Jefferson any important issues such as serious and/or continuing non-compliance, unanticipated problems involving risks to participants or others, and issues of non-compliance. Any necessary reporting to federal agencies will be accomplished as per the IRB Reliance agreement.

If an institutional FCOI is identified for a greater than minimal risk study after the Jefferson IRB has approved and assumed regulatory oversight for the study, the PI must submit the study to an external IRB as soon as possible, and in any case, no later than six (6) weeks from time of notification from the COI Committee that an institutional FCOI exists. The Jefferson IRB will continue to oversee the study until the external IRB has approved the study, at which point Jefferson's primary regulatory oversight for the study will cease.

4. References

JOHRP Policy OP 201, *Institutional Review Board Membership*

Jefferson Office of Human Research Protection Policies and Procedures Manual

400 Research Review (RR)

Policy RR 415: Undergraduate Research

1. Purpose

To differentiate between undergraduate student educational research projects and undergraduate student academic research projects and describe how undergraduate student academic research projects will be overseen and regulated.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Undergraduate Faculty

2. Policy

2.1 Background

In general, the primary aim of undergraduate student research projects is educational. This is to be differentiated from graduate and professional academic research, whose primary aim includes contributing to the body of academic and generalizable knowledge. Generalizable knowledge is knowledge that can be applied in diverse settings outside the confines of Jefferson. The Jefferson IRB follows the federal definition of human research stipulated in Department of Health and Human Services (HHS) regulations in The Common Rule (45 CFR 46) when determining whether research conducted at Jefferson falls within the purview of the Institutional Review Board (IRB) and thus requires IRB approval prior to initiation. Key to this definition is the concept of generalizability, which also can be gauged by the researcher's primary intention to publish or publicly present the research findings beyond the boundaries of the classroom or institution. As this usually is not the intention of undergraduate student research projects, this research usually does not fall under Common Rule oversight, and thus does not require IRB approval.

To clarify, undergraduate student research is not the same as "exempt" research. "Exempt" is a term specifically used in the Common Rule to designate research that does constitute human subjects research, but, because of the minimal level of risk that it imposes upon human subjects, does not need to comply with the Common Rule, and is

thus exempt from its requirements. Undergraduate student research, on the other hand, usually does not constitute human subjects research, as discussed above, and so the term “exempt” does not apply.

That being said, JOHRP believes that an iterative process for undergraduate student research is useful both from an educational as well as a compliance standpoint. The process is outlined below.

3. Procedure

The undergraduate student senior thesis project is considered academic research and is subject to this policy because it resembles an academic research study and represents the culmination of the undergraduate student’s training in a major. In contrast, research-type activity that occurs in the course of class or over several classes and that relies upon immediate proposition and enactment will be considered primarily as undergraduate student educational activity and will not be subject to this policy. The IRB will have discretion in making determinations that deviate from the above statements and may request that an OHR-35, *Checklist for Undergraduate Research Study,* be submitted where necessary to address special situations, specifically, determining which undergraduate student research projects constitute academic research.

The OHR-35 will act as a decision tool for faculty when determining whether the project will need formal IRB review.

3.1 Undergraduate Student Compliance in Academic Research

When involved in the conduct of academic research, undergraduate students should be aware they must conduct themselves in adherence with all Jefferson standards and policies regarding appropriate behavior, safety and integrity. In particular, undergraduate students must adhere to the JOHRP Policy GA 129, *Protection of Privacy Interests of Research Participants and Confidentiality of Participant Data*, as it pertains to collecting protected health information (PHI) from individuals for the purpose of conducting undergraduate student research.

Students also should be familiar with the basic principles of conducting ethical research, as embodied in *The Belmont Report*.

4. References

The Common Rule (45 CFR 46)
JOHRP Form OHR-35, *Checklist for Undergraduate Research Study*

JOHRP Policy GA 129, *Protection of Privacy Interests of Research Participants and Confidentiality of Participant Data*
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research

Jefferson Office of Human Research Protection Policies and Procedures Manual

500 Review Requiring Special Consideration (SC)

Policy SC 501: Determining Whether a Device Study Involves a Significant Risk or Nonsignificant Risk

1. Purpose

To distinguish between a significant risk (SR) device and a nonsignificant risk (NSR) device and to indicate the procedure the Institutional Review Board (IRB) must follow when reviewing studies involving such devices.

1.1 Responsible Parties

IRB Members
Principal Investigators (PIs)
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Policy

2.1 Policy Statement

The Investigational Device Exemption (IDE) regulations (21 CFR 812) describe two (2) types of investigational devices, SR and NSR. An "investigational device" is defined here as a device whose safety and/or effectiveness is being evaluated in a clinical trial and thus falls under the IDE regulations. Other devices being used in a clinical trial whose safety and/or effectiveness are not being evaluated do not fall under IDE regulations.

Investigational devices determined to be SR devices are governed by IDE regulations at 21 CFR 812.3. Investigational devices determined to be NSR devices are governed by the abbreviated requirements at 21 CFR 812.2(b).

The major differences regarding research involving these devices are in the approval process, in record keeping, and reporting requirements. NSR device studies do not require a submission of an IDE application to and approved by the U.S. Food and Drug Administration (FDA). Furthermore, sponsors and IRBs do not have to report the IRB approval of a NSR device study to the FDA. In NSR device studies, the IRB serves an essential function for the FDA by acting as its surrogate with respect to the review, approval and continuing review.

3. Procedures

3.1 The IRB Decision Process for a Device Study

The January 2006 FDA *Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies* provides guidance on how to determine the differences between SR and NSR medical device studies. It also contains an updated list of examples of significant and nonsignificant risk devices.

- What is a Significant Risk (SR) Device?

  Under 21 CFR 812.3 (m), a significant risk device means an investigational device that:

  - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant
  - Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant
  - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant; or
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant

- What is a Nonsignificant Risk (NSR) Device?

  An NSR device is one that does not meet the definition for a SR device.

3.2 IRB Review

3.2.1 Nonsignificant Risk Device Studies

If an investigator or sponsor proposes a study to the IRB that involves a NSR device, the IRB must review the study at a convened meeting.

The investigator or sponsor must provide the IRB with:

- An explanation of its determination of the device as NSR
- The rationale used in making its risk determination
- A description of the device

Investigator also should provide, as appropriate:

- Reports of prior investigations with the device
- Information about other IRBs and their determinations
- Any other information that an IRB would need to review and approve the study

The risk determination should be based on the proposed use of the device in the specific investigation and not on the device alone. The IRB must consider any potential harm that may result from the use of the device. The IRB may consult with the FDA for its opinion.

The IRB may agree or disagree with a sponsor's or independent investigator's initial NSR assessment. If the IRB agrees with the assessment that the study involves a NSR device and approves the study, the study may begin when the investigator receives the approval letter from the IRB. Submission of an IDE application to the FDA is not required.

If the IRB disagrees with the sponsor's designation of the device as NSR, the sponsor must notify the FDA that the IRB has made a SR determination. In this case the study can be conducted as a SR study only after the FDA approves an IDE and an IRB approves the study.

Once the NSR/SR decision has been made by the IRB, the IRB must determine whether the study should be approved. The criteria for approval are the same as those for any other FDA regulated study. Investigational Device studies require initial review at a convened meeting of the IRB. In some cases, a study involving an NSR device may qualify as minimal risk, in which case, the IRB may review the study under its expedited review procedure for further study review (21 CFR 56.110).

3.2.2 Significant Risk Device Studies

In deciding if a device to be employed in a study poses a significant risk, the IRB must consider the nature of the harm that may result from the use of the device. Studies where the potential harm to participants could be life threatening, could result in permanent impairment of a bodily function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent damage to body structure should be considered a SR device. If the participant must undergo a procedure as part of the investigational study, e.g., surgery, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

The FDA considers studies of investigational SR devices to present more than minimal risk and requires IRB review at a convened meeting. The FDA has the ultimate decision in determining if a device is SR. If a sponsor files an IDE with the FDA because it believes the device to be a SR and the FDA disagrees or does not accept SR designation, the FDA will return the IDE application to the sponsor and the IRB will be responsible for determining whether it represents a NSR device.

3.3 IRB Responsibilities following SR/NSR Determination

Following determination of SR/NSR status, the IRB will:

- Notify the sponsor and investigator of an SR decision
- Review the study according to the requisite criteria at 21 CFR 56.111 and 45 CFR 46.111
- Document the SR/NSR determination in the minutes of the convened IRB

The IDE status for the study is documented with a copy of the IDE approval letter from the FDA.

4. References

21 CFR 812
FDA *Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies* (January 2006)
21 CFR 56
45 CFR 46.111

Jefferson Office of Human Research Protection Policies and Procedures Manual

500 Reviews Requiring Special Consideration (SC)

Policy SC 503: Review and Approval of a Humanitarian Device Exemption

1. Purpose

To delineate the policy and procedure for Institutional Review Board (IRB) review, approval, and supervision of a proposal involving a humanitarian device exemption (HDE).

Humanitarian Use Devices (HUDs) are devices that are intended to benefit patients by treating or diagnosing a disease or condition that affects no more than 8000 individuals in the United States per year. The U.S. Food and Drug Administration (FDA) has determined the use of an HUD under an HDE is not considered research because of the high cost of conducting large-scale clinical trials for devices designed for small target populations, thus, there is no requirement for presenting the results of scientifically valid clinical investigations demonstrating effectiveness. However, sufficient information must be presented to the FDA to determine whether the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of illness or injury from its use.

Although use of an HUD under an approved HDE is considered clinical care and not research, FDA requires that the IRB review and regulate the clinical protocol, much as it would a research protocol.

1.1 Responsible Parties

IRBs
Principal Investigators (PIs)
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Policy

2.1 Policy Statement

An approved HDE authorizes the marketing of the HUD. However, an HUD may only be used in facilities where an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for the HUD must state that the device is an HUD and that, although federal law authorizes the device, the effectiveness of the device for the specific indication has not been demonstrated.

HDE applications do not have to be renewed by the FDA and are valid as long as the use of the device continues to meet the conditions of the HDE application. An IRB-approved HUD protocol does, however, require periodic continuing review for the duration of its use at the institution.

3. Procedures

3.1 Responsibilities of the IRB regarding HDEs

The IRB may consider the following items that are generally included in the HDE application:

- The generic and trade name of the device
- The FDA-assigned HDE number
- The date of the HUD designation
- Indications for the use of the device
- Description of the device
- Sponsor's determination that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of illness or injury from its use
- Demonstration that no comparable devices are available for that purpose and that the device could not otherwise be brought to market without receiving HUD status
- Any contraindications, warnings, and precautions for the use of the device
- Adverse effects of the device on health
- Alternative practices and procedures
- Marketing history
- Summary of studies using the device

The IRB must conduct both initial and continuing review of the HUD and monitor adverse events (AEs). Approval may be granted for a maximum of one (1) year. It may also be approved for a shorter period, depending on the perceived risk.

3.2 Initial Review

Initial IRB approval of the HDE application must be performed at a convened meeting of the IRB. The IRB need not approve individual uses of an HUD but may approve the use of the device without any restrictions as long as the use remains within the scope of the FDA-approved indication. Determination of significant/non-significant risk by the IRB is not required since the device is being used for clinical care.

Regulations do not require the use of an IRB approved consent form for HUDs, but a consent form may be required by the IRB. The IRB can also require that the investigator and the participant sign the Device Brochure to indicate that both parties have discussed the HUD and the participant has understood the use of the device and its potential risks.

3.3 Continuing Review

Continuing review must follow the requirement found at 21 CFR 56. The FDA has determined that the IRB may elect to conduct the review using expedited review procedures since the initial review was performed by a convened IRB and the use of the HUD within its approved indication(s) does not constitute research.

The use of an HUD outside its FDA approved indication(s) (e.g. in a clinical research trial for another indication) requires an IRB submission as per FDA regulations for an Investigational Device Exemption (IDE) 21 CFR 812 and JOHRP Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Nonsignificant Risk*.

If an HUD is used in an emergency situation that is not within the FDA approved indication(s), the regulations at 21 CFR 814.124 and JOHRP Policy GA 112, *Emergent Use of an Investigational Drug, Biologic, or Medical Device*, apply.

3.4 Adverse Events (AEs)

The IRB shall receive and review serious adverse event (SAE) reports from the investigator.

4. References

21 CFR 814
Humanitarian Device Exemption (HDE) Program, Guidance for Industry and Food and Drug Administration Staff

JOHRP Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Nonsignificant Risk*
JOHRP Policy GA 112, *Emergent Use of an Investigational Drug, Biologic, or Medical Device*
21 CFR 56
21 CFR 812

Jefferson Office of Human Research Protection Policies and Procedures Manual

500 Reviews Requiring Special Consideration (SC)

Policy SC 504: Populations Requiring Special Consideration (Pregnant Persons, Prisoners, Children)

1. Purpose

To define investigator and Institutional Review Board (IRB) requirements for populations requiring special consideration (45 CFR 46 Subparts B, C, and D).

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
IRB Members
Investigators
Key Personnel

2. Policy

2.1 Definitions

The definitions used are those found in The Common Rule (45 CFR 46).

3. Procedure

3.1 General Regulatory Requirements

Research involving pregnant persons, human fetuses, and neonates, prisoners, and children, requires additional protections most prominently defined in 45 CFR 46, Subparts B, C, and D. For federally funded research, the IRB will only approve research that satisfies the conditions of the applicable subpart sections and will extend these protections to all human research as applicable.

3.2 Pregnant Persons

Investigators and the IRB must ensure that research involving pregnant persons meets the requirements in 45 CFR 46 Subpart B.

Research not otherwise approvable per 45 CFR 46.204 or 45 CFR 46.205 but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting

the health or welfare of pregnant persons may be approvable if all the conditions of 45 CFR 46.207 are met.

The protocol must be reviewed for opportunities to reduce the risk benefit ratio for both the pregnant person and the fetus. The protocol should have clear plans for follow-up of the pregnant person up to and after delivery. The risks to the pregnant person and the fetus should be considered separately. The minutes of the IRB meeting should reflect the discussion regarding the protection of the pregnant person and the fetus.

For studies that enroll persons of child-bearing potential where there are potential risks to a fetus, the IRB and the investigator should consider necessary safeguards, such as frequent pregnancy tests, reliable means of contraception, and abstinence, that can mitigate these risks.

Consent requirements are as follows:

Studies with:	Requires the consent of:
Pregnant persons with minimal risk	The pregnant person
Pregnant persons with possibility of benefit only to the fetus	Both parents
Neonates	One (1) parent
Neonates of uncertain viability	One (1) parent
Non-viable neonates	Both parents (There are no surrogates or exceptions per protocol or waiver. Notes A and B below still apply)
Minimal risk or greater than minimal risk and possible benefit to the child	One (1) parent
Greater than minimal risk and no direct benefit to the child, or for studies involving serious health conditions	Both parents (see Notes A and B below)

Note A: When the consent of both parents is required, in general, if one (1) parent is deceased, unknown, not practically available, incompetent, incapacitated, or if one (1) parent has full legal responsibility, the consent of only one (1) parent is required.

Note B: If pregnancy is the result of incest or rape, the consent of the father is not required.

As applicable, the consent document must include a statement that the particular treatment or procedure may involve risks to the participant, and to the embryo or fetus if the participant is or may become pregnant, that are currently unforeseeable (45 CFR 46.116(c)(1)).

3.3 Human Fetuses and Neonates

Investigators and the IRB must ensure that research involving human fetuses and viable neonates meets the requirements in 45 CFR 46 Subparts B and D. Investigators and the IRB must ensure that research involving neonates of uncertain viability and nonviable neonates meets the requirements in 45 CFR 46.205.

Investigators and the IRB must ensure that in post-partum research and research involving the placenta, the dead fetus, or fetal material meets the requirements in 45 CFR 46.206.

Research not otherwise approvable per 45 CFR 46.204 or 45 CFR 46.205 but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of fetuses or neonates may be approvable if all the conditions of 45 CFR 46.207 are met.

3.4 Prisoners

Investigators and the IRB must ensure that research involving prisoners meets the requirements in 45 CFR 46 Subpart C.

This section includes procedures for research involving participants who are prisoners or may reasonably be expected to become prisoners at some time during enrollment.

In addition to the definitions found in 45 CFR 46, the Office of Human Research Protection (OHRP) has provided the following clarification regarding the definition of prisoners and parolees:

1. Parolees who are detained in a residential treatment center as a condition of their parole are considered prisoners for purposes of research taking place within that facility

2. Regardless of whether they are described as parolees or probationers, persons living within the community and sentenced to court-supervised monitoring or treatment are not considered prisoners

3. Persons wearing monitoring devices are generally not considered to be prisoners. However, situations of this type may require an analysis of the particular circumstances of the planned participant population

3.4.1 Composition of Institutional Review Boards where Prisoners are Involved.

In addition to other regulations governing the constitution of the IRB, when reviewing research involving prisoners, the IRB shall also meet the following specific requirements:

- A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board

- At least one member shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except when a study is reviewed by more than one (1) Board. Only one (1) Board needs to satisfy this requirement

The main scenarios that must be considered are:

- A participant now meets the definition of a prisoner after enrolling in a study not approved as a prisoner study

- A participant who meets the definition of a prisoner is proposed for enrollment in a study not approved as a prisoner study

In both scenarios the investigator must notify the IRB in writing as soon as possible. The IRB will then review the protocol again at its earliest opportunity according to 45 CFR 46 Subpart C and this policy.

If a participant now meets the definition of a prisoner after enrolling in a study not approved as a prisoner study:

The IRB can either approve the involvement of the prisoner–participant in the research in accordance with this policy or determine that the participant be withdrawn from the study. If it is determined that the participant be withdrawn from the study and, if the incarceration of additional participants is probable, the consent form should indicate that incarceration may result

in the termination of the participant's participation by the investigator without the participant's consent.

The IRB will determine one (1) of the following:

- IRB review and approval is not required if the research interactions and interventions, including the collection identifiable information, will not occur during the incarceration period.

- Approval of the continued participation of the participant if all applicable requirements will be met and there will be no significant increase in risk.

- Approval of research participation for non-prisoner participants but pending approval of participation for prisoner-participants until all applicable requirements are met including confirmation from OHRP that the proposed research falls within the categories of research permissible under 45 CFR 46.306. All study specific activities for the prisoner-participant, including the collection of data, must stop until all requirements are met.

- The prisoner-participant must be withdrawn from the study because it will not be possible to meet applicable requirements. When this occurs, plans should be made for safe withdrawal of the participant from the study.

NOTE: OHRP has allowed one important exception. If the Principal Investigator (PI) asserts that it is in the best interests of the participant to remain in the research study while incarcerated, the IRB Chairperson may determine that the participant may continue to participate in the research until the requirements of Subpart C are satisfied.

Before any Department of Health and Human Services (HHS) supported research involving prisoners can begin, the IRB must submit a certification letter to HHS through OHRP that the conditions in 45 CFR 46 Subpart C have been met. The certification letter must provide the following information:

- An IRB designated under the Federalwide Assurance (FWA) has determined the appropriate conditions have been met (45 CFR 46.305) and that the research falls within the permissible categories (45 CFR 46.306). OHRP does not require that the certification letter include a specific listing or rationale behind the IRB findings, but the IRB may wish to include a brief, protocol-specific explanation of the IRB's rationale for each finding.

- Which of the categories of permissible research involving prisoners in 45 CFR 46.306(a)(2) is applicable to the proposed research.

- A statement that indicates that the IRB was constituted as per requirements in 45 CFR 46.304. OHRP does not require that the certification letter include information about the manner in which the IRB fulfills the requirements of 45 CFR 46.304, but the name of the prisoner representative may be included.

- The IRB should submit the Subpart C Certification Form

- The IRB must inform the PI in writing that no prisoner-participants can be enrolled in the research until the letter from OHRP is received, acknowledging receipt of the prisoner certification letter and indicates the OHRP Secretary's determination that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

3.5 Children

Investigators and the IRB must ensure that research involving children meets the requirements in 45 CFR 46 Subpart D.

Note: The FDA has also adopted the provisions of Subpart D except for 46.408 (c) that pertains to the waiver of the consent provisions of 45 CFR, Subpart A.

NIH Research: For research involving children supported or conducted by the NIH, the *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects* (March 6, 1998) must be followed.

Research with children requires that the IRB carefully considers the risk and benefit to children involved in research. The IRB should have appropriate expertise to review pediatric research. The investigator should also have adequate experience to conduct pediatric research.

The IRB must find that the research meets the applicable requirements as follows:

- Research not involving greater than minimal risk (45 CFR 46.404).
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants (45 CFR 46.405).
- Research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406).
- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407).

3.5.1 Research Involving Wards of the State (45 CFR 46.409)

Per 45 CFR 46.409(b), if the research is approved for wards of the state, the IRB shall require the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. The individual serving as the advocate:

- May serve as an advocate for more than one (1) child.
- 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
- Is not associated in any way with the research, the investigator(s), or the guardian organization, except in the role as an advocate or member of the IRB

Requirements for permission by parents or guardians and for assent by children that must be followed are found in 45 CFR 46.408 and JOHRP Policy

IC 704, *Child Assent and Parental Permission for Participation in Research*. Signature requirements appear in the above table in section 3.2.

4. References

The Common Rule (45 CFR 46)
45 CFR 46 Subparts B, C, and D
NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (March 6, 1998)
Subpart C Certification Form

Jefferson Office of Human Research Protection Policies and Procedures Manual

500 Reviews Requiring Special Consideration (SC)

Policy SC 508: Pennsylvania and New Jersey Reporting Requirements

1. Purpose

To provide guidance on Pennsylvania and New Jersey state laws related to human subjects research.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Investigators
Key Personnel

2. Procedure

The Principal Investigator (PI) is responsible for following all applicable federal and state laws and Jefferson policies and must contact the Director or Associate Director of JOHRP for any necessary clarification. The Director or Associate Director of JOHRP will work with the Enterprise Office of Legal Affairs as needed to provide the necessary information to the investigator.

Jefferson Hospital Policies 113.58, *Human Immunodeficiency Virus (HIV) Testing* and 113.12, *Suspected Abuse, Neglect, Domestic Violence or Exploitation - Assessment And Management*, must also be followed as appropriate. Jefferson New Jersey policies 1104, *HIV Antibody Testing*, E202 *Child Abuse*, and E203 *Adult Violence*, must also be followed as appropriate.

2.1 Special Considerations Concerning Confidentiality Related to Required Disease, Abuse, and HIV Reporting:

2.1.1 Confidentiality of Records

Consent forms must include a statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained. Limits on confidentiality, including the Commonwealth of Pennsylvania's requirement for reporting of suspected child abuse or neglect, and reportable communicable and

infectious diseases including HIV/AIDS, must be clearly explained in the consent form, as applicable. For example, a phrase may be added to the appropriate section of the consent form as follows:

> Because this study involves questions regarding [child abuse][a reportable disease], you should be aware that the laws of the Commonwealth of Pennsylvania require healthcare professionals learning of suspected [abuse or neglect][disease/condition] to report it to the proper authorities.

2.1.2 Mandatory Reporting of Diseases, Infections, and Conditions

Researchers should be aware that the laws of Pennsylvania and New Jersey require health care professionals and health care facilities to report specific diseases, infections, and conditions to the Pennsylvania Department of Health, New Jersey Department of Health, or the appropriate local health authority in the required manner and timeframe (PA Code, Title 28, Chapter 27.2, et seq.; New Jersey Administrative Code, Title 8, Chapters 57 & 58).

The up-to-date list can be found on the Pennsylvania Department of Health, List of Reportable Diseases.

2.1.3 HIV/AIDS Related Considerations

No HIV-related test shall be performed without first obtaining the informed, documented, written consent of the participant or legally authorized representative (LAR). Any consent shall be preceded by an explanation of the test, including its purpose, potential uses, limitations, and the meaning of its results. (35 P.S. 7605)

Blinded HIV-related testing for purposes of research performed in a manner by which the identity of the test participant is not known and may not be retrieved by the researcher, is prohibited unless reviewed and approved by the IRB established by the Pennsylvania Department of Health.

Consent requirements for HIV-related tests shall not apply to the following:

i. The performance of an HIV-related test on a cadaver by a health care provider that procures, processes, distributes or uses a human body or a human body part, tissue, or semen for use in medical research, therapy or transplantation; or

ii. The performance of an HIV-related test for the purpose of medical research not prohibited by the Pennsylvania Department of Health if the testing is

performed in a manner by which the identity of the test participant is not known and may not be retrieved by the researcher.

Reference 35 P.S. 7601, et seq., for the complete regulations.

In New Jersey, participants may opt-out of HIV-related testing under the general written consent. (See Jefferson New Jersey Policy No. 1104).

2.2 Other Reporting Requirements

Healthcare providers in Pennsylvania and New Jersey are also required to report:

- Serious or imminent plans to harm oneself or another
- Suspected child neglect or abuse
    - Suspected child sexual abuse

3. References

Hospital Policy 113.58, *Human Immunodeficiency Virus (HIV) Testing* (Internal Jefferson Link)
Hospital Policy 113.12, *Suspected Abuse, Neglect, Domestic Violence or Exploitation – Assessment and Management* (Internal Jefferson Link)
Jefferson New Jersey Policy *HIV Antibody Testing*
Jefferson New Jersey Policy E202 *Child Abuse*
Jefferson New Jersey Policy E203 *Adult Violence*
PA Code, Title 28, Chapter 27.2, et seq.
New Jersey Administrative Code, Title 8, Chapters 57 & 58
35 P.S. 7605
35 P.S. 7601, et seq.
Jefferson New Jersey Policy No. 1104
Pennsylvania Department of Health: List of Reportable Diseases

Jefferson Office of Human Research Protection Policies and Procedures Manual

500 Reviews Requiring Special Consideration (SC)

Policy SC 509: International Research

1. Purpose

To establish guidelines to ensure that research fully or partially outside the United States, regardless of funding source, is conducted in a compliant and ethical manner.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Institutional Review Board (IRB) Members
Investigators
Key Personnel

2. Procedure

2.1 Principal Investigators

Researchers must follow all applicable regulations including those of the sponsoring agency, Jefferson, and JOHRP policies.

Jefferson researchers and international research under the oversight of Jefferson IRB are also expected to abide by the tenets of the International Congress of Harmonization Good Clinical Practice (ICH GCP) guidelines.

Principal investigators (PIs) must ensure that participants in research conducted outside of the U.S. have equivalent protections to participants in the U.S.

The PI must either obtain Jefferson IRB approval or establish a reliance agreement with the local Ethics Committee (EC) in the host country that will assume oversight for the study. If the study is federally funded, Jefferson cannot rely solely on the local IRB. If an Ethics Committee or other similar review committed does not exist, then a letter of support from a community leader, liaison, or official from the institution where the research will take place must be obtained and submitted to the Jefferson IRB, which would then serve as the designated IRB for the study. Note that some countries require multiple levels of ethics review (e.g., national, regional, local).

The PI also must obtain a letter of support from the facility at which the research will be conducted, if the facility is not under the jurisdiction of the local EC. All documents from the country in question must be translated into English before being provided to Jefferson IRB for the purposes of verification and auditing.

Investigators are required to be knowledgeable about and comply with local laws while conducting their research. They also must take into account local customs and cultural context which may require them to modify certain aspects of the research with IRB/EC approval. Consultation with researchers or other individuals familiar with the culture in which the research will take place is advised. Care must be taken to ensure that the cultural norms of the host country are respected and that the participants will not suffer adverse consequences from participation in the research, such as being subjected to retaliation from local authorities or community members.

The PI must provide information about local context to the IRB to affirm that the research is culturally appropriate. The IRB will use the information to determine whether any modifications are needed to make the research more culturally appropriate. This information may be obtained or supplemented by legal or cultural consultants to the IRB for its review of the research.

2.2 IRB

The Jefferson IRB will review the research in accordance with the applicable Department of Health and Human Services (HHS) and U.S. Food and Drug Administration (FDA) regulations. If the Jefferson IRB chooses to rely on the local EC of the country in which the research will be conducted, it must be documented that the EC is guided by at least one of the following ethical documents:

- *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Nuremburg Code
- The World Medical Association's Declaration of Helsinki (current version)
- Other appropriate international ethical standards recognized by U.S. Federal departments and agencies that have adopted the Common Rule (45 CFR 46).

If the study is federally funded, Jefferson cannot rely solely on the local IRB. In this instance, either both Jefferson IRB and the EC will review the study, or Jefferson IRB will serve as the designated IRB and the EC will rely upon the IRB's review.

Office of Human Research Protections (OHRP) maintains a compiled document of guidelines that govern human subjects research in other countries, as well as standards from a number of international and regional organizations (OHRP International Compilation of Human Research Protections). JOHRP directs researchers to these guidelines and requires compliance with local standards cited by OHRP when conducting international research.

If the research receives U.S. federal funding, any international institution involved with the research will be required to have a Federalwide Assurance (FWA) with the OHRP prior to initiation of the research in that country.

Conflicts arising between U.S. federal law and national and/or other applicable laws of the country in which the research is to be conducted are referred to Jefferson's Enterprise Office of Legal Affairs for guidance and resolution.

The IRB will confirm the qualifications of the Jefferson researchers and research personnel conducting research in the designated country.

When the Jefferson IRB is the designated IRB for the research that involves international sites, it also will be responsible for:

- Initial review, continuing review, and review of modifications to previously approved research

- Post-approval oversight, such as auditing and third-party monitoring

- Handling participant complaints, noncompliance, and/or unanticipated problems (UAPs) involving risk to participants or others. When there is cultural and language differences and geographical distance to negotiate, the IRB may rely on the PI and the local EC, community leader or liaison, or institutional or governmental official to mediate the review and resolution process

Any problems encountered with the research should be reported to the study sponsor, relevant regulatory bodies and all reviewing IRBs and/or Ethics Committees as appropriate. Research that is federally funded and is FDA regulated must comply with both HHS and FDA regulations.

For research conducted jointly under Jefferson IRB and local Ethics Committee and any other involved IRBs providing oversight, the Jefferson IRB will be responsible to apply the above-listed duties only to those specific research procedures conducted by Jefferson researchers and Affiliates, unless otherwise documented through reliance agreement or agreements with individuals unaffiliated with Jefferson. The local Ethics Committee and any other involved IRBs will assume responsibility for all other research conduct, as applicable.

2.3 Consent

Obtaining consent in non-U.S. populations presents certain challenges. Especially in non-Western populations, conceptions of individuality, gender roles, and permission may be substantially different. The investigator should be sensitive to differing norms pertaining to informed consent and design the consent process accordingly, while adhering to applicable regulations. Moreover, while Jefferson researchers should respect local custom, they must adhere to the principles of *The Belmont Report* and the Common Rule. If these standards cannot be met in the given circumstances, the participant should not be enrolled.

All consent documents and verbal consent statements must be translated into the local language. Written translations should be certified as accurate per JOHRP Policy IC 705, *Informed Consent – Non-English-Speaking Participants and Translations*. In some cultures, it may be inappropriate to document consent by using standard written consent. The 2018 Common Rule provides for an additional route of consent when research is to be conducted with members of a distinct cultural group or community in which signing forms is not a standard practice. For minimal risk research in these groups, an appropriate alternative mechanism for documenting consent can be used (45 CFR 46.117(c)(1)(iii)).

There may be different laws regarding determination of who may serve as a legally authorized representative (LAR) and the age of adulthood and consent that both the PI and the IRB must take into consideration when applying regulatory standards.

2.4 Payment

If participants of international research will be compensated for their participation, the IRB must ensure that the amount to be provided to participants is appropriate and reflective of the standard of living in the country in which the research is being conducted as to not unduly influence participants to participate.

3. References

The Common Rule (45 CFR 46)
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research
ICH E6 Guidelines for Good Clinical Practice (R3)
Declaration of Helsinki
Nuremberg Code
OHRP International Compilation of Human Research Protections
JOHRP Policy 705, *Informed Consent – Non-English-Speaking Participants and Translations*
45 CFR 46.117(c)(1)(iii)

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 601: Definition of Key Personnel in Human Subjects Research

1. Purpose

To define key personnel as listed in the Institutional Review Board (IRB) Master Application for purposes of IRB oversight.

1.1 Responsible Parties

Investigators
Key Personnel
Departmental or Divisional Administrative Staff

2. Policy

2.1 Policy Statement

Key personnel in human subjects research are those individuals who are substantially involved in the research. Key personnel must have completed the appropriate human subjects research training and have a current Conflicts of Interest (COI) Disclosure as required by Jefferson.

Examples of activities performed by key personnel include but are not limited to:

- Involvement in the conduct of study procedures
- The ability to view protected health information (PHI)
- Access study-related data that is not de-identified for statistical analysis or other study-related activities
- Interact with research participants
    - During recruitment
    - During the study (including administration of questionnaires)

Persons who are not key personnel are those who perform “contract” type duties or provide administrative support that does not require interaction with participants. Examples include but are not limited to:

- A nurse injecting a study medication according to orders but collecting no study-related data
- A pharmacist working in the Investigational Drug Service (IDS) who dispenses study medication or maintains drug randomization schedules
- A statistician analyzing de-identified or aggregate data
- A technician drawing blood
- An administrator preparing IRB paperwork, study-related budgets, and case report form templates, etc.

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 607: Certificates of Confidentiality

1. Purpose

To provide an overall discussion of the use of Certificates of Confidentiality in research and a description of how to obtain an application for a certificate.

1.1 Responsible Parties

Investigators
Key Personnel
Institutional Review Board (IRB) Members
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Guidance

Investigators generally do not disclose identifying information about research participants to individuals or entities not associated with the research. However, there may be occasions where, because of a court or administrative agency subpoena, the investigator may be required to disclose records of clinical research study participation that could include name, address, medical history, and other personal information of a participant.

The U.S. Congress, realizing that individuals would not be willing to participate in research involving sensitive issues unless their privacy was protected, enacted a law allowing researchers to obtain Certificates of Confidentiality. Public Health Service Act 301 (d), Title 42 US Code, permitted investigators to protect the privacy of participants by refusing to disclose their names or other identifying characteristics, even if asked to do so by courts or governmental agencies. As long as a Certificate of Confidentiality is in place when a participant enrolls in a study, information identifying the participant will never be disclosed unless:

- Volunteered by the participant or, in certain specific circumstances, the investigator, or
- The certificate expires

A Certificate of Confidentiality can help to promote recruitment into a study involving sensitive issues. The IRB can suggest that an investigator apply for one when appropriate.

The Office of Human Research Protection (OHRP) has determined that the research is of a sensitive nature if it involves collecting information:

2.1 How is a Certificate of Confidentiality Obtained?

A request for a Certificate of Confidentiality must be made for a particular study to the agency responsible for the funding and is not transferable to any other study. National Institutes of Health (NIH) funded and federally funded studies automatically receive a Certificate of Confidentiality. U.S. Food and Drug Administration (FDA) also accepts applications for Certificates of Confidentiality for non-federally funded research.

2.2 Limitations on Certificates of Confidentiality

A Certificate of Confidentiality:

- Does NOT protect medical records from subpoena
- Does NOT apply to voluntary disclosure of identifying information by either the participant or the investigator:
    - The participant may voluntarily disclose information about themselves
    - The investigator may also voluntarily disclose specific urgent issues such as child abuse involving a participant or a participant's threats about violence to self or others. Participants should be advised about the exceptions to the protections the certificate offers
- DOES expire

2.3 Mechanics of Certificates of Confidentiality

- A researcher may obtain a certificate of confidentiality only if it is determined that the research is of a sensitive nature and protection is necessary to reach the objectives of the research.
- Certificates of Confidentiality are valid from the date of issue to the date of study expiration, and if the research is not completed by the termination date of the certificate, the recipient must make a written application for an extension.

- A Certificate of Confidentiality is not transferable from one study to another. Any significant changes to the protocol, study personnel, or the test article to be administered requires notification of the issuing agency by the submission of an amended application.

2.4 Contacts for Information about obtaining a Certificate of Confidentiality

The OHRP website contains a list of contacts at different federal agencies for information about obtaining an application for a Certificate of Confidentiality.

3. Reference

Public Health Service Act 301(d), Title 42 US Code
NIH Certificates of Confidentiality Webpage Certificates of Confidentiality - Privacy Protection for Research Subjects: OHRP Guidance (2003)

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 608: Socio-Behavioral Research and Deception in Research

1. Purpose

To provide guidance for issues specific to socio-behavioral research.

1.1 Responsible Parties

Institutional Review Board (IRB) Members
Investigators
Key Personnel

2. Guidance

2.1 Federal Regulations

Federal regulations apply not only to biomedical research, but also to socio-behavioral research in such areas as human behavior, social science, anthropology, epidemiology, pedagogy, and education. Studies of these types often present only minimal risk and may be exempt from IRB review or given an expedited review.

2.2 Psychological/Social Risk

Socio-behavioral research generally does not involve any physical risk to the participant because there is no physical intervention. They do carry concerns for other types of potential harm, including psychological, economic, social, and legal risks to the participants that may be as harmful as any risk faced by a participant in a medical study. And while socio-behavioral studies often do not benefit the participant, they may benefit society at large.

Type of Harm	Type of Risk(s)
Psychological harm	Risks range from temporary anxiety and distress to relapse in a behavioral disorder or precipitation of a disorder
Economic harm	Includes decreased employability and/or possible job loss
Social harm	Includes personal embarrassment, ostracism, stigmatization, or possible loss of social status
Legal harm	Includes arrest, prosecution, and civil or criminal liability

Many of these potential harms would be the result of the risk of a breach of confidentiality. In assessing the potential risks presented by a socio-behavioral study, investigators and IRBs should ensure the design of the study provides an adequate level of protection against these potential risks.

2.3 Deception in Socio-Behavioral Research

Deception in a clinical research study involves intentionally misleading participants or withholding full information about the study in order to achieve study aims. This may include withholding or misrepresenting the purpose of the research, the role of the investigator, or what procedures are experimental.

Deception interferes with the ability of the participant to give fully informed consent and presents a limitation on the protections afforded by informed consent. However, it is important to note that humans act differently depending on the circumstances, and that in some cases the participants' full knowledge of the study would bias the results. In such instances of socio-behavioral research, deception may be necessary. According to the American Psychological Association's (APA's) Ethical Principles of Psychologists and Code of Conduct, deception is permitted with the limitations that it must be ethically and scientifically justified by the investigator. (Deception is not specifically addressed in federal regulation.) Any research involving deception also must be approved by an IRB prior to initiation.

2.3.1 Approval of research involving deception

Approval of research involving deception requires the investigator to obtain a waiver or alteration of the consent process from the IRB. If the IRB approves deception in the consent process or conduct of the study, the participants must be fully debriefed at the end of the study. Furthermore, the participants must be given the opportunity to ask questions about the new information and the opportunity to withdraw both themselves and their data from the study.

2.4 Vulnerable Participants

Additional protections are required for vulnerable persons participating in research. These added protections may include the use of witnesses, requiring consultants and/or advocates, review of consent at specified stages in the study, and limiting the scope of certain research projects.

2.5 Privacy and Confidentiality

Privacy and confidentiality are central considerations in all types of research. A violation of an individual's privacy is not only harmful, but also may result in loss of personal

protection. Breaches of privacy involving public exposure erode trust on all levels. Investigators must design studies to maximize confidentiality of data and should avoid violations of privacy by removing identifiers or making data anonymous unless there is a valid rationale for not doing so.

3. Reference

APA deception in research (sections 8.07 and 8.08)

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 610: Burden of Research Interventions

1. Purpose

To provide an awareness of the burden of research interventions as they pertain to a research protocol involving human subjects, and a list of some specific burdens that should be addressed in the design of a protocol, with the intent to minimize the effect on the research participant to the greatest possible degree.

1.1 Responsible Parties

Investigators
Key Personnel
Institutional Review Board (IRB) Members

2. Guidance

The demands of participation in a research study have the potential to disrupt the normal daily life of a participant. Well known side effects such as prolonged pain and suffering may decrease the quality of life. However, even surveys and questionnaires can potentially cause psychological distress. Investigators may underestimate the impact of study assessments and procedures on participants.

But beyond the design or requirements of the protocol, the burden imposed by the research, while not properly designated as risk, may affect a research participant's day-to-day activities. These issues, therefore, constitute added hardship and thus should be considered in the design of a human research study and clearly communicated to the participant as possible experiences during their participation in the study.

Some issues to consider include the following:

- Lengthy screening and enrollment procedures
- Inconvenient scheduling/frequency of study visits
- Requirement for extra procedures (blood draws between study visits)

- Lengthy questionnaires or study procedures
- Travel time/cost of travel
- Imposition of time and effort on family members, caregivers, or parents particularly in pediatric studies
- Restricted diets
- Washout periods/withholding of certain medications during study participation

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 615: Institutional Review Board Fees

1. Purpose

To provide guidance regarding institutional Review Board (IRB) fees.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
JOHRP Personnel
Investigators
Key Personnel
Office of Research Support Services (ORSS) Contracts personnel

2. Guidance

2.1 Application of IRB Fees

IRB fees apply to all commercially sponsored studies unless fees are waived by prior agreement with the Director of JOHRP. ORSS, Contracts personnel ensure that contracts with commercial sponsors reflect the current IRB fee schedule.

IRB fees apply to commercially sponsored research studies as follows:

- Full Board review of new proposals, continuing review, and amendments
- Expedited review of new studies, amendments and continuing reviews

2.2 Departmentally Funded Investigator-Initiated Trials (IIT)

IITs that are partially funded through grants from non-federal sources or foundations (such as the American Cancer Society, the Arthritis Foundation, etc.) are not assessed IRB fees.

For IITs that are partially funded by grants from commercial entities, the ORSS, Contracts personnel include the IRB fees in the contracts as a line item expense that should not

affect the amount of money received by the investigator. Waiver of fees for these partially funded studies requires approval from the Director of JOHRP.

If a funding entity is supplying drug only and no additional funding, then IRB fees are usually waived. However, if the funding entity is receiving data collected in the IIT then, absent any extenuating circumstances, IRB fees are assessed by contract.

2.3 Other Clinical Research

IRB fees are not assessed for:

- Federally funded studies, unless Jefferson IRB serves as single IRB for funded, multi-site study
- Clinical studies that are sponsored by foundations such as the American Cancer Society, American Lung Association, etc., or
- Clinical studies supported solely by departmental funds

600 Guidance (G)

Guidance G 616: Independent Monitoring of Investigator-Initiated Clinical Trials

1. Purpose

To provide guidance to investigators for establishing acceptable monitoring procedures for investigator-initiated clinical trials.

1.1 Responsible Parties
Investigators
Key Personnel
Institutional Review Board (IRB) Members/Chairs

2. Guidance

Investigator-initiated trials are those in which the investigator is considered to be the sponsor, regardless of whether or not they receive partial funding from an external source to conduct the study. In those instances where there is partial funding, the funding agency, commercial or non-commercial, will not provide monitoring. Therefore, in the absence of professional sponsor monitoring, independent monitoring of investigator-initiated trials (IIT) that employ new drugs, biologicals, or medical devices becomes an issue of great importance for ensuring adequate protection of the rights and safety of human subjects and the quality and integrity of the resulting data.

The method and degree of monitoring needed is related to the degree of risk involved. Establishing a monitoring plan for clinical trials is required to address safe and effective conduct of the trial and to recommend conclusion of the trial when significant benefits or risks have developed, significant efficacy has been demonstrated, or the study is unlikely to be concluded successfully. Risks associated with participation in research must be minimized to the extent possible.

Monitoring may be conducted in various ways and by various individuals or groups, depending on the size, scope and risk of the research effort. This continuum includes monitoring by the Principal Investigator (PI), a Jefferson-based Data Safety Monitoring Board (DSMB) for a small phase I study, or the establishment of an independent DSMB for a large phase III clinical trial.

Minimal risk trials in general do not require monitoring beyond that provided by the PI and any annual review required by the IRB, since the Continuing Review form addresses the required safety and enrollment elements pertinent to the trial.

Greater than minimal risk studies require monitoring procedures that may include:

- Establishing a Data Safety Monitoring Plan (DSMP)
- Appointing an individual as an Independent Study Monitor (ISM), or
- Appointing a DSMB

2.1 Independent Study Monitor (ISM)

An ISM should be an appropriately trained and qualified individual not involved in the study in any other way. The study monitor may be a Jefferson employee or someone who is not employed by Jefferson.

If the study is partially or wholly funded by a non-Jefferson entity, the ISM should not be an employee of that entity. The ISM should sign a confidentiality statement and a Conflict of Interest (COI) Disclosure (Attachment D of University Policy 107.03). The ISM should be familiar with the protocol and risks of the study and should provide periodic written reports in accordance with the monitoring plan to the PI and the IRB on a quarterly, bi-annual, or other regular basis. The monitoring plan should be described in the study application.

2.2 Data Safety Monitoring Plan (DSMP)

Elements of a DSMP should include the following:

- Reviews of adverse events (AEs) and unanticipated problems (UAPs) posing risks to participants or others
- Depending on the complexity of the research, the plan may include assessments of data quality, participant recruitment, accrual and retention; and
- A plan to assure data accuracy and protocol compliance
- Parameters, also known as ‘stopping rules’, that would define the need for suspension of enrollment or closure of the study

2.3 Data Safety Monitoring Board (DSMB)

The following research situations require the oversight of a DSMB:

- The study is intended to provide definitive information about the effectiveness and/or safety of a medical intervention
- Prior data suggests that the intervention under study has the potential to induce a potentially unacceptable toxicity
- The study is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has immediate implications for research participants regarding both safety and effectiveness; or
- The primary question has been definitively answered, even if secondary questions or complete safety information have not yet been fully addressed

2.4 Composition of DSMB

The composition of a DSMB varies but should include multidisciplinary representation, such as physicians from relevant medical specialties, biostatisticians, and possibly other experts such as bioethicists, epidemiologists and basic scientists. Members must be free of significant COIs (e.g., financial, intellectual, professional, or regulatory) with the study under the DSMB's oversight.

2.5 IRB Review of the DSMB

The IRB will review the DSMB as described in the study application at the time of initial review of the protocol and at each Continuing Review.

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 618: HIPAA and Activities Preparatory to Research

1. Purpose

To define and provide guidance regarding the Health Insurance Portability and Accountability Act (HIPAA) permitted activities preparatory to research and some recruitment activities.

1.1 Responsible Parties

Investigators
Key Personnel
Institutional Review Board (IRB) Members/Chairs
Privacy Officer

2. Guidance

2.1 Definitions

- **Activities Preparatory to Research**: Activities involved in preparing for research such as:

  1. Preparing a research protocol
  2. Designing a research study, including developing a hypothesis
  3. Assessing the feasibility of conducting a study, or
  4. Obtaining the number of potential participants for a study to determine if there is a sufficient number or type of patients to conduct the research

- **Covered Entity**: An organization that must adhere to HIPAA requirements. For Jefferson, this includes its controlled clinical affiliates.

- **Individually Identifiable Health Information**: Information that is a subset of health information, including:

- Demographic data collected from an individual is created or received by a Covered Entity

- Information that relates to the past, present, or future physical or mental health or condition of an individual

- Information about the provision of health care to an individual, or the past, present or future payment for the provision of health care to an individual; and

- Identifiers, or a combination of de-identified information from which there is reasonable basis to believe an individual can be identified

- **OHR-29, *Review Preparatory to Research Request***: A Jefferson Office of Human Research Protection (JOHRP) form to be used by researchers to request to engage in activities preparatory to research.

- **Protected Health Information (PHI)**: Means Individually Identifiable Health Information transmitted or maintained in electronic or any other form.

- **Researchers**: Jefferson investigators and key personnel conducting research at Jefferson.

- **Records**: Paper or electronic patient treatment records or billing records maintained by Jefferson.

2.2 Overview

For activities preparatory to research, a covered entity, may use PHI or disclose PHI to a researcher without securing a patient's authorization, a waiver or alteration of authorization, or a data use agreement (DUA). A researcher, making a request to a covered entity for a disclosure of records or to provide researcher access to records for information preparatory to research, must represent that:

- The use or disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research

- The PHI will not be removed from the covered entity during review; and

- The PHI for requested use or access is necessary for the research.

2.3 Guidance Specifics

Jefferson Enterprise Policy No. 134.04, *Requests for Use and Disclosure of PHI for Research Purposes*, addresses activities preparatory to research in Attachment 1 specific to Jefferson as the covered entities. If researchers desire to use or access the records of other covered entities, researchers will need to comply with the policies of those covered entities.

Application: Consistent with the enterprise policy, researchers must complete a form OHR-29, to request records. The covered entity must receive a completed form OHR-29 from the researcher. This form certifies that:

- The use of disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research
- The PHI will not be removed from the Covered Entity during the course of review
- The PHI will not be subsequently disclosed once it is determined that there is sufficient basis for a clinical trial or research study
- The PHI for which use or access is requested is necessary for the research; and
- The appropriate IRB forms will be submitted for IRB review and approval if it is determined that the information obtained will be used to conduct a research study

PHI may not be removed from the covered entity. Researchers may record information using the PHI from the covered entity; such information must be de-identified.

A researcher may not disclose PHI secured under an OHR-29 with a non-Jefferson researcher unless and until the researcher requests and obtains an OHR-3, *Waiver of Authorization*, and/or consults with Jefferson's Enterprise Office of Legal Affairs to secure an appropriate data sharing agreement, e.g., a Limited Data Set Use Agreement, or a Business Associates Agreement (BAA).

The completed OHR-29 should be submitted to the Privacy Office at privacyoffice@jefferson.edu.

In addition to the submission of the OHR-29 form to the covered entity, the researcher must comply with the covered entity procedures to receive information or gain access to

PHI. For example, if a researcher desires to obtain a patient count for specific diagnosis code(s) to determine study feasibility, the researcher may make a request for such data consistent with the enterprise policy. Under such enterprise policy, the Privacy Office has delegated responsibility to the Jefferson Clinical Research Institute (JCRI) to process requests for data. Upon receipt of approval for the PHI, the researcher may submit a request to obtain the data by following the process set forth in Attachment B of the enterprise policy.

2.4 Recruitment and Contacting Prospective Participants

Following approval of the OHR-29 form by the covered entity's privacy officer, the researcher may conduct activities preparatory to research. Only if the researcher decides to pursue a clinical study and secures IRB approval may the researcher contact prospective participants to seek further authorization for use of those individuals' PHI and to obtain informed consent to participate in a research study. IRB requirements for contacting participants must be followed. See JOHRP Policy GA 129, *Protection of Privacy Interests of Research Participants and Confidentiality of Participant Data*.

2.5 Accounting for Disclosures

Each covered entity must maintain a log of PHI disclosures and whether such disclosures were for internal or external research-related purposes. Researchers must comply with the covered entity's Accounting of Disclosures of Protected Health Information policies. (See Hospital Policy No.: 135.01, *Privacy/Confidentiality of Health Information*)

3. References

45 CFR 164.512(i)(1)(ii)
OHR-29, *Review Preparatory to Research Request Form*
JOHRP Policy GA 127, *Participant Recruitment and Enrollment*
Enterprise Policy No. 134.04, *Requests for Use and Disclosure of PHI for Research Purposes* (Internal Jefferson Link)
OHR-3, *Waiver of Authorization*
JOHRP Policy GA 129, *Protection of Privacy Interests of Research Participants and Confidentiality of Participant Data*
Hospital Policy No. 135.01, *Privacy/Confidentiality of Health Information* (Internal Jefferson Link)

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 619: Radioactive Materials

1. Purpose

To provide guidance for approval and use of radioactive materials.

1.1 Responsible Parties

Investigators
Key Personnel
Director of Office of Radiation Safety

2. Guidance

2.1 Definitions

- **Radioactive Drug**: Any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term “radioactive drug” includes a “radioactive biological product”. (21 CFR 310.3(n))

- **Radioactive Biological Product**: A biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide. (21 CFR 600.3(ee))

3. Procedure

Various aspects of the use of radioactive materials in human research are regulated by the U.S. Food and Drug Administration (FDA) and by the U.S. Nuclear Regulatory Commission (NRC). Under NRC regulations, the NRC may enter into agreements with individual states, effectively transferring regulatory authority to the states, if state regulations are compatible with NRC regulations. Pennsylvania and New Jersey are “Agreement States” and directly incorporate NRC regulations by reference.

The FDA regulates the manufacturers of radiation-producing machinery (e.g., sets performance standards for x-ray equipment) and medical devices that incorporate radioactive materials. The individual states regulate the use of radiation producing machinery. Regulatory authority in Pennsylvania for radioactive and machine-produced sources of radiation rests with the Pennsylvania Department of Environmental Protection, Bureau of Radiation Protection. The regulatory authority in New Jersey for licensing and regulating byproduct, source, and certain special nuclear radioactive material users is the New Jersey Department of Environmental Protection, Bureau of Environmental Radiation.

3.1 Categories of Use

The use of ionizing radiation sources in or on human research studies can fall into one (1) of the following categories:

- Category 1: To obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of the radioactive drug or regarding human physiology, pathophysiology, or biochemistry (see 21 CFR 361.1).

- Category 2: To study the safety and effectiveness of a radioactive drug or radiation emitting device for diagnostic, therapeutic, or similar purposes (i.e., clinical trials).

- Category 3: To use already FDA-approved radiopharmaceuticals for uptake, dilution, or excretion studies or for imaging and localization studies, or to use FDA approved x-ray imaging equipment as a means of assessing the effectiveness of a clinical regimen (e.g., use of a non-radioactive study drug) or physiologic process being studied.

- Category 4: To use a non-radioactive study drug or a regimen not involving a radiation source in conjunction with a standard radiation therapy or diagnostic radiation procedure used to assess whether the study drug or regimen increases the efficacy of a standard therapeutic or diagnostic modality (i.e., the participant/patient would undergo the radiation procedure regardless of participation in the study).

3.1.1 Category 1 Guidance

Each proposed human subjects research protocol involving the research-related use of radioactive material and/or other sources of ionizing radiation (i.e., not clinically indicated procedures) requires the approval of:

1. Jefferson Radiation Safety Committee (RSC) or the Radiation Safety Officer (RSO) (as appropriate – RSC procedures permit RSO only approval in limited circumstances)

2. The Jefferson Radioactive Drug Research Committee (RDRC), and

3. The Jefferson Institutional Review Board (IRB)

The use of radioactive materials for research use is permitted only by or under the supervision of an authorized user approved by the TJUH/TJU Radiation Safety Committee (RSC).

When research involves investigational or unlicensed test articles, Jefferson must confirm that the test articles have appropriate regulatory approval or meet exemptions for such approval.

FDA regulations found in 21 CFR 361 apply to this category of research. Oversight at Jefferson is handled by the RDRC which is chartered by the FDA to review both basic science and human subjects research in which radioactive devices or drugs are employed. The research study is approved the RDRC based on the following requirements (21 CFR 361.1(b)(1)(iv)):

- Qualified study investigators
- Properly licensed medical facility to possess and handle radioactive materials
- Appropriate selection and consent of research participants
- Appropriate quality assurance of radioactive drug administered
- Sound research protocol design
- Reporting of adverse events (AEs) by the investigator to the RDRC
- Approval by an appropriate IRB
- Approval by the RSC

- The pharmacologic dose of the radioactive drug to be administered is known not to cause any clinical detectable pharmacologic effects in humans (21 CFR 361.1(b)(2))

- The radiation dose to be administered is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain (21 CFR 361.1(b)(1)(iii)) and is within the limits specified in 21 CFR 361.1(b)(3)(i) as shown below. Furthermore, as stated in 21 CFR 361.1(b)(3), the amount of radioactivity to be administered shall be such that the participant receives the smallest radiation dose which is practical to perform the study without jeopardizing the benefits to be obtained from the study.

Radiation Dose Limit Guidelines (for this category)

Age of Participant	**Radiation Dose Limit**
Under 18 years	300 millirem (3 millisievert) to the whole body (i.e., “effective dose”), active blood forming organs, lens of the eye, and gonads from a single administration, and 500 mrem (5 mSv) annual total dose commitment.
18 years or older	3,000 mrem (30 mSv) to the whole body (i.e., “effective dose”), active blood forming organs, lens of the eye, and gonads from a single administration, and 5,000 mrem (50 mSv) annual total dose commitment. 5,000 mrem (50 mSv) to other organs from a single administration, and 15,000 mrem (150 mSv) annual total dose commitment.

Note: Any radiation doses received by a participant from any imaging (e.g., x-ray) studies that would not have occurred but for participation in the study, must be included in the dose assessment.

Use of radioactive materials in research participant to 21 CFR 361.1 is also subject to NRC (or Agreement State) regulations. The Jefferson RSC (or RSO in limited circumstances) approves the research based on the following considerations:

- Properly licensed facility to possess and handle radioactive materials

- Properly licensed facility for the administration of radioactive materials or application of radiation to humans

- Physician(s) appropriately authorized to supervise the administration of radioactive materials to humans

- Appropriate radiation safety procedures/precautions
- Appropriately trained personnel
- Appropriate provision for radioactive waste disposal and (where necessary) shipping radioactive samples.
- Appropriate radiation doses
- Approval by the IRB (Note: RSC approval may be made contingent upon subsequent IRB approval.)
- Approval by the RDRC

3.1.2 Category 2 Guidance

Most human subject research involving radiation is conducted under the terms of an Investigational New Drug (IND) or an Investigational Device Exemption (IDE) issued by the FDA and must also be reviewed and approved by the IRB.

As defined in 21 CFR 361.1 the RDRC has no oversight responsibility or authority over an investigation carried out under an IND exemption. This authority is retained by the FDA. If a radiopharmaceutical cannot be classified as "generally recognized as safe and effective," (see FDA *Guidance for use of Radiology Devices and Radioactive Materials in Research Protocols*) the RDRC may not review and approve the research, and an IND may be needed.

Regulation 21 CFR 361.61 specifically does not apply to:

- Research intended for immediate therapeutic, diagnostic or similar purposes (e.g. preventive benefit to the study participant from the research)
- Research intended to determine the safety and effectiveness of a radioactive drug in humans.

Approval by the RDRC is therefore not required.

Use of radioactive materials and radiation-producing machines or devices in research is, however, subject to NRC (and/or State) regulations. The Jefferson RSC (or RSO in limited circumstances) approves the research based on the following considerations:

- Properly licensed facility to possess and handle radioactive materials or radiation producing device

- Properly licensed facility for the administration of radioactive materials or application of radiation to humans

- Physician(s) appropriately authorized to supervise the administration of radioactive materials or ionizing radiation to humans

- Appropriate radiation safety procedures/precautions

- Appropriately trained personnel

- Appropriate provision for radioactive waste disposal and, where necessary, shipping radioactive samples

- Appropriate radiation doses (e.g., similar to doses received from similar, already approved diagnostic or therapeutic uses and justified by the aims of the research)

- Approval by the IRB. Note: RSC approval may be made contingent upon subsequent IRB approval

3.1.3 Category 3 Guidance

This category applies to uses of standard techniques already in clinical use (e.g., imaging procedures involving FDA approved radiopharmaceuticals, standard x-ray, or CT imaging techniques) in research on other new non-radioactive/radiation drugs or regimens, for the purpose of assessing the efficacy of the study drugs or regimen. All uses of ionizing radiation are subject to federal and/or state regulation. However, whether RSC (or RSO) approval is needed for is based on one (1) criterion:

> "*Will the research participant undergo any procedures involving radiation exposure solely because they participate in the study?*" If yes, IRB and RSC (or RSO) approval is warranted.

The Jefferson RSC (or RSO in limited circumstances) approves the research based on the following considerations:

- Properly licensed facility to possess and handle radioactive materials or radiation-producing device
- Properly licensed facility for the administration of radioactive materials or application of radiation to humans
- Physician(s) appropriately authorized to supervise the administration of radioactive materials or ionizing radiation to humans
- Appropriate radiation safety procedures/precautions
- Appropriately trained personnel
- Appropriate provision for radioactive waste disposal and, where necessary, shipping radioactive samples
- Appropriate radiation doses (e.g., similar to doses received from similar, already approved diagnostic or therapeutic uses and justified by the aims of the research)
- Approval by the IRB. Note: RSC approval may be made contingent upon subsequent IRB approval

3.1.4 Category 4 Guidance

In this category, the radiation doses received by the participant are part of the clinical standard of care and would be received regardless of participating in the study. Review and approval by the RSC (or RSO) is NOT required. IRB review and approval based on considerations other than radiation exposure may be required as per federal regulations. The RSO may nevertheless review study protocols to make a determination as to whether the proposed studies are Category 3 or Category 4.

3.2 Guidance Specifics

All human research studies involving use of radioactive materials or radiation-emitting devices that exceed expected radiation exposure encountered in usual clinical care require review and approvals as described above prior to initiating the research.

Pregnant participants may not participate in research studies using “radioactive research drugs” as described under Category 1 above. Likewise, pregnant participants may not participate in research studies using radioactive drugs or radiation-emitting devices as described under Categories 2 and 3 above, unless a purpose of the study is specifically aimed at the pregnant person population. Pregnant participants are not required to be denied participation for Category 4. It is the responsibility of investigator to ensure participants of childbearing age are not pregnant at the time of dose administration. Either urine or blood pregnancy test is recommended to be performed prior to the administration of study drug.

Informed consent forms should address all required consent elements including appropriate precautions for pregnant participants and risks of radiation.

The completed OHR-32, *Radiation Research Review Form*, is submitted to:

Radiation Safety Officer, TJU/TJUH
Nevil Building, Suite 820
919 Walnut St.
Philadelphia, PA 19107
Phone: 215-955-1950
Phone: 215-955-7813
Fax: 215-923-9039

4. References

FD&C Act Section 201(g)(1)
21 CFR 310.3(n)
21 CFR 600.3(ee)
21 CFR 361
OHR-32, *Radiation Research Review Form*

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 620: Department of Defense Requirements for the Conduct of Human Subjects Research

Publication withheld for further editing.

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 621: Safeguarding and Protection of Children in Research Studies

1. Purpose

A substantial portion of research conducted at Jefferson involves pregnant persons, parents, and children. Therefore, consistent with its mission, Jefferson is committed to reviewing, approving and overseeing research that ensures the safety and well-being of all children who participate in research studies conducted by research personnel, including students, faculty, employees or contracted personnel, consultants, contractors, or volunteers. The term "children" has a meaning consistent with the definition found in the U.S. Code of Federal Regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" (45 CFR 46.402; 21 CFR 50.3(o)).

The purpose of this guidance is:

- To compile the various policies, guidelines, codes, and assurances that contribute to the protection and safeguarding of children involved in research
- To promote awareness of the Institutional Review Board's (IRB's) commitment to the protection of children from harm, neglect and abuse, whether physical, emotional or psychological; and
- To alert the research community that Jefferson has systems in place to enforce these policies and procedures

1.1. Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
IRB Members
Investigators
Key Personnel
Office of Research Integrity, Conduct, & Compliance (ORCC)
Office of Research Support Services (ORSS)

2. Guidance

2.1. A designated Compliance Officer (CO), who has appropriate knowledge and skills to promote child-safe environments and respond to safety concerns, has responsibility for accepting and investigating any report of a known or suspected violation of applicable policies or a concern about the safety and well-being of a child involved in research occurring at Jefferson.

2.2. When JOHRP receives concerns of child safety not covered under human subjects regulations, the concerns will be forwarded to the CO for attention and follow-up.

2.3. When Jefferson has a need for employing or contracting new personnel for its research activities, the rules associated with Jefferson's recruiting and hiring policies and practices will apply. Consistent with the Pennsylvania Child Protective Services Act, Jefferson's procedures include a provision for special screening of an individual who would be in regular contact with children in the form of care, guidance, supervision or training. The screening includes:

- The Pennsylvania State Police criminal background check
- The Pennsylvania Department of Welfare child abuse criminal background clearance, and
- A Federal Bureau of Investigation (FBI) fingerprint based federal a criminal records check

Researchers should be aware that New Jersey state law includes different requirements. For both Pennsylvania and New Jersey, researchers should work with Jefferson Human Resources to ensure compliance. Employment or contractor engagement cannot occur if any of the screenings indicate background that results in an individual being at high-risk for behavior contrary to safeguarding and protecting children.

2.4. Jefferson's IRBs apply applicable regulations governing human research and, when necessary to adequately protect children, IRB members may recommend that a study protocol encompass special protections for children involved in research.

2.5. Jefferson Principal Investigators (PIs) conducting research involving children should periodically conduct safeguarding risk assessments to ensure the research is conducted in an appropriate environment and locations where processes are applied to ensure safe, inclusive environments for children. When subcontractors are involved in the research, PIs shall ensure that subcontractors meet the same expectations.

2.6. When Jefferson and its subcontractors involve children who have reached the age of reason (usually about seven (7) years of age) in research, opportunities will be provided for such children to express what risks are a concern to them. Further, assent (i.e., affirmative agreement to participate in research) should generally be sought from children judged capable of providing it. In addition, a parent generally will be present when a child under seven (7) is involved in a research activity, and the researcher will be receptive to recommendations from the parent about safeguarding and protecting the child during a research activity.

2.7. Jefferson will consider whether any independent oversight is necessary to ensure adequate protection of a child involved in research. For example, if a child has a "court appointed special advocate," the advocate may help ensure that the child's needs and interests are met. Measures may also be implemented to promote a child-friendly and protective environment during a research activity. Such an environment is understood to mean:

- One in which child abuse (physical, sexual, emotional, or resulting from neglect) is unlikely
- Proactive steps have been taken to prevent all forms of violence against children; and
- Child protection is a priority and results in a prompt response when a child is at risk for physical and/or mental violence, injury and/or abuse, neglect and/or negligent treatment, maltreatment and/or sexual exploitation, and/or sexual abuse

Researchers should request copies of any relevant court documents and include these documents in the research file(s).

2.8. Anyone involved in research implemented by Jefferson, including subcontractors, who suspects a violation of any of these policies or has a concern that research activities present a risk to children should register the violation, complaint or concern with JOHRP or its Research Compliance Officer as set forth in applicable policies. Any compliance matter may also be reported to Jefferson's Chief Compliance Officer through the Jefferson Alert Line at 833-ONE-CODE (833-663-2633) or Jefferson.MyComplianceReport.com. A complaint, suspicion, or concern will be investigated by the appropriate official and a decision will be reached about the facts associated with the complaint, suspicion, or concern. The appropriate official will present a recommendation for prompt action to the violator's supervisor should it be determined

that a violation of applicable policies has occurred or there is a need for changing processes or procedures to better safeguard and protect children involved in research.

2.9. Reporting a violation (or suspected violation) of applicable policies or a child safety concern is strongly encouraged, and one means to protect a whistleblower is anonymous reporting (as outlined above). Additionally, the appropriate official need not make the name of an individual who reports a possible violation or child safety concern known unless there is an atypical and justified reason for doing so. Further, it is the intent of Jefferson to protect the whistleblower, to the best of its ability, from retaliation for reporting a violation, suspected violation, or concern related to this policy.

2.10. Jefferson is committed to assurance of Enterprise policy, 132.01, *Corporate Code of Conduct & Ethical Behavior,* for students, faculty, employees, or contracted personnel, consultants, contractors, or volunteers engaged in its research. The following are specific expectations:

i. When Jefferson is involved in research being conducted outside of Jefferson's research area and participants are recruited from another country, the Jefferson Principal Investigator will ensure that applicable Jefferson child protection policies are met as well as the rules of a recognized Ethics Committee and/or other review committee of the country in which the research is being conducted.

ii. Community-based approaches for publicizing research involving children are the preferred means of communicating an approved research project involving children, and generally social media sites (such as Facebook) will not have messages directed at children or otherwise be used unless the specifics of use of such social media sites have been detailed in an application for review and approved by the appropriate IRB and/or Ethics Committee.

3. References

45 CFR 46.402
21 CFR 50.3(o)
Pennsylvania Child Protective Services Act
Enterprise Policy 132.01, *Corporate Code of Conduct & Ethical Behavior*
Jefferson.MyComplianceReport.com

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 622: Research Device Acquisition, Use, and Tracking

1. Purpose

To provide guidance to investigators regarding ordering, receipt, use, storage, securing, and return or disposal of devices used in Institutional Review Board (IRB) approved human research conducted on Jefferson premises.

1.1 Responsible Parties

Investigators
Key Personnel

2. Guidance

2.1 Application

This guidance applies to all medical research devices used or implanted on Jefferson premises as part of an IRB-approved research study.

2.2 Definitions

- **Investigational New Device (IND)**: A device permitted by the U.S. Food and Drug Administration (FDA) to be tested in humans but not yet determined to be safe and effective for a specified use in humans and not yet licensed for marketing. This includes devices already approved for indications other than the one(s) under investigation.

  Even a device designated as 510(k) remains "investigational" until the 510(k) is cleared by FDA. Until such time, the investigational use is subject to the requirements of the Investigational Device Exemption (IDE) regulation, informed consent and IRB review (21 CFR 812, 21 CFR 50 and 21 CFR 56).

- **Investigational Device Exemption (IDE)**: This status is assigned by FDA to significant risk devices authorized to be used in clinical research studies. The term ‘exemption’ in the designation pertains to exemption from certain regulations found in the Federal Food Drug and Cosmetic (FD&C) Act and allows shipment of unapproved devices for use in clinical investigations. These investigations collect

safety and efficacy data required to support a Premarket Approval application or a Premarket Notification [501(k)] submission to the FDA. All clinical evaluations of investigational devices must be approved by the IRB and, unless determined by the IRB to be "non-significant risk," have an FDA-approved IDE before study is initiated.

- **Sponsor-investigator**: An investigator who has been granted an IDE number by the FDA.

- **Jefferson Premises**: Any facility owned, operated, or controlled by Jefferson.

2.3 Introduction

Medical devices used in human research are classified into one of two categories, "significant risk" (SR) and "non-significant risk" (NSR). (Jefferson Office of Human Research Protection (JOHRP) Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Nonsignificant Risk*)

SR Devices are defined in, and their use in human subjects research is governed by, regulations at 21 CFR 812.

The investigator is responsible for maintaining records of investigational device(s), SR and NSR, under their oversight.

2.4 Review, Approval, and Ordering Process

All device research involving humans, whether the device is deemed SR or NSR, must be approved by the IRB prior to study initiation. The study application must include documentation of any required training of the Principal Investigator (PI) or Co-Investigators (Co-Is) in the use of the device and how competency of investigators' use of the device will be ensured.

In addition, approval of all devices, equipment, and supplies ordered through Supply Chain Management and used on Jefferson premises must be requested using the Value Analysis process defined in Hospital Policy 108.11, *Enterprise Value Analysis Policy/Procedure*. Use of these research devices is not permitted until such approval is granted, regardless of the status of the trial within or outside of Jefferson.

2.5 Receipt, Storage, and Return of Devices

Research devices delivered to the research site (such as the Gastrointestinal (GI) endoscopy suite, Cardiovascular and Interventional Radiology (CVIR), etc.), or, when

appropriate, directly to the investigator by the manufacturer must be clearly labeled “For Research Use Only” and placed in secure storage. Secure storage access must be restricted to members of the research team.

In addition to the “For Research Use Only” designation on the device package, the following information must appear on the device package label:

- Device manufacturer
- Catalog or part number
- Description of the device
- IRB control number and study title

Upon study closure, any unused/unopened devices should be discarded, destroyed, returned, reused, or retained according to sponsor instruction and/or agreement.

2.6 Tracking

Responsibility for device tracking for IDEs, regardless of who holds the IDE ultimately resides with the site PI as of the time site receives device.

3. References

FD&C Act
21 CFR 812
21 CFR 50
21 CFR 56
JOHRP Policy SC 501, *Determining Whether a Device Study Involves a Significant Risk or Nonsignificant Risk*
FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006
Hospital Policy 108.11, *Enterprise Value Analysis Policy/Procedure*

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 623: Human Research Protection Program

1. Purpose

To define the Jefferson Human Research Protection Program (HRPP). This guidance applies to all human subjects research conducted at Jefferson.

1.1 Responsible Parties

Director/Associate Director of the Jefferson Office of Human Research Protection (JOHRP)
Senior Research Compliance Officer
JOHRP Personnel
Director of Research Planning

2. Guidance

2.1 The Human Research Protection Program (HRPP)

HRPP is the network of offices and personnel at Jefferson, that work together to uphold the protection of human subjects in research at Jefferson. Each stakeholder in HRPP contributes their expertise to the overall goal of protection.

The major stakeholders are as follows:

2.1.1 **The Jefferson Office of Human Research Protection (JOHRP)**: The core of Jefferson's HRPP. JOHRP provides administrative support for the Jefferson Institutional Review Boards (IRBs). JOHRP:

- Accepts submissions for IRB review
- Creates IRB meeting agendas
- Distributes submitted materials to reviewers
- Maintains record of all studies conducted at Jefferson, and

- Ensures that the IRBs review clinical research activities in compliance with all applicable regulations and policies

The Quality Assurance Program of JOHRP conducts routine and for-cause audits of clinical research studies. Consent Observations are also conducted as needed. In addition, the group audits IRB files and processes on a regular basis.

JOHRP is part of the Jefferson corporate structure. The Senior Research Compliance Officer has general oversight responsibilities for JOHRP. The Director of JOHRP reports to the Senior Research Compliance Officer regularly. The Senior Research Compliance Officer reports directly to the University Provost.

2.1.2 **The Office of Research Support Services (ORSS)**: assists researchers in applying for and managing sponsored funding. ORSS:

- Serves as the official point of contact for the various sponsors of scientific and scholarly activity including human subjects research

- Manages all sponsored projects in accordance with sponsor regulations and Jefferson policies

- Consults with JOHRP regularly concerning subcontracts involving human subjects research, compensation to research participants in case of research-related injury, Medicare coverage analysis for clinical trials, and other human research-related issues

2.1.2.1 **The Jefferson Clinical Research Institute (JCRI)**, within ORSS also provides recurrent training and educational programs and resources related to the financial management, and associated processes, of sponsored clinical research. JCRI, in coordination with ORSS, provides contract, budget review, administrative, regulatory, and clinical key personnel support for investigators on an as needed basis. JCRI also has dedicated staff that provide training and education on the performance of human subjects research, as well as resources to support investigators and research personnel.

2.1.2.2 **ORSS, Contracts** coordinates and collaborates with the JOHRP during and after contract negotiation and execution to ensure the study will be conducted in a manner consistent with good clinical practices, the Statement of Investigator Form 1572 is signed by the Principal Investigator

(PI) and on file with the sponsor, and all other applicable local, state, and federal rules, laws, and regulations, including privacy regulations promulgated pursuant to the Health Insurance Portability and Accountability Act (HIPAA).

While both JOHRP and ORSS recommend commencement of the IRB and ORSS processes simultaneously, a sponsored study may not be initiated and study drug/device will not be shipped prior to final IRB approval. Whenever possible, it is recommended that the IRB submission, budget, and contract review and negotiations occur simultaneously.

2.1.3 **The Enterprise Office of Legal Affairs (OLA)**: Maintains Jefferson policies on conflicts of interest (COI) for employees, COI for the Board of Trustees, and HIPAA. A member from OLA provides information regarding COI and local and federal law, when applicable, to the convened boards. OLA is also involved in the writing of new, and review of existing IRB policies and procedures.

2.1.4 **The Investigational Drug Service (IDS)**: Within the Department of Pharmacy, reviews all in-patient clinical research protocols involving drugs and dispenses all research-related drugs used in inpatient and some outpatient clinical trials. Members of the IDS serve as voting members of Jefferson IRBs.

2.1.5 **The Office of Animal Resources (OAR)**: Oversees animal protocols, including those that use tissue from living human beings, and does not permit initiation of such research without documentation of IRB approval.

2.1.6 **The Office of Radiation Safety (ORS)**: Through the Radiation Safety Committee reviews all protocols in which radiation greater than that used in usual clinical practice is employed. The Director of ORS communicates all Radiation Safety Committee decisions that involve human subjects in research to JOHRP.

2.1.7 **The Conflict of Interest Committee (COIC)**: Reviews all financial COIs for Jefferson faculty, including those pertaining to investigators involved in the conduct of human subjects research. COIC works with the IRB to determine the best route to managing COIs for these investigators.

2.1.8 Other Offices and individuals including:

- **The Provost of Thomas Jefferson University:** ensures that there are adequate resources to support the goals of the HRPP

- **The Senior Research Compliance Officer:** the Senior Officer with oversight responsibility for research, research integrity, and science policy. The Senior Research Compliance Officer is the Institutional Official (IO) for the HRPP and in that role answers directly to the Provost who in turn answers to the President.

- **The Sidney Kimmel Comprehensive Cancer Center (SKCCC) Quality Assurance and Education (QAE)** group conducts routine and for-cause audits of oncology clinical research studies and will report serious and continuing compliance issues to JOHRP.

- **The SKCCC Clinical Trials Office (CTO)** provides administrative and key personnel support for oncology studies conducted by the Sidney Kimmel Cancer Center

- **The SKCCC Protocol Review & Monitoring Committee (PRMC)** reviews all oncology studies for science and merit prior to IRB review.

All the personnel and entities involved in the HRPP make a valuable contribution towards the goal of ensuring that the protection of human subjects is held to the highest ethical standards at Jefferson.

2.2 Responsibility of the Offices and Personnel Involved in the HRPP

The Director of JOHRP, the Senior Research Compliance Officer, and the Director of Research Planning meet at least annually, or as needed, to evaluate resources including but not limited to:

- Space requirements
- Personnel
- HRPP education program
- Legal counsel needs
- COI
- Quality assurance plan

- IRB functions and needs

All offices and personnel that are part of the HRPP are mandated by the Enterprise policy 132.01, *Corporate Code of Conduct & Ethical Behavior*, to uphold and abide by all relevant federal and local regulations and laws and to conduct their activities in accordance with the highest ethical standards.

3. References

Enterprise policy 132.01, *Corporate Code of Conduct & Ethical Behavior*
Health Insurance Portability and Accountability Act (HIPAA)

Jefferson Office of Human Research Protection Policies and Procedures Manual

600 Guidance (G)

Guidance G 624: Enrollment of Women and Minorities as Participants in Clinical Research

1. Purpose

To define the requirements for the inclusion of women and minorities in research involving human subjects based on the National Institute of Health (NIH) Revitalization Act of 1993, PL 103-43, and the subsequent NIH Policy Guidelines as amended in October 2001, and provide a procedure for the enrollment of such individuals in clinical trials conducted at Jefferson.

While inclusion of women and minorities is mandated for NIH-supported clinical research studies, Jefferson applies these requirements to all applicable research studies.

1.1 Responsible Parties

Investigators
Research Coordinators
Institutional Review Board (IRB) Members
Jefferson Office of Human Research Protection (JOHRP) Administrative Staff

2. Policy

2.1 Policy Statement

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH clinical research, unless a clear and compelling rationale and justification established to the satisfaction of the relevant institute/center director that inclusion is inappropriate with respect to the health of the participants or the purpose of the research.

Cost is not an acceptable reason for exclusion except where the study would duplicate data from other sources. Furthermore, women of childbearing potential should not be routinely excluded from participation in clinical trials.

3. Procedures

Jefferson investigators developing a grant (contract proposal) submission to the NIH for a clinical trial must construct a research plan that addresses the inclusion of women and minorities and their subpopulations appropriate to the scientific objective of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethic groups and provide a rationale for selection of such participants.

3.1 Investigator-Initiated NIH-Defined Phase III Clinical Trials

When a NIH Phase III clinical trial is proposed, the investigator must review the evidence whether or not clinically important sex/gender and race/ethnicity differences in the intervention effects(s) are to be expected. This evidence may include but is not limited to: data derived from animal studies, clinical observation, metabolic studies, genetic, observational, natural history, epidemiology, and other relative studies.

Based on prior studies, the investigator must consider which of the following three (3) situations will apply when planning, conducting, analyzing, and reporting an NIH-defined Phase III clinical trial:

i. Prior studies support the existence of significant differences

If the data from prior studies indicate significant differences in the response of men and women to an intervention, then the Phase III clinical trial must be designed to answer two (2) primary questions, one for men and the other for women, with adequate sample size for each.

The research plan or proposal must include a description of plans to conduct analyses to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable.

The investigator must include in their annual progress report cumulative participant accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. Inclusion of the results of the sex/gender, race/ethnicity analysis in any publication submission is strongly encouraged. If the analyses reveal no differences, a brief statement to that effect is adequate.

The IRB must approve the final plan for analysis.

ii. Prior studies support no significant differences

If the data from prior studies do not support a significant difference(s) of clinical or public importance in the intervention effect, then sex/gender, race/ethnicity will not be required as participant selection criteria. However, the Department of Health

and Human Services (HHS) strongly encourages the inclusion and analysis of sex/gender and racial/ethnic subgroups.

iii. Prior studies neither support nor negate significant differences

If data from prior studies neither supports or strongly negate the existence of significant differences of clinical or public health importance of the intervention effect based on sex/gender, or race/ethnicity and relevant subpopulation comparisons, then the investigator conducting the NIH-defined Phase III clinical trial must include sufficient and appropriate entry of sex/gender and racial/ethnic participants so that a valid analysis of the interventions effects can be determined. The conditions to be followed in the research plan or proposal are the same as those described above.

For all three (3) situations, cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

The final protocol submitted to the IRB for review and approval must contain a plan for valid analysis. “Valid analysis” means an unbiased assessment that will, on average, yield the correct estimate of the difference in outcomes between two (2) groups of participants. The principal requirements for ensuring a valid analysis of the question of interest are:

1. Allocation of study participants of all sex/genders and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization

2. Unbiased evaluation of the outcomes of study participants

3. Use of unbiased statistical analysis and proper methods of inference to estimate and compare the intervention effects among sex/gender and racial/ethnic groups

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 701: Informed Consent and HIPAA Authorization: General Requirements

1. Purpose

To describe the general requirements for obtaining and documenting informed consent.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
Institutional Review Board (IRB) Members

2. Procedure

Informed consent must be legally effective and prospectively obtained (45 CFR 46.116; 21 CFR 50.20). Except as described in JOHRP Policy IC 706, *Waiver and Alteration of Informed Consent and HIPAA Authorization*, before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the participant or their legally authorized representative (LAR). The consent must be IRB approved and contain the appropriate privacy authorization language (e.g. Health Insurance Portability and Accountability Act (HIPAA)).

Separate medical treatment consent must also be obtained for any procedure cited in relevant hospital policy, including Hospitals Policy 117.03, *Informed Consent,* and the policies listed below.

The consent form document may be either of the following:

- A written informed consent form that encompasses the elements of informed consent and the required elements of a HIPAA authorization. The investigator shall give the participant or LAR adequate opportunity to read it before it is signed. Alternately, this form may be read to the participant or LAR. The participant or LAR shall receive a written copy of the signed and dated consent document.

- A written “short form” stating that the elements of informed consent have been presented orally to the participant or their LAR, and that the key information was

presented first to the participant, before other information was provided. The IRB shall approve a written summary of what is to be said to the participant or LAR. When this method is used, there shall be an impartial witness to the oral presentation. The participant or LAR will sign the short form. The witness shall sign both the short form and the summary, and the person actually obtaining the informed consent shall sign the summary. A written copy of the signed and dated summary and the signed and dated short form shall be given to the participant or LAR.

The *Consent Guidance* is a guidance document available on the JOHRP website with details about commonly encountered consent scenarios. It includes information about which consent forms to use and which signatories are required. In addition, please reference the policies about specific scenarios.

Electronic signatures are acceptable if the signatures are legally valid within the jurisdiction where the research is to be conducted. For U.S. Food and Drug Administration (FDA) regulated research, electronic signatures must meet the requirements of 21 CFR Part 11.

To ensure that the correct, IRB approved versions of consent forms and other participant materials are used, the following must be done:

- Documents that are readily copied (e.g. consent forms, questionnaires) will be stamped by the IRB when approved

- Copies of the fully signed, stamped document will be offered to the participants. However, the study team must ensure (e.g. by the use of version date/number) the version approved by the IRB is identical to the version given to the participants

The investigator must not deviate from the consent plan approved by the IRB.

Privacy is generally the right of a person to be free from intrusion into matters of a personal nature, including control over how personal information is collected, used, maintained, shared, disclosed, and destroyed. The principles of respect for persons and beneficence in *The Belmont Report* support the need for privacy. 45 CFR 46.111 and 21 CFR 56.111 require the IRB to determine there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data as appropriate.

Researchers and the IRB must respect the privacy of prospective research participants and active research participants. Extra care to protect privacy must be taken during recruitment and consent. This is when the voluntary nature of participation and the extent of privacy must be made clear. Once a participant has consented, the researcher should continue to maintain

participant privacy. This may include allowing for appropriate flexibility, such as only contacting a participant using the requested method or at the requested time of day.

Privacy also includes an individual's desire not to be approached or contacted. Other than research related activities specifically designed to safely withdraw a participant from a study, once a prospective participant or active participant has indicated their decision, it must be respected. Any further questions or contact could be considered coercion. Once a participant is no longer in the study, the privacy of the patient and confidentiality of the data must be protected according to the protocol.

2.1 General Requirements for Informed Consent

These requirements apply to both written and verbal consent.

- Before involving a human subject in research, the Principal Investigator (PI) must ensure that the legally effective informed consent of the participant or their LAR, is obtained

- An investigator shall seek informed consent only under circumstances that provide the prospective participant or LAR sufficient opportunity to discuss and consider whether to participate and that minimize the possibility of coercion or undue influence

- The information given to the participant or LAR shall be in language understandable to the participant or LAR

- The prospective participant or LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information with research personnel

- For standard informed consent:
    - Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective participant or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension

    - Informed consent must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective

participant's or LAR's understanding of the reasons why one might or might not want to participate

- For informed consent to be given, it is not sufficient for a consent form to be signed. Instead, informed consent involves the provision of information sufficient to facilitate the prospective participant's understanding of the information, provide adequate opportunity for the prospective participant to ask questions and to consider whether to participate prior to enrollment, and continue to provide information as the clinical investigation progresses or as the enrolled participant or situation requires

- No informed consent may include any exculpatory language through which the participant or LAR is made to waive or appear to waive any of the participant's legal rights, or releases, or appears to release, the investigator, the sponsor, the institution, or its agents from liability for negligence

  Exculpatory language would include any language "through which a subject is made to waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agents from liability for negligence." Any language that has the intended "general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt" should be avoided

  - An example of such language, per the FDA, includes phrases such as: "I waive any possibility of compensation, including any right to sue for injuries that I may receive as a result of being in this study."

2.2 Required Elements of Informed Consent

The following elements must be present in all IRB-approved informed consent documents:

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected duration of the participant's participation
- A description of the procedures to be followed

- Identification of any procedures which are experimental or investigational

- Per FDA requirements, a description of any "reasonably foreseeable risks or discomforts" to the participant, e.g. in the form of "tests, interventions and procedures required by the protocol (including protocol-specified standard medical procedures, exams, and tests), with a particular focus on those that carry significant risk of morbidity or mortality." In addition, if there is a possibly of unintended disclosures of private information, the participants should be made aware of such possibility and provided with information on the measures taken to protect the privacy of the information. The FDA notes, however, that "it is not necessary to describe all possible risks, especially if doing so could make the form overwhelming for participants to read"

- A description of any potential benefits to the participant or to others which may reasonably be expected from the research. Participants should be made aware of the potential benefits of the research directly affecting themselves and the greater societal benefits. "For clinical investigations involving the comparison of an investigational product to one or more standards of care, it may be acceptable to generally describe the benefits of the standard of care in the informed consent form and provide more specific information about the standard of care as part of the consent discussion rather than in the consent document." FDA has also flagged some prohibited behavior related to the language used to inform participants of benefits:

    - FDA prohibits "overly optimistic representations of the benefits" because such representations "may be misleading and may violate FDA regulations that prohibit promotion of investigational drugs and devices." FDA prohibits researchers from identifying payments and reimbursements as "benefits"

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that the participant can pursue outside of the study

- A statement describing the extent to which, if any, the confidentiality of records identifying the participant will be maintained and that states the possibility that the FDA and representatives of the IRB may inspect the records

- For research involving greater than minimal risk, or any study reviewed by the convened Board, an explanation as to whether any compensation is available and

that medical treatments are available if injury occurs and where further information may be obtained

- The informed consent document must not waive or appear to waive the rights of the participant or release, or appear to release, those conducting the study from liability for negligence

- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant. The consent document must include the contact names, email addresses, and telephone numbers of who the participant may contact with questions about the clinical investigations, the participants' rights, and research-related injuries. "FDA recommends that the individual or office named for questions about participants' rights not be part of the investigational team, because participants may be hesitant to report specific concerns or identify possible problems to someone who is part of the investigational team"

- A statement that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. The informed consent must also include language informing the participant even if they do participate, they have the right to stop participating at any time. The consent form may not use language "that limits the participant's right to decline to participate or withdraw from the" study and if special procedures should be followed for the participant to withdraw from the clinical investigation, the consent process must outline and explain the procedures

- One (1) of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the participant or LAR, if this might be a possibility; or

    - A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies

2.3 Additional Elements of Informed Consent

When appropriate, one (1) or more of the following elements also may be required in the informed consent document:

- A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus if the participant is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant
- A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant
- The approximate number of participants involved in the study at Jefferson and, if a multi-site study, other participating sites
- A statement that the participant's biospecimens, even if identifiers are removed, may be used for commercial profit, and whether the participant will or will not share in this commercial profit
- A statement regarding whether clinically relevant research results including individual research results, will be disclosed to participants, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)

2.4 Elements of HIPAA Authorization

If protected health information (PHI) will be collected, HIPAA authorization language must be in the consent form or separate document unless the IRB approves a waiver. HIPAA authorization language is in the *Informed Consent Form Template*. The required elements of a HIPAA authorization can be found in 45 CFR 164.508 (c).

2.5 Obtaining Informed Consent – General Requirements

The PI has ultimate responsibility for ensuring that consent is properly obtained. Informed consent must be obtained before any study specific procedures are performed.

The consent form is reviewed with the participant and the participant is given the opportunity to read and discuss the consent form, ask questions, and consider participation.

To indicate consent, the participant or LAR signs and dates the consent form. The person obtaining/assisting with consent and the investigator also sign and date the consent form at this time.

For minimal risk studies, and if the IRB has approved the investigator signature option in the *Instruction Manual for the Consent Form for a Research Study* for studies without Medical Care Availability and Reduction of Errors (MCARE) procedures (see Section 2.6), the investigator does not have to be present during the consent process but should be available for questions as necessary. In this case, the investigator signs and dates the consent form as soon as possible after the participant has consented.

The original, signed consent form is maintained in the participant's study file. A copy of the signed consent form is provided to the participant. It must be documented that a copy was provided to the participant.

2.6 Obtaining Informed Consent – MCARE

These MCARE requirements apply to all Jefferson studies regardless of location. The IRB has the discretion to modify the MCARE requirements in the *Instruction Manual for the Consent Form for a Research Study* on a per study basis.

If a study involves MCARE procedures, a physician investigator or "qualified practitioner" must review the purpose, procedures, risks, benefits, and alternatives to participation with the study participant. The other elements of consent may be provided by properly trained and qualified key personnel.

For the purpose of this policy, the term "qualified practitioner" means a Co-Investigator (Co-I) or key personnel who is one (1) of the following: physician assistant, certified registered nurse practitioner, midwife, certified registered nurse anesthetist, another physician or a physician participating in a medical residency or fellowship training program who has knowledge of the patient's condition and the procedure to be conducted on the patient and shall be acting under the supervision of, at the direction of, or in collaboration or cooperation with, the physician.

At the time of consent, all signature lines are completed. In part, the investigator's signature certifies that the appropriate individual(s) reviewed the consent information with the study participant (see *Informed Consent Form Template*). The appropriate investigator signature option must be included in the consent form.

The following list of procedures is based on Pennsylvania's MCARE law, and the list provided in hospital policy, such as Hospital Policy 117.03, *Informed Consent*.

1. Administration of anesthesia (local, general, conscious sedation, etc.)
2. Performance of surgical procedures
3. Administration of chemotherapy and therapeutic radiation
4. Administration of blood and/or human source products
5. Refusal to allow transfusion of blood and/or human source products
6. Insertion of a surgical device or appliance
7. Performance of abortion
8. Performance of sterilization
9. Performance of any HIV-related testing (See Policy #113.58, *HIV Testing*, for specific documentation requirements)
10. Performance of Electroconvulsive therapy (ECT)
11. Administration of an experimental medication, use of an experimental device, use of an approved medication or device in an experimental manner or the removal of bone, fluids or tissue for use in research or in the manufacture of a product.

Experimental procedures and consent forms must be approved by the IRB. Note: Only an IRB approved informed consent is required.

12. Invasive procedures, such as halo placement, central venous catheterization, pulmonary artery catheterization

13. Performance of vaginal delivery/cesarean section

2.7 Other Requirements

- Second Person: The consent document should use the second person ("You"/"your") style writing so the consent form conveys a dialogue with information being provided and that there is a choice to be made by the participant rather than presumption of the participant's consent found with the use of the first person style ("I"/"mine").

- Plain Language: The information provided in the informed consent documents must be in a language understandable to the participant. The informed consent document should not use complex language that would not be understandable to all participants. Technical and scientific terms should be adequately explained using common or lay terminology.

- FDA-Regulated Test Articles: For research involving test articles regulated by the FDA, informed consent documents must include a statement that the purpose of the study includes evaluation of the safety and/or efficacy of the test article. The consent form must also include a statement that the FDA has access to the participant's medical records.

2.8 IRB Review of Consent Process

The IRB will take the following into consideration when reviewing the protocol and consent document:

- Who will conduct the consent process?

- Matters of timing of obtaining informed consent and the waiting period between informing the participant and obtaining consent

- If the process provides ample time for the person conducting the consent interview and the prospective participant to exchange information and ask questions

2.9 Posting of Clinical Trial Consent Form

For each clinical trial conducted or supported by a federal department or agency, one (1) IRB-approved informed consent form used to enroll participants must be posted by the awardee or the federal department or agency component conducting the trial on a publicly available federal website that will be established as a repository for such informed consent forms.

If the federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a federal website (e.g. confidential commercial information), such federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any participant, as required by the protocol.

3. References

The Common Rule, 45 CFR 46
45 CFR 164.508
21 CFR Part 11
21 CFR 56
Consent Guidance
Informed Consent Form Template
Instruction Manual for the Consent Form for a Research Study
HHS Guidance: Use of Electronic Informed Consent
Jefferson Entities Policies on Informed Consent:

- Jefferson Hospital Policy 117.03, *Informed Consent*
- Jefferson Abington Hospital, Policy 19.07, *Informed Consent*
- Landsdale Hospital, Policy 1.68, *Informed Consent*
- Jefferson Health Northeast, Policy 910-029, *Informed Consent*
- Jefferson Health Magee Rehabilitation, *Informed Consent*
- Kennedy University Hospital, Policy E013, *Informed Consent*
- Albert Einstein Health Network Policy A0248.5, *Informed Consent*

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 702: Documentation, Waiver, and Alteration of Informed Consent

1. Purpose

To describe the requirements for documenting informed consent.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
Institutional Review Board (IRB) Members

2. Policy

2.1 Policy Statement

Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the participant or their legally authorized representative (LAR) unless waiver or alteration is approved by the IRB.

3. Procedure

Note: A guidance document is available with details about commonly encountered consent scenarios. It includes information about which consent forms to use and which signatories are required. The document is called *Consent Guidance*, and it is located on the JOHRP website. In addition, please reference the policies about specific scenarios.

3.1 Documentation of Informed Consent

Each participant or their LAR must sign and date a written copy of the current IRB-approved consent form prior to enrollment or any participation in any phase of a research study, unless the requirement is waived by the IRB. The participant must be given a written copy of the signed document that has also been signed by an investigator and the person conducting the consent interview. At the discretion of the IRB, these signature requirements may be waived. For example, the signature of the Principal Investigator (PI) or Co-Investigator (Co-I) may be waived for selected minimal risk studies. For information on electronic signatures, see JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*.

The IRB may approve procedures for documentation of informed consent that involve:

1. A written consent form signed by the participant (see Section 3.1.1)

2. A short form written consent form with oral presentation (see JOHRP policy IC 701); or

3. In limited circumstances a waiver or alteration of a written consent form (see JOHRP Policy IC 706, *Waiver and Alteration of Informed Consent and HIPAA Authorization*). It is the responsibility of the IRB to determine which of the procedures described below is appropriate for documenting informed consent

3.1.1 Written Consent Form Signed by the Participant or Their LAR

In most circumstances, the IRB requires that informed consent is documented by the use of a written consent form approved by the IRB and signed by the participant or their LAR as well as by an investigator. The investigator must allow the participant or their LAR adequate opportunity to read the consent document before it is signed.

Some studies involving participants with anticipated or fluctuating impaired decision-making capabilities may take place over extended periods. For these studies, the IRB should consider whether periodic re-consenting of individuals or their LARs should be required to ensure that a participant's continued involvement is informed and voluntary. Additionally, the IRB should consider whether and when to require a reassessment of participant's decision-making capacity.

The written informed consent document must contain, in a language understandable to the participants of the study, all the elements necessary for legally effective informed consent (see JOHRP Policy IC 701). Participants who do not understand English are generally presented with an informed consent document written in a language understandable to them (see JOHRP Policy IC 705, *Informed Consent – Non-English-Speaking Participants and Translations*).

3.1.2 Participants Physically Unable to Sign a Consent Form

After the participant has indicated the intention to consent, the participant's name and the current date may be written in the appropriate places on the consent form signature page. In addition, the signature page or other documentation should include a statement with the following information:

- The participant is physically unable to sign the consent form

- All pages of the consent form were reviewed with the participant, who voluntarily consented to participate in this study

A witness, independent of the study, must be present for the entire consent discussion and must sign to verify the participant's consent.

3.1.3 Illiterate Participants

Consent documents may be read to participants who understand the language but cannot read the language.

3.1.4 Research Data Retention

In accordance with U.S. Food and Drug Administration (FDA) guidance:

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

- The investigator may ask a participant who is withdrawing whether the participant 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 participant must 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 participant's information

    - The investigator must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document

- If a participant 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 participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data

related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status

3.1.5 Use of Electronic Copy or Mail to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by mail or electronic copy to the participant or their LAR, and to conduct the consent interview by telephone when the participant or their LAR can simultaneously read the consent document as it is discussed. Consent may also be obtained by mail. When using this procedure, the participant or their LAR will first sign and date the consent form and mail it to the investigator.

The investigator will then sign and date the consent form and mail a copy of this form to the participant or their LAR. The investigator will then sign and date the consent form and mail a copy of this form to the participant or their LAR.

3.2 Reconsenting

Re-consent of research participants is required when there is new information about a trial that could affect the participant's willingness to continue in the trial. Examples include increased or new risks and changes in the protocol that materially affect the participant, such as additional study visits, increased length of visits, new questionnaires, or changes in treatment modalities.

If written information (e.g. consent form) has been approved for the study, the participants must be presented with a revised version of the written information unless otherwise specified by the IRB. Attention should be drawn to the revisions in the written information (e.g. highlight). In the event that re-consent is required, the revisions must be discussed with the participant. All appropriate signatures must be obtained, and a written copy provided to the participant. All information provide to the participants must be approved by the IRB.

4. References

45 CFR 46.116
Consent Guidance
JOHRP Website
JOHRP Policy 701, *Informed Consent and HIPAA Authorization: General Requirements*
JOHRP Policy 705, *Informed Consent – Non-English-Speaking Participants and Translations*
JOHRP Policy 706, *Waiver and Alteration of Informed Consent and HIPAA Authorization*

Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations, December 2023
Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors, August 2023

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 704: Child Assent and Parental Permission for Participation in Research

1. Purpose

To define the procedures to ensure that effective assent and consent are obtained when children are participating in research.

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
Institutional Review Board (IRB) Members

2. Policy

2.1 Definitions

- **Assent**: A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

- **Children**: Persons who have not attained the legal age for consent to treatments or procedures involved in the research/clinical investigation, under the applicable law of the jurisdiction in which the research/clinical investigation will be conducted.

  Under the laws of the Commonwealth of Pennsylvania, persons under the age of 18 generally meet the definition of children, and will be considered children for purposes of this policy, with the exceptions set forth below:

  - The research involves (i) the provision of medical, dental and health services, care or treatment, (including care or treatment deemed to be experimental) AND (ii) the person has married, has been pregnant, or has graduated from high school

  - The person is an emancipated minor. A minor may be determined by a court of competent jurisdiction to be emancipated, i.e. is self-supporting, and does not live with parents. To demonstrate emancipation, such minor

will be required to present appropriate documentation. If an emancipated minor provides consent for themself, the court order should be copied and included in the research records with the consent document

Under the laws of the State of New Jersey, persons under the age of 18 generally meet the definition of children and will be considered children for purposes of this policy with the exceptions set forth below:

- The research involves (i) the provision of medical care or treatment, (including care or treatment deemed to be experimental) AND (ii) the person is married or currently is or previously has been pregnant.

- The person is an emancipated minor. A minor may be determined by a court of competent jurisdiction to be emancipated, i.e. is self-supporting, and does not live with parents. To demonstrate emancipation, such minor will be required to present appropriate documentation. If an emancipated minor provides consent for themself, the court order should be copied and included in the research records with the consent document.

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

  Consistent with the laws of the Commonwealth of Pennsylvania and State of New Jersey, a legal custodian may provide the effective consent on behalf of a child to general medical care. In Pennsylvania and New Jersey, the ability for a court-appointed guardian to consent to research is limited by what a court has explicitly authorized in the guardianship paperwork.

  For purposes of this policy, a “guardian” means an individual appointed by a court of competent jurisdiction to serve in the capacity as a legal custodian who may consent on behalf of a child to general medical care **when such includes participation in research**. Except for research involving no greater than minimal risk, if a guardian provides consent on behalf of a child, the court order or legal authorization to consent to general medical care must be copied and included in the research records with the documentation of permission.

- **Legally authorized representative (LAR)**: an individual or judicial or other body authorized under applicable law to consent on behalf of prospective participant to the participant’s participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, LAR means an individual recognized

by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective participant to the participant's participation in the procedure(s) involved in the research.

For purposes of this policy and consistent with the laws of the Commonwealth of Pennsylvania, State of New Jersey, and federal regulations, a "LAR" capable of providing consent on behalf of a child to participate in research must meet the definition of a parent or guardian.

- **Parent**: A child's biological or adjudicated, adoptive parent. Where 'parent' is used in this policy, it includes guardians and LARs as defined in the policy.

- **Permission**: The agreement of parent(s) or guardian to the participation of their child or ward in a research study.

- **Ward**: A child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable federal, state, or local law. Under the laws of the Commonwealth of Pennsylvania, an agency must obtain consent from a ward's parent or legal guardian for experimental procedures or treatment. (See, 55 Pa. Code Section 3680.52)

  For purposes of this policy, a parent or a guardian must provide consent on behalf of a ward to enable the ward to participate in research studies. In the event the parent or guardian cannot be located, a court order authorizing participation in the research will be required.

  If parental consent is given for a minor's participation in research and the legal status of the child changes (the child is adopted or becomes a ward), the consent previously provided will continue to be valid unless the new legal guardian withdraws the child from participation in the study.

3. Procedure

As required by regulation, the assent of a child must be accompanied by the permission of a parent/guardian/LAR. Generally, children ages seven (7) to 17 should be given the opportunity to assent. The IRB will determine the appropriate assent requirements and documentation pursuant to determinations made with the appropriate form. The investigator is responsible for determining if the participant (minor or individual with impaired decision-making capacity) is capable of assent.

3.1 Assent

The IRB shall determine adequate provisions are made for soliciting the assent of the children when, in the judgement of the IRB, the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the age, maturity, and psychological state of the children involved, as well as the risks and benefits to the child. This judgment may be made for all children involved in the research under a particular protocol or for each child individually, as the IRB deems appropriate.

The Common Rule at 45 CFR 46.116(a)(5)(i) indicates, "Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective participant or legally authorized representative in understanding the reasons why one might or might not want to participate in the research."

This summary of key information, or a separate assent document, may be used for assent. The study will be explained to the participant at the appropriate level of understanding. Participants who would have difficulty understanding a written consent document will not be required to read a written consent document. Those at a higher level of understanding will be given the opportunity to read the summary of key information, or the entire consent form as appropriate. A separate assent form approved by the IRB is also acceptable. The signature and date of the parent/guardian are obtained on the consent form. The signature and date of the minor participant are obtained on the consent form, or on the separate assent form.

The IRB may waive the requirement for assent if:

- The capability of some or all the children is so limited that they cannot reasonably be asked to provide assent

- 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 children and is available only in the context of the research

Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement for some of the same reasons consent would be waived (45 CFR 46.116).

If a child dissents, this should be respected and documented. If the research may provide direct benefit to the child, the dissent of the child may be overruled by the parent and the child can be enrolled in the research with parental permission.

3.2 Parental Permission

As required by regulation, the permission of a parent or guardian must be obtained before a child may participate in research. Parental permission follows the same process as obtaining consent. A consent form may be used as a parental permission form.

When possible, the permission of both parents should be obtained. The permission of both parents must be obtained for the following types of research unless one (1) parent is deceased, unknown, incompetent, or not reasonably available, or when only one (1) parent has legal responsibility for the care and custody of the child:

- Research involving greater than minimal risk and no prospect of direct benefit to individuals participants, but likely to yield generalizable information about the participant's disorder or condition (45 CFR 46.406)

- Research meeting criteria at 45 CFR 46.407 that is not otherwise approvable under the other regulatory categories in Subpart D which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

The permission of only one (1) parent is permitted for:

- Research not involving greater than minimal risk. (45 CFR 46.404)

- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants. (45 CFR 46.405)

If the IRB determines that a research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), it may waive the parental permission requirements, provided an appropriate mechanism for protecting the child participants who will participate as participants in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition. A possible mechanism would be seeking a court appointment of an alternative guardian.

3.3 Research Involving Children Conducted in Other Jurisdictions

If the research includes enrollment of child participants in other states or countries, and a Jefferson IRB is the designated IRB, the Principal Investigator (PI) is responsible for providing JOHRP with acceptable verification of the following as it pertains to child participants in those states or countries:

- The age at which participants can consent to research and medical treatments and procedures
- Who may act as a guardian or LAR for children participating in research
- Privacy requirements. The PI may consult with the Privacy Office
- Regulations on genetic research when applicable

JOHRP will consult with the Enterprise Office of Legal Affairs as necessary. For research conducted in other jurisdictions where an external IRB is serving as the designated IRB, Jefferson will defer to the external IRB for review of the above issues.

4. References

The Common Rule, 45 CFR 46
45 CFR 46 Subpart D
21 CFR 50.3
21 CFR 50 Subpart D
55 Pa. Code Section 3680.52

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 705: Informed Consent – Non-English-Speaking Participants and Translations

1. Purpose

To define the policy and procedures for informed consent translations.

1.1 Responsible Parties

Investigators
Key Personnel
Institutional Review Board (IRB) Members
Jefferson Office of Human Research Protection (JOHRP) Personnel

2. Procedure

In general, non-English-speaking participants should not be excluded from studies with possible therapeutic benefit unless there is a valid scientific, ethical, or logistical reason. Per 45 CFR 46.116, the consent information that is given to a participant must be in a language understandable to the participant. This will typically be done with translated, written documents approved by the IRB unless appropriate waiver criteria are met (45 CFR 46.116 and 46.117). Ad hoc oral translations are not permitted. All consent documents must be submitted to and approved by the IRB before being used to consent a participant.

2.1 Non-English-Speaking Participants

The consent documentation for non-English-speaking participants can be divided into two (2) categories:

1. When non-English-speaking participants are expected (e.g. common in the study population), the full English consent form is translated into the participant's language. Both the English and translated versions are submitted to the IRB for approval.

2. When a non-English-speaking participant unexpectedly presents for possible inclusion in a study, the short form process is used. For the short form process, the full English consent form is discussed with the participant using a translator.

The short form is in the participant's language and verifies that the elements in the English version have been discussed with the participant. There are short forms in several languages on the JOHRP website. Only the study specific information prompted should be added to the short form. The short form in the participant's language must be provided to the IRB for approval with the full English version of the consent form (if not yet approved). In the case of newly translated short forms, the certification of translation (see below) must also be provided to the IRB. For information about the required signatories on each document, see the Consent Guidance document located on the JOHRP website.

After a participant consents using the short form process, the IRB will determine the requirements for providing an English translation of the study information (e.g., no further translation or a translation of a study summary or the full English consent). The determination will be based on the duration and risk of the study. The participant's receipt of the translated study information should be documented, but re-consent and signatures are not required.

2.2 Re-Consent of Non-English-Speaking Participants

If the consent form for the study has to be amended and participants must be re-consented, the short form process should not be used, because now any non-English-speaking participants already in the study would be expected. There are two (2) options in this case:

1. Amend the full English consent form and have it translated or

2. Create an English addendum, which just states the changes to the consent form and have it translated.

In either case, the consent form must be approved by the IRB.

2.3 Obtaining Translations of Consent Documents

Consent forms may be translated by a translation agency or an individual. Translation agencies will provide a certification of translation. For individuals, the certification of translation consists of the translator's name, qualifications, and a statement that the translation is accurate. All translated consent documents must be submitted to the IRB for review and approval. If there are no substantive changes to a short form on the JOHRP website, only the translated form must be submitted to the IRB. For other translated documents, provide the English version, the translated version and the certification of translation.

2.4 Translators for the Consent Discussion

The translator present during the consent process can be a professional translator, study personnel, other non-study staff, or a family member. The translation phone may also be used. The translator must have an adequate understanding of both languages in order to translate the full meaning of the consent form, including medical and scientific terms. The translator must be present for the entire consent discussion and available throughout the study if needed.

2.5 Witnesses and Translators

When required for consent involving non-English-speaking participants, a witness must be present for the entire consent discussion and available throughout the study if needed. The witness must be bilingual to confirm that the information was presented correctly to the participant. When using the translation phone, the translator may act as the witness. This must be documented but the signature of the translator is not required.

3. References

45 CFR 46.116
45 CFR 46.117
JOHRP website
Consent Guidance

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 706: Waiver and Alteration of Informed Consent and HIPAA Authorization

1. Purpose

To describe the procedures by which an Institutional Review Board (IRB) may waive or alter informed consent or authorization use and/or disclosure protected health information (PHI).

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
IRB Members

2. Policy

2.1 Policy Statement

In certain circumstances, the IRB may waive the requirement to obtain informed consent or may approve a consent procedure that omits or alters some or all the elements of informed consent.

3. Procedure

3.1 Waiver and Alteration of Informed Consent

- Waiver

  An IRB may waive the requirement to obtain informed consent provided that pertinent regulatory criteria are met at 45 CFR 46.116.

  An IRB may approve a consent procedure that omits or alters some or all the elements of informed consent, provided the IRB satisfies the requirements below. An IRB may not omit or alter any of the general requirements of informed consent (see JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*).

- Requirements for Waiver and Alteration

  For an IRB to waive or alter consent, the IRB must find and document that:

- The research involves no more than minimal risk to the participants
- The research could not practicably be carried out without the requested waiver or alteration
- If the research involves using identifiable private information or identifiable biospecimen, the research could not practicably be carried out without using such information or biospecimen in an identifiable format
- The waiver or alteration will not adversely affect the rights and welfare of the participants; and
- Whenever appropriate, the participants or their legally authorized representatives (LARs) will be provided with additional pertinent information after participation

IRB waiver or alteration of informed consent must be documented in the IRB meeting minutes. As exempt studies are exempted from *The Common Rule* (45 CFR 46) requirements, the IRB is not required to make formal waiver/alteration determinations of consent for these studies. However, these determinations do need to be made for the Health Insurance Portability and Accountability Act (HIPAA).

- Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs

  For waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials:

  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:

  - Public benefit or service programs
  - Procedures for obtaining benefits or services under those programs
    - Possible changes in or alternatives to those programs or procedures; or

        - Possible changes in methods or levels of payment for benefits or services under those programs; and

    - The research could not practicably be carried out without the waiver or alteration.

3.2 Screening, Recruitment, or Determining Eligibility

An IRB may approve a research proposal in which an investigator will obtain information or biospecimen for the purpose of screening, recruiting, or determining the eligibility of prospective participants without the informed consent of the prospective participant or their LAR, if either of the following conditions are met:

- The investigator will obtain information through oral or written communication with the prospective participant or their LAR, or

- The investigator will obtain identifiable private information or identifiable biospecimen by accessing records or stored identifiable biospecimen.

In these instances, the IRB does not have to make the regulatory determinations for waiver/alteration of consent. However, if a researcher is communicating directly with a potential participant either through written or verbal means and with intent to collect personal information to be used for the above-mentioned reasons, the investigator should make a good faith effort to communicate the goal of this information-gathering to the individual. (45 CFR 46.116(g))

3.3 Waiver of the Requirement to Obtain Written Consent

An IRB may waive the requirement for the investigator to obtain written consent, i.e. a signed informed consent form for some or all participants if it finds any of the following:

- The only record linking the participant and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant (or their LAR) will be asked whether they want documentation linking them with the research, and their wishes will govern

- That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context; or

- If the participants or their LARs are members of a distinct cultural group or community in which signing forms is not a typical practice that the research presents no more than minimal risk of harm to participants and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide participants or legally authorized representatives with a written statement regarding the research.

3.4 Waiver of Authorization to Use and/or Disclose Protected Health Information (PHI)

Investigators may use and/or disclose PHI of the covered entity for research purposes without prospective authorization from participants provided they complete the section of the study application pertaining to such request. The following criteria must be adequately addressed:

The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on:

- The provision of an adequate plan to protect the identifiers from improper use and disclosure
- The provision of an adequate plan to destroy the identifiers at the earliest possible opportunity consistent with the conduct of the research unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law
- The provision of adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by law
- The research could not be practicably conducted without the waiver or alteration
- The research could not be practicably conducted without access to and use of the PHI

4. References

The Common Rule, 45 CFR 46

JOHRP Policy IC 701, *Informed Consent and HIPAA Authorization: General Requirements*

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 707: Surrogate Consent

1. Purpose

To ensure that if a prospective participant cannot consent on their own behalf, that surrogate consent is obtained from a legally authorized representative (LAR) according to federal regulations and local law, and that the process and associated forms are properly approved by the Institutional Review Board (IRB).

1.1 Responsible Parties

Jefferson Office of Human Research Protection (JOHRP) Personnel
Investigators
Key Personnel
IRB Members

2. Policy

2.1 Definitions

- **Legally authorized representative (LAR)**: an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, LAR refers to an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of an individual to undergo clinical procedures.

- **Types of LARs**:
  - **Parent**: Natural or adoptive
  - **Guardian**: Appointed by a court of law.
  - **Health Care Agent**: Appointed by the patient in a written health care power of attorney, which must be dated and signed by the patient (or someone else at the patient's direction). Agent may have broad powers to direct all care including participation of patient in research. Power of attorney may vest authority in the agent while the patient is still competent. Power of

attorney must be consulted to determine the scope and any limitations on the authority of the health care agent. Any questions should be directed to the Jefferson Enterprise Office of Legal Affairs.

- **Health Care Representative**: May be designated by the patient in writing or verbally, or absent designation by the patient, determined by operation of law.

3. Procedure

In general, surrogate consent is used with adults with a condition that impairs decision-making capacity.

All adults (including those with cognitive impairments) are presumed competent to consent unless legally judged to be incompetent. In most cases, minors are presumed to not be competent to consent for themselves. For minors, see IC 704, *Child Assent and Parental Permission for Participation in Research*.

Cognitively impaired persons are considered a vulnerable research population because their mental disability may compromise their capacity to make a reasoned decision about participation in a study. People with Alzheimer's disease, dementia, mental illness, and developmental disabilities may be considered cognitively impaired and may not be able to provide informed consent for participation in research.

In certain circumstances, when it is determined that a potential research participant is cognitively impaired, federal regulations and state laws permit researchers to obtain consent from a LAR via surrogate consent.

The National Bioethics Advisory Commission issued a report on *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity* (December 1998). The recommendations set forth in that report should be carefully reviewed by Principal Investigators (PIs) considering research involving such a population.

The investigator must determine if surrogate consent is a possibility for the study. JOHRP may be consulted as needed. Please refer to the surrogate section of the *Informed Consent Form Template* or an acceptable list of surrogates.

The law in Pennsylvania regarding consent to participate in research for incapacitated persons can be granted by court-appointed guardians or healthcare powers of attorney who must have explicit authorization to consent a legally incompetent patient into research studies. The relevant statute is found at 20 Pa. C.S. § 5521(d), which reads:

> **Unless specifically included in the guardianship order** after specific findings of fact or otherwise ordered after a subsequent hearing with specific findings of fact, a guardian or emergency guardian shall not have the power and duty to consent on behalf of the incapacitated person to the performance of any experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment.

Similarly, New Jersey law allows the court-appointed guardian to consent if the guardianship paperwork explicitly authorizes the guardian to provide consent for research purposes (N.J. Stat. § 3B:12-52).

The IRB will determine if surrogate consent is appropriate. In its decision, the IRB will consider:

- The risks vs. the benefits
- The plan to assess the capacity of the participant to consent or assent
- The necessity and plan for assent
- In cases of abuse, neglect, or endangerment, the plan to disqualify an individual to serve as a surrogate

The PI is responsible for reporting cases of abuse, neglect, or endangerment as required by local law and must document the decision to disqualify an individual to serve as a surrogate. The circumstances surrounding the use of the surrogate and the surrogate's relationship to the participant should be thoroughly documented in the research record.

If the participant is determined to be capable of assent, assent is also obtained at this time.

If the participant actively refuses assent, the investigator must assess the following:

- The participant has been found legally incapable of decision making through the use of formal assessment
- The study has potential benefit to the participant

If all conditions are met, surrogate consent may be used. If any of these conditions are not met, the participant's wishes will be respected, and the participant will not be enrolled.

In the event of a disagreement among potential surrogates, the investigator will attempt to facilitate a consensus. If consensus cannot be reached, the participant cannot be enrolled in the study unless further mediation is sought for the parties in disagreement.

When a surrogate provides consent, it is advised that they should remain the responsible party for all research decisions throughout the duration of the participant's participation in the research.

If the participant is initially capable of providing informed consent, but it is likely that the participant will lose this capacity during the study, the participant should appoint a surrogate before beginning the study. The appointed person can then assume the surrogate role as necessary for the duration of the study, unless the participant again attains decision/cognitive capacity and can resume autonomous decision-making.

If the initial consent is provided by the surrogate, and the participant is later determined to be capable of autonomous decision-making, consent should be obtained from the participant as soon as possible. If the participant does not consent to continued participation, the participant will be withdrawn from the study and the data obtained will not be used without the participant's written agreement and signature.

3.1 Research Being Conducted in Other Jurisdictions

If the research includes enrollment of participants in other states or countries, the PI is responsible for providing JOHRP with acceptable verification of the following:

- The circumstance under which surrogate consent is allowable
- Who may act as a surrogate
- Other legal requirements

The PI and/or JOHRP will consult with the Enterprise Office of Legal Affairs as necessary.

4. Reference

45 CFR 46.102
JOHRP Guidance G 621, *Safeguarding and Protection of Children in Research Studies*
JOHRP Policy IC 704, *Child Assent and Parental Permission for Participation in Research*
Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity (December 1998)
20 Pa. C.S. § 5521(d)

N.J. Stat. § 3B:12-52

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 708: Planned Research in Emergency Settings

1. Purpose

To describe planned emergency research, the exception from informed consent requirements for such research and the requirement for prospective Institutional Review Board (IRB) review. NOTE: This policy does NOT apply to emergent use of a drug, biologic, or medical device, which is addressed in the Jefferson Office of Human Research Protection (JOHRP) Policy GA 112, *Emergent Use of an Investigational Drug, Biologic, or Medical Device*.

1.1 Responsible Parties

Director/Associate Director of JOHRP
IRB Members

2. Procedure

The aspect of planned emergency research that distinguishes it from all other types of clinical trials is that it can proceed with a waiver of informed consent. This raises the standard of protection for individuals who will be enrolled. However, because of special regulatory limitations relating to research involving fetuses, pregnant persons, and human in vitro fertilization (45 CFR 46, Subpart B), and research involving prisoners (45 CFR 46, Subpart C), this waiver is inapplicable to these categories of research.

In order to waive informed consent for this type of research, the IRB must find and document that:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific data, which may include data 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:

- The participants will not be able to give their informed consent as a result of their medical condition

- The intervention under investigation must be administered before consent form the participant's legally authorized representation (LAR) is feasible; and

- There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation

3. Participation in the research holds out the prospect of direct benefit to the participants because:

   - Participants are facing a life-threatening situation that necessitates intervention

   - Appropriate animal and other pre-clinical studies have 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 participants; and

   - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of prospective participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity

4. The clinical investigation could not practicably be carried out without a waiver

5. The proposed research plan defines the length of the potential therapeutic window based on scientific evidence

6. The investigator has committed to attempting to contact a legally authorized representative for each participant within the window of time and, if feasible, to ask the LAR contacted for consent within the window rather than proceeding without consent.

   The investigator will summarize efforts made to contact LAR(s) and make this information available to the IRB at the time of continuing review.

7. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and

the informed consent document are to be used with participants or their LAR in situations where use of such procedures and documents is feasible.

8. Additional protections of the rights and welfare of the participants will be provided, including at least:

   - Consultation carried out by the study team, its designees, and/or other stakeholders with representatives of the communities in which the clinical investigation will be conducted and from which the participants will be drawn

   - Public disclosure to the communities in which the clinical investigation will be conducted, and from which the participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits

   - Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results

   - Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

   - If obtaining informed consent is not feasible and an LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact, within the therapeutic window, the participant's family member who is not an LAR, and asking whether they object to the participant's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review

   - The study plan must ensure that, at the earliest feasible opportunity, each participant or, if the participant remains incapacitated, an LAR of the participant or, if such a representative is not reasonably available, a family member, will be informed of the participant's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

     The study plan must ensure that there is a procedure to inform the participant, or, if the participant remains incapacitated, an LAR of the participant, or, if such a representative is not reasonably available, a family member, that they may

discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. If an LAR or family member is told about the clinical investigation and the participant's condition improves, the participant is also to be informed as soon as feasible. If a participant is entered into a clinical investigation with waived consent and the participant dies before an LAR or family member can be contacted, information about the clinical investigation is to be provided to the participant's LAR or family member, if feasible.

If the IRB determines it cannot approve a clinical investigation because the investigation does not meet the criteria provided in the above section or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation.

If the IRB makes this determination and the Principal Investigator (PI) is the sponsor of the IND, the PI must promptly disclose this information to the FDA.

3. References

21 CFR 50
Federal Register 61(192): 51531-51533
JOHRP Policy GA 112, *Emergent Use of an Investigational Drug, Biologic, or Medical Device*
FDA *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research*, March 2011 Updated April 2013
45 CFR 46 Subparts B & C

Jefferson Office of Human Research Protection Policies and Procedures Manual

700 Informed Consent (IC)

Policy IC 709: Treatment and Cost of Research-Related Injury

1. Purpose

To define what treatment and compensation will be provided to research participants as a result of a research-related injury.

1.1 Responsible Parties

Investigators
Institutional Review Board (IRB) Members
Jefferson Office of Human Research Protection (JOHRP) Personnel
Key Personnel
Director, Office of Research Support Services (ORSS)
Director, Jefferson Clinical Research Institute (JCRI)
Deputy Provost of Research Affairs
Enterprise Office of Legal Affairs

2. Policy

2.1 Policy Statement

Jefferson is required to conform with federal regulations pertaining to informed consent, and pertinent accreditation standards. Federal regulations require that one (1) of the provisions of consent is that prospective participants be provided with the following information:

> "For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments will be provided if an injury occurs and if so, what they consist of, or where further information may be obtained." (21 CFR 50.20)

Those regulations also prohibit any informed consent, oral or written, from including:

> "Any exculpatory language through which the subject or their representative is made to waive or appear to waive any of the subject's legal rights, or releases or

appears to release the investigator, the Sponsor, the institution, or its agents from liability for negligence" (45 CFR 46.116).

2.2 Definitions

- **Funding Source**: The organization or person providing financial or other support, such as the provision of drugs/devices, for a study. The funding source may be internal, e.g. a Jefferson department, or external, i.e. non-Jefferson owned entities, such as a pharmaceutical company, grant agency, or private individuals.

- **Sponsor**: The entity that takes responsibility for and initiates a research study. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the study unless the sponsor is a sponsor-investigator. The FDA delineates specific responsibilities for the study sponsor, see 21 CFR 312 Subpart D

- **Sponsor-Investigator**: An individual who both initiates and conducts clinical research, and under whose immediate direction the investigational drug/device is administered or dispensed. The requirements applicable to a sponsor-investigator include those applicable to an investigator and a sponsor

- **Participant Injury Costs**: Costs for treatment of illness or injury suffered by a research participant that directly results from participation in the research

3. Procedure

3.1 Participant Injury Cost Applicable Rules

The Centers for Medicare and Medicaid Services (CMS) has taken a position that a promise to pay for Participant Injury Costs in a contract (even conditional payment), of itself, is sufficient to be considered a liability insurance policy or plan such that Medicare would not be the primary payor (Medicare Secondary Payor (MSP) provisions). As a result, CMS requires that if a sponsor chooses to pay Participant Injury Costs for participants covered by Medicare, then the sponsor must be treated as the primary payor for those costs. The MSP provisions require that Medicare is the secondary payor. The same principles apply to Medicaid, the payor of last resort.

For Commercially Sponsored Research, applying the CMS position, Jefferson shall prohibit scenarios that could result in Medicare becoming a primary payor when another "primary plan" exists. In order to avoid Medicare Secondary Payor violations for participant injury claims, contractual obligations shall require commercial sponsors to pay

for all participant injuries without an obligation to first bill insurance programs, followed by a Commercial Sponsor payment for denied claims. Medicare will not be charged for Medicare eligible participants and therefore Medicare will remain a "secondary payor." Commercial Sponsors shall be the Primary Payor for all participant injuries.

For clarity, Jefferson will NOT agree to initially bill Medicare, Medicaid HMO plans or any other governmental healthcare insurance or any other payor for Participant Injury Costs, and then bill the Commercial-Sponsor for what the governmental healthcare programs or other payors do not pay. The reason for the above is that Jefferson accepts funding from Medicare and other governmental health care programs and under the National Coverage Determination (NCD) for Routine costs in Clinical Trials (310.1), Medicare provides coverage for items or services needed for reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis or treatment of complications. Additionally, because Medicare may pay for certain costs in the study, but other payors will not and the sponsor provides those items or services for those study participants, Medicare must not be billed for those items and services provided for non-Medicare study participants.

For government or philanthropic grant-funded research and Jefferson-funded research (also known as departmentally funded), Jefferson will not promise to pay Participant Injury Costs and will not become a primary payor but will make every effort to seek reimbursement from a participant's health plan. The participant will be responsible for any deductibles and co-payments required under their health plan and for any claims ultimately denied by the health plan.

Jefferson and its investigators share responsibility for complying with the laws, rules, regulations, and operating guidance relating to treatment of research-related injury and compensation for Participant Injury Costs. The purview of the IRB is to provide an ethical and regulatory review of the research, including evaluating the participant injury language.

3.2 Funding Types

- Commercially Sponsored Research

  Although Commercial Sponsors are not legally required to pay for Participant Injury Costs for any participant, Jefferson will require that sponsors pay for Participant Injury Costs. These terms shall be negotiated as part of the clinical trial agreement. If the Commercial Sponsor elects not to pay for any Participant Injury Costs, additional endorsement of the research must be obtained from the Department Chair and the Deputy Provost of Research justifying that the research

participants should bear the costs that may arise as a result of research-related injury.

- Governmental or Philanthropic Grant Funded Research

  In situations where the funding source is a grant from the government or a philanthropic institution or foundation, Jefferson will offer reasonably necessary treatment for a research-related injury or illness, but Jefferson will not pay for Participant Injury Costs. Jefferson will make every effort to seek reimbursement from a participant's health plan, but the participant will be responsible for any deductibles and co-payments required under their health plan and for any claims ultimately denied by the health plan.

- Jefferson Sponsored Research (also known as Departmentally Funded)

  Jefferson Sponsored Research means research studies that are sponsored by Jefferson and whose funding source may be internal or external. For Jefferson sponsored research, Jefferson shall provide medical care to participants and handle Participant Injury Costs on the same terms as government or philanthropic grant-funded studies.

- Other Compensation

  No other compensation for claims in connection to research-related injuries, such as lost wages, pain and suffering, and other types of additional expenses beyond medical treatment related to the research-related injury, will be offered for any type of research including commercially sponsored research, governmental or philanthropic grant-funded research, or Jefferson-sponsored research.

- Informed Consent Form and Clinical Trial Agreement (CTA)

  Participant Injury Costs provisions will be added to the informed consent form and Clinical Trial Agreement. The wording of the CTA and the consent form must be consistent. The CTA should be compared to the consent form approved by the IRB to ensure that the language between the two (2) documents is consistent, though not necessarily identical. If the language is inconsistent, one (1) of the documents should be modified appropriately to reflect the agreement of the parties. In the event of an inconsistency between an executed CTA and the IRB approved informed consent form, the CTA will not be released to the Principal Investigator (PI), and/or the study account will not be established until both documents are aligned.

3.3 Clinical Trial Agreement (CTA) Template

For all Commercially Sponsored research, Jefferson's CTA template provision for Participant Injury Costs is as follows:

In the section of the CTA titles Indemnification of this Agreement/Letter of Indemnification, if a study participant suffers an adverse reaction, illness, or injury which, in the reasonable judgment of Institution, was directly caused by a study drug or study device or any properly performed procedures required by the protocol ("Study Injury"), sponsor shall reimburse for the reasonable and necessary costs of diagnosis and treatment of any study Participant Study Injury, including hospitalization, but only to the extent such expenses are not attributable to:

i. Institution's gross negligence or willful misconduct, or

ii. The natural progression of a documented underlying or pre-existing condition or events, unless exacerbated by participating in the study

The sponsor shall not delay or withhold reimbursement from any such study participant based upon the belief that the Study Injury was due to the institution's gross negligence. In that event, sponsor's sole remedy shall be with respect to institution under the indemnification provisions of this agreement.

In addition, it is the policy of Jefferson that, other than what is set forth in the above-mentioned template language, no CTA shall permit the sponsor to limit its own indemnification, or shift to participants its indemnification risk with respect to claims or causes of action that arise from the conduct of the sponsor, whether related to the manufacturing, distribution, or quality of a test article, or with respect to the actions of the sponsor in design, conduct, and reporting of the research. Further, no CTA shall permit the sponsor to limit compensation for participant injury based on the participants' actions such as not following the directions of the study.

3.4 Participant Injury Costs

Jefferson's position for Participant Injury Costs for government or philanthropic grant-funded research or Jefferson-sponsored research shall be as follows:

Jefferson will offer participants reasonable and necessary care to treat injuries directly resulting from a participant taking part in this research. Jefferson may bill the participant's insurance company or other third parties, if appropriate, for the costs of the care provided for the injury, but the participant will be advised that they may also be responsible for

some of the costs. There are no plans for Jefferson to compensate participants for the injury. Participants do not give up their legal rights by consenting to take part in the research.

All consent forms that involve research with greater than minimal risk must contain and some of the consent forms that involve research with minimal risk may contain the language related to participant injury and cost set forth in the *Informed Consent Form Template* provided on the JOHRP website.

3.5 Principal Investigator (PI) Responsibilities

- Coverage for Research-Related Injury

  The PI shall be responsible to know how research-related injuries will be covered, e.g., medical expenses for research-related injury, or the cost of reasonably foreseeable medical care in the event of a research related injury, will be covered:

  i. By the commercial sponsor

  ii. By the government, philanthropic, or other grant, or

  iii. By the participant

  As noted above:

  - For commercially sponsored clinical trials, the sponsor will cover the costs
  - For Jefferson sponsored clinical trials, the participant will be responsible for the costs of participant injury.

- Informing Participants:

  The PI is responsible for ensuring the appropriate language is included in the consent form and discussing obligations for research related injuries as part of the informed consent process. The consent form language must be consistent with contractual obligations.

- Determination of Injury:

  The PI of the study is responsible for evaluating a participant who claims to have a research-related injury or illness and reporting this to the IRB (see JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*), the Enterprise Office of Legal Affairs, and the JCRI

Business Operations Office. Investigators should report all claims and outcomes to the IRB and Enterprise Office of Legal Affairs regardless of whether it is determined to be research-related or not. If the injury is determined to be research-related, a meeting will be held with the PI, representatives from the IRB, contracting office, clinical trial billing, and the Enterprise Office of Legal Affairs to determine the additional steps which need to be taken and to designate a point of contact for the research participant in addressing the claim.

4. References

21 CFR 50.20
45 CFR 46.116
21 CFR 312 Subpart D
National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1)
JOHRP Policy GA 120, *Reporting and Reviewing Unanticipated Problems Involving Risks to Participants or Others*