

ST. LUKE'S UNIVERSITY HEALTH NETWORK IRB POLICIES AND PROCEDURES MANUAL

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100 General Administration (GA)

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

1. PURPOSE

The purpose of this policy is to:

- State the institutional authority under which the 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 subjects are protected;
- State the authority of the IRBs

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO; Appointed/Elected IRB Members

3. POLICY STATEMENT

The Institutional Review Board (IRB) of St. Luke's University Health Network has been established in accordance with the laws of the State of Pennsylvania and New Jersey; the regulations of the Department of Health, the Department of Health and Human Services, and the Food and Drug Administration; the Medical Staff Bylaws; and in accordance with the guidelines of ICH-GCP; the Belmont Report, and the Declaration of Helsinki.

This manual serves to establish guidelines and procedures for the SLUHN IRB, and to provide assistance to investigators so that they will maintain compliance with the rules and regulations that have been established for research conducted at St. Luke's University Health Network as set forth in this manual.

This policy pertains to the activities of the SLUHN IRB operating under the authority of St. Luke's University Health Network's Federalwide Assurance (FWA).

3.1: Statement of Institutional Authority

The Institutional Review Board is established and empowered under the authority of SLUHN Legal Counsel and the SLUHN Federal Wide Assurance (FWA) with the Department of Health and Human Services.

SLUHN requires that all research involving human subjects, or material or personal information from living humans, be reviewed and approved by the SLUHN IRB prior to initiation of any research activities. This includes recruitment and screening activities.

3.2: Purpose of the IRB

The purpose of the IRB is to protect the rights and welfare of human subjects participating in biomedical and behavioral research conducted at SLUHN. The IRB is responsible for the review, approval and oversight of such research to assure that it meets the ethical principles established for human subject's research, and that it complies with federal regulations that pertain to human subjects protection at 45 CFR, Part 46 and 21 CFR, Part 56 and any other pertinent regulations and guidance.

3.3: Governing Principles

The IRB 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: Ethical Principles and Guidelines for the Protection of Human Subjects in Research ("The Belmont Report"). The defining principles in the Belmont Report are:

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- Beneficence—The sum of the benefit derived by the subject from participation and the importance of the knowledge to be gained from the study to outweigh the risks to the subject as to warrant a decision to allow the subject 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 that meet the provisions of applicable regulations.
- Justice—The selection of subjects is equitable and is representative of the group of subjects that will benefit from the research.

3.4: IRB Authority

The function of the IRBs is to review and approve biomedical and behavioral research involving human subjects that is conducted by SLUHN employees, utilizing SLUHN patients, or utilizing SLUHN facilities 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); 108(b)(3); 109(a) (f); 113 and 45 CFR 160, 164. Consequently, the IRBs will review all research that:

- is sponsored by St. Luke's University Health Network
- is conducted by or under the direction of any faculty of SLUHN in connection with his/her institutional responsibilities
- is conducted by or under the direction of faculty of SLUHN using any property or facility of the University
- involves the use of the SLUHN nonpublic information to identify and contact human research subjects
- involves the use or disclosure of protected health information

The SLUHN IRB may approve, require modifications to secure approval, or disapprove all human subjects research activities overseen and conducted by the organization (45CFR46.109(b)). In addition, the IRB has the authority to place restrictions on a study or require progress reports from the investigators and observe, or have a third party observe, the consent process (21CFR56.109(f)) and/or the conduct of the research (21CFR56.109(f)). They may also 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 (45CFR46.113

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Policy GA 102: Activities Requiring IRB Review

1. PURPOSE

To describe specific activities that require IRB review and, conversely, those that do not require IRB review.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO; Appointed/Elected IRB Members.

3. DEFINITIONS

- **Research:** A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.
- **Human Subject:** An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used. Can be any living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with an individual or identifiable private information.
- **Clinical Investigation:** Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505 (i) or 520 (g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug and Cosmetic Act, but then later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. (21 CFR 50.3(c), 21 CFR 56.102(c))
- **Generalizable Knowledge:** Knowledge that is drawn from systematic qualitative or quantitative investigation that may be applied outside of the investigation from which it was derived.

4. POLICY STATEMENT

No intervention or interaction with human subjects in research, including recruitment, may begin until the IRB has reviewed and approved the research protocol. "Human subjects research is any activity that either 1) meets the HHS definition of "research" involving "human subjects" as defined at 45 CFR 46.102(d)(e)(f) or 2) meets the FDA definition of "clinical investigation" involving "human subjects" as defined at 21 CFR 56.102(c)(e).

All research of any kind, and in any field, that involves human subjects as defined by HHS or FDA regulations, regardless of sponsorship, must be reviewed and approved by the SLUHN IRB. Under certain conditions, SLUHN may rely on another institution's IRB through execution of an IRB Authorization Agreement (IAA). An IAA can be initiated by contacting the IRB Chair, IRB Vice Chair, IRB Manager.

5. POLICY SPECIFICS – ACTIVITIES REQUIRING IRB REVIEW

All research involving human subjects, unless declared exempt by appropriate IRB personnel as per Policy RR 403, must have review and approval by the IRB prior to initiation of research activities.

5.1: Specific activities that require IRB review include but are not necessarily limited to:

- Any experiment that involves a test article and one or more human subjects.
- Collection of data about a series of standard procedures or treatments for dissemination or generalization if the activity meets the definition of "human subject research."
- Patient care or the assignment of normal participants to any intervention that is altered for research

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purposes in any way.

- A diagnostic procedure for research purposes that is 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 will repeat the innovation with other participants in order to compare it to the accepted standard.
- Emergency use of an investigational drug or device (see Policy GA 107). One-time emergency uses of an investigational drug or device may proceed without prospective IRB review. When emergency medical care involves an investigational article, the patient is a research subject as defined by FDA regulations but may not be considered a research subject as defined by HHS regulations, and data generated from such care **cannot be included in any prospectively conceived report of an HHS-regulated research activity**.
- Planned Emergency Research (See Policy IC 608), “Research in Emergency Settings (Prospective Review)” which describes the exception from informed consent requirements for emergency research and the requirement for prospective review (note: this is not the same as Emergency use of an investigational drug or device as noted above).
- Data, Human Cell, or Tissue Repository: Data, human cell or tissue research typically involves repositories that collect, store, and distribute these materials for research purposes. (See “OHRP Issues to Consider in the Use of Stored Data or Tissues”, November 1997.)
- Investigator-Initiated Research: A Principal Investigator who initiates and conducts a research project or clinical trial involving human subjects.
- Student Conducted Research: All activities that meet the definition of research with human subjects, and that are conducted by students for a class project or for work toward a degree must be reviewed by the IRB. Some projects involving participants may meet IRB exemption qualification as defined in 45CFR46.101(b)(1-6)
- 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. One or two case reviews do not require IRB review unless they meet the criterion of providing generalizable knowledge.
- Access to protected health information: Investigators within any of the covered entities of SLUHN who require protected health information for the conduct of research must provide the IRB with appropriate information to obtain approval of the activity prior to access of the protected health information.
- Collaborative research requires IRB review by each performance site unless an IRB Authorization Agreement is in place, by which one institution’s IRB can accept the review and approval from another institution’s IRB.

5.2: Activities that do not meet the regulatory definition of human research or clinical investigation do not require IRB approval; however, the investigator must obtain documentation from the IRB that the activity is not subject to IRB review.

Some examples that usually do not require IRB approval are:

- Proposals that lack definite plans for involvement of human subjects will not require IRB review.
- Activities such as quality improvement, assurance or quality control, programs and fiscal audits, and certain disease monitoring activities as prescribed by the Public Health Department generally do not qualify as research unless the activity meets either FDA or HHS definitions of research involving participants.
- Research on Decedents: Research on decedents is usually not subject to IRB review. However, if the research on decedents involves tissue (specimen) from a participant in an FDA-regulated device trial, either as the recipient of the device or as a control, then the research is subject to IRB review [21CFR812.3(p)]. HIPAA does require review of research on decedents and the Network Compliance Office should be consulted regarding protected health information (PHI) and privacy issues.

5.3: Determining Whether an Activity Already Begun or Completed Represents Human Subjects Research (for example a quality improvement or assurance exercise).

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If an investigator: (1) has begun a project without prospective IRB review and approval and later learns that the project required IRB approval or; (2) realizes that data that has been obtained will contribute to generalizable knowledge and should be published, the investigator must consult with the SLUHN IRB to determine whether the project represented human subjects research, and thus requires a proposal to be submitted to the IRB.

Prior to beginning research activities, investigators must seek an official determination about whether an activity qualifies as research involving human subjects if they are unsure about whether IRB review is required. In order to do this, investigators must complete a one-page project feasibility form that is evaluated by the SLUHN GME Data Management and Outcomes Assessment Director (DMOA). Once the DMOA has informed investigators that their project has been deemed feasible, they may proceed.

If the proposal qualifies as human subject research, it will be forwarded to the IRB for review and approval unless the research qualifies for exemption. If the study is approved, it must also be determined whether data collected prior to the Board's approval may be used for publication.

Finally, if it is determined that the investigator conducted human subjects research prior to IRB approval, it must also be determined whether there are issues of non-compliance that need to be investigated.

6. REFERENCES

45 CFR 46.102(d)(f)
21 CFR 50.3(c)(d)(g)
21 CFR 56.102(c)(d)(e)
21 CFR 56.108(b)(1)
21 CFR 812.3(p)
45 CFR 46.103(b)(4)
21 CFR 312
21 CFR 50.24
FDA Information Sheets for IRBs and Investigators

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Policy GA 103: Determination of Conflict of Interest

1. PURPOSE

It is the policy of St. Luke's University Health Network ("St. Luke's") to promote scientific integrity, patient safety and investigator objectivity in human subjects research. Conflicts of interest on the part of investigators and other individuals responsible for the design, conduct, or reporting of clinical research, if not identified, assessed and either eliminated or appropriately managed, can compromise the safety and well-being of human subjects and the integrity of study data and results.

This policy reflects the purpose of 42CFR§50, Subpart F: Promoting Objectivity in Research: "This subpart promotes objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under Public Health Service (PHS) grants or cooperative agreements will be free from bias resulting from Investigator financial conflicts of interest." This policy also reflects the requirements set forth in 21 CFR part 54 related to financial disclosures by clinical investigators for new drug and medical device applications to the Food and Drug Administration (FDA).

This policy requires that individuals involved in the design, conduct or reporting of clinical research at St. Luke's disclose Significant Financial Interests that could have an effect on how an individual conducts his/her professional responsibilities on behalf of St. Luke's, including research, research consultation, professional practice, and committee or board memberships. A conflict of interest exists when St. Luke's, through its **Research Integrity Officer** or designee, determines that a Significant Financial Interest could directly and significantly affect the design, conduct or reporting of research. St. Luke's will take action to eliminate or manage identified financial conflicts of interest in research through the mechanisms set forth in this policy.

This policy is intended to supplement and not circumvent other policies adopted by St. Luke's, including, but not limited to, Conflicts of Interest Board of Trustees Policy Manual (No. 25); however, in the event of conflict, this policy shall supersede on matters related to Investigator conflicts of interest in clinical research.

St. Luke's will update this policy as needed based on changes to applicable federal, state, and local laws and regulations governing clinical research. This Policy shall be publicly available on the St. Luke's website.

2. RESPONSIBILITY for EXECUTING the POLICY

Research Integrity Officer; IRB Chair; IRB Vice-Chair; HRPO; Appointed/Elected IRB Members

3. DEFINITIONS

- **Alternative Policy:** means any conflict-of-interest policy maintained by a sub-recipient that purports to comply with the applicable federal regulations.
- **Clinical Research:** means a systematic investigation involving the participation of human subjects designed to develop or contribute to generalized knowledge relating broadly to public health, including behavioral health and social-sciences research, and including investigations funded and supported by the PHS or investigations regulated by the FDA. The term encompasses basic and applied research (e.g., a published article, book or book chapter) and product development (e.g., a diagnostic test or drug).
- **Clinical Study:** means Clinical Research being conducted or intending to be conducted at a Research Site.
- **Conflict of Interest:** means any activity, commitment or interest of an Investigator, including a Financial Conflict of Interest (FCOI), that could directly and significantly affect the design, conduct or reporting of Clinical Research.
- **FCOI Report:** means St. Luke's report of FCOI that is sent to a PHS Awarding Component
- **Financial Interest:** means anything of monetary value, whether or not the value is readily ascertainable.
- **Financial Conflict of Interest (FCOI):** means a Significant Financial Interest that could directly and significantly affect the design, conduct or reporting of Clinical Research and/or PHS-funded research.
- **Immediate Family:** the spouse and dependent children of an Investigator.

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- **Institution:** means St. Luke's and its affiliates that is applying for or that receives, PHS research funding.
- **Institutional Official:** means the executive designated by St. Luke's as the Signatory Official on the St. Luke's Federal Wide Assurance.
- **Investigator:** means the project director, Principal Investigator or sub-investigator, Senior/Key Personnel, Clinical Study coordinators, and any other person, regardless of title or position, who is responsible for the design, conduct or reporting of Clinical Research, which may include, for example, collaborators or consultants. "Investigator" also includes Subrecipient Investigators, who are those individuals or companies that St. Luke's may contract with to carry out a Clinical Study.
- **PHS:** means the Public Health Service of the U.S. Department of Health and Human Services, and any components of the PHS to which authority involved may be delegated, including the National Institutes of Health (NIH).
- **PHS Awarding Component:** means the organizational unit of the Public Health Service that funds the Clinical Research that is subject to the requirements of this policy.
- **PHS Funded Research:** means research that is funded by PHS and any components of the PHS to which the authority involved may be delegated, including the NIH.
- **Research Integrity Officer ("RIO"):** means the person designated by St. Luke's to be responsible for implementing this Policy.
- **Research Site:** means the facility or site engaged in Clinical Research that is (i) under the jurisdiction of the St. Luke's IRB; or (ii) contractually or otherwise affiliated with St. Luke's for the purpose of engaging in Clinical Research, including subcontractors or Subrecipients.
- **Senior/Key personnel:** means Investigators and any other person(s) identified by the Institution as Senior/Key personnel who are essential to the performance of the research project in the grant application, progress report or any other report submitted to the PHS or FDA.
- **Significant Financial Interest:** that is required to be disclosed means:
- A financial interest of one or more of the following interests of an Investigator (**and those of the Investigator's Immediate Family**) that is with an individual or entity sponsoring, conducting or seeking to engage in a Clinical Study at an St. Luke's Research Site; reasonably appears to be related to the Investigator's Institutional Responsibilities; and (i) for PHS funded research is conveyed in the one year prior to the disclosure required under this policy, or (ii) for FDA regulated research is conveyed during the course of the Clinical Study and for one year after completion of the Clinical Study:

1. Publicly traded entity:

- For PHS funded research, a disclosure of Significant Financial Interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of the disclosure, when aggregated, exceeds \$5,000 in value. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value.
- For FDA regulated research, a disclosure of Significant Financial Interest exists if the value of any equity interest in the entity during the time of carrying out the Clinical Study and for one year following completion of the Clinical Study exceeds \$50,000 in value. Equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value.

2. Non-publicly traded entity:

- For PHS funded research, a disclosure of Significant Financial Interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated, exceeds \$5,000, or when the Investigator or Investigator's immediate family holds any equity interest in the entity (e.g., stock,

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stock option, or other ownership interest) or intellectual property rights and interests (e.g., patents, copy rights) upon receipt of income related to such rights and interests; and

b) For FDA regulated research, a disclosure of Significant Financial Interest exists if the Investigator holds any equity interest in the sponsor of a Clinical Study (i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices) during the time of carrying out the Clinical Study and for one (1) year following completion of the Clinical Study.

1. For PHS funded and FDA regulated research, Investigators must disclose the occurrence of any reimbursed or sponsored travel (i.e., that which is paid on behalf of the Investigator and not reimbursed to the Investigator so that the exact monetary value may not be readily available); provided, however, this disclosure requirement does not apply to travel that is reimbursed or sponsored by a government agency, institution of higher education, academic teaching hospital, medical center or research institute affiliated with an institution of higher education. The disclosure must include, at a minimum, the purpose of the trip, the identity of the sponsor/organizer, the destination, and the duration. The Institution's RIO will determine if further information is needed, including a determination or disclosure of monetary value, in order to determine whether the travel constitutes a FCOI.

2. For PHS funded and FDA regulated research, a disclosure of Significant Financial Interest consists of intellectual property or other proprietary rights and interests (e.g. patents, copyrights, royalties, or licensing agreement) in the item being studied or tested, and any receipt of income related to such rights or interest.

3. For PHS funded and FDA regulated research, a disclosure of Significant Financial Interest consists of any compensation or remuneration made to the Investigator in which the value of the compensation or remuneration could be affected by the Clinical Study outcome.

A Significant Financial Interest does not include the following interests, which are not required to be disclosed:

1. Salary, royalties, or other remuneration paid by the Institution to the Investigator if the Investigator is currently employed or otherwise appointed by the Institution, including intellectual property rights assigned to the Institution and agreements to share in royalties related to such rights;
2. Any ownership interest in the Institution held by the Investigator, if the Institution is a commercial or for-profit organization;
3. Income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles;
4. Income from seminars, lectures, or teaching engagements sponsored by a government agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education; or
5. Income from service on advisory committees or review panels for a government agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education.

- **Sponsor:** means any person or entity that initiates, funds, or otherwise supports the Clinical Research, including the PHS, or an owner, patent-holder, license holder or other controller of the drug, device, biologic or treatment that is the subject of the Clinical Study.
- **Subrecipient or Subrecipient Investigators:** means entities or individuals that St. Luke's contracts with to carry out Clinical Study activities.

4. PROCEDURES (when St. Luke's is the prime recipient)

When applicable to the researchers of the subrecipient, St. Luke's will enter into a written agreement with the subrecipient that provides legally enforceable terms requiring that a financial conflicts of interest policy be acceptable to St. Luke's as long as the research is carried out in cooperation with or through a subrecipient

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(subrecipients or consortium members) as well as applies to the researchers of the subrecipient.

The subrecipient must certify its policy is consistent with the requirements of any applicable federal regulations when the policy of the subrecipient applies to its researchers.

The agreement must specify the time periods for the subrecipient to report identified financial conflicts of interest to St. Luke's. The time periods must be sufficient for St. Luke's to make any reports required by federal regulation.

5. EDUCATION

Each Investigator must acknowledge annually that he or she has read this policy and is aware of his/her responsibilities regarding disclosure of financial interests and of applicable federal regulations.

The individual designated as the Human Protections Administrator in the Institution's Federal wide Assurance shall serve as the Institution's Research Integrity Officer ("RIO"). The RIO or the RIO's designee is responsible for ensuring that each Investigator is informed of this policy and its requirements upon its initiation and at least annually thereafter, and within sixty (60) days of any revisions to this policy.

The RIO or designee shall require that each Investigator complete the FCOI Training presented by the NIH Office of Extramural Research at <HTTP://grants.nih.gov/grants/policy/coi/tutorial2011/fcoi.htm> as follows:

- a) Prior to engaging in any Clinical Research related to any PHS-funded
- b) Immediately when
 - o this policy is revised;
 - o An Investigator is new to the Institution; or
 - o The RIO or determines that an Investigator is not in compliance with this policy, or any management plan approved by the RIO to Manage an identified Conflict of Interest.

If neither (a) nor (b) above are applicable, then no less frequently than every 4 years. The RIO or designee shall maintain a record of certifications of all Investigators attending each training session.

6. CONFLICT OF INTEREST

6.1: Disclosure Requirements

1. An Investigator must complete or update a financial interest disclosure statement. Each Investigator is required to disclose Significant Financial Interests involving themselves and their Immediate Family that are related to his or her Institutional Responsibilities by submitting to the Institutional Review Board a complete Conflict of Interest Statement using the Financial Conflicts of Interest Disclosure Form, and any associated documents, in accordance with the following schedule:
 - Prior to the submission of an application for PHS sponsored Clinical Research;
 - Prior to the commencement of a Clinical Study at a Research Site for all non-PHS Sponsored Clinical Research;
 - At least annually, while a Clinical Study is being conducted at a Research Site;
During the conduct of the Clinical Study, within thirty (30) days of discovering or acquiring a new Significant Financial Interest or any change in any prior reported information; and/At the request of the RIO.

At the request of the RIO, each Investigator is required to submit for each Significant Financial Interest or other Significant Financial Interest copies of any contracts, sponsor agreements, grants, leases, licensing agreements, corporate organization documents, equity subscriptions agreements, equity option agreements, stockholder agreements, and/or documents setting forth the current or potential terms of any Significant Financial Interest or other Significant Financial Interest.

6.2: Physician Payments Sunshine Act

The Physician Payment Sunshine Act (Sunshine Act) was created to ensure transparency in physicians' interactions with the pharmaceutical, biologic and medical device industries as well as group purchasing

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organizations. Many interactions between physicians and the pharmaceutical, biologic and medical device industries occur to advance clinical research that is essential to discovering treatments and improving patient care.

At St. Luke's, research payments are made to the institution, not to individual physicians. However, the Sunshine Act requires that physicians who are investigators on research supported by manufacturers be listed in connection with the research payments to the institution. These payments will be listed in a separate research reporting section of the Centers of Medicare and Medicaid Services' web site.

Physicians, who are investigators on research, are expected to disclose the compensation and remuneration, on the St. Luke's Conflict of Interest Disclosure Statement for transparency and tracking purposes.

St. Luke's physicians who consult, serve on a scientific advisory board, or engage in other compensated activity for manufacturers of drugs, devices, or biologics, details of your income and other payments (e.g., lunch or travel reimbursement) from those companies and the purpose of the payment will be publicly accessible by website when the physician acts in a private capacity with the manufacturer.

Physicians and other providers will have the opportunity to review and work with manufacturers to correct the payment information and resolve the discrepancy during a 60-day period before information is posted. The physician must contact the manufacturer directly to address any inaccurate postings. St. Luke's is not responsible for the details and reviewing the data.

6.3: **Conflict of Interest Review**

- The RIO or designee shall collect a Conflict-of-Interest Statement and any associated or additional documents, from each Investigator in accordance with the above schedule.
- The RIO or designee shall review each Conflict-of-Interest Statement for completeness and may request that the Investigator submit additional documents or statements in order to accurately describe any Significant Financial Interests or other Significant Financial Interests.
- The RIO or designee will conduct a preliminary review to determine whether a disclosed Significant Financial Interest or other Significant Financial Interest could reasonably be related to Clinical Research and, if so related, could be considered a potential or actual Conflict of Interest. Significant Financial Interests are related to Clinical Research when the RIO or designee reasonably determines that the Significant Financial Interest could be affected by the Clinical Research or is in an entity whose financial interest could be affected by the Clinical Research. The RIO or designee may involve the Investigator in this determination. A Significant Financial Interest that is related to Clinical Research can be considered a Conflict of Interest if the RIO determines that it could directly and significantly affect the design, conduct or reporting of the Clinical Research.
- Within thirty (30) days of receipt of a completed Conflict of Interest Statement and associated documentation from the RIO, shall convene a meeting.
- The RIO shall notify the Investigator of the date and time of the meeting.
- The meeting shall consist of a review of all Conflict-of-Interest statements and all relevant documents and listen to any statements from any Investigator concerning any disclosed Significant Financial Interest.
- The interested Investigator may present any information or be available to answer any questions of the Clinical Research Integrity Committee regarding the disclosed Significant Financial Interest and the documents provided. The interested Investigator shall leave the meeting following the presentation and question and answer period.

6.4: **Determination of Conflict of Interest**

The RIO shall review all information regarding the disclosed Significant Financial Interests and determine the following:

- Whether the disclosed Significant Financial Interest is related to Clinical Research because it could be affected by the Clinical Research, or is in an entity whose financial interest could be affected by the

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- Clinical Research, and
- Whether a Significant Financial Interest that is related to Clinical Research is considered a Conflict of Interest because it could directly and significantly affect the design, conduct or reporting of the Clinical Research.

7. ACTIONS TO MANAGE, REDUCE, OR ELIMINATE CONFLICT OF INTEREST

If RIO determines that an Investigator has a Conflict of Interest, a plan to Manage the Conflict of Interest will be determined and implemented by the RIO within sixty days of identifying the Conflict of Interest. All violations of federal or state statutes and guidelines shall be handled consistent with the requirements of the applicable law. Examples of conditions or restrictions that might be imposed to Manage a Financial Conflict of Interest include, but are not limited to:

- Requiring public disclosure of the Conflict of Interest (e.g., when presenting or publishing the research; to staff members working on the Clinical Study; and to the St. Luke's Institutional Review Board);
- Disclosing the Financial Conflict of Interest to the human subjects participating in the Clinical Study;
- Monitoring the Clinical Study with independent monitors, which may include transferring oversight jurisdiction of the Clinical Study to a third party Institutional Review Board;
- Requiring modification of the Clinical Study plan;
- Change of Investigator responsibilities, or requiring disqualification of the Investigator from participation in all or a portion of the Clinical Study;
- Requiring divestiture of the Investigator's Financial Interest;
- Requiring severance of the Arrangement between the Investigator and the party(s), including the Sponsor, that creates the actual or potential Conflict of Interest;
- In the case of PHS funded studies, reporting the Conflict of Interest to the PHS Awarding Component; or
- Take such other action that the RIO determines to be appropriate.

8. NOTIFICATION

Within fifteen (15) days following the meeting, the RIO shall provide the Investigator and/or Sponsor with a written determination and the actions that must be taken by the Investigator to Manage, reduce or eliminate a Conflict of Interest.

For PHS sponsored research, the RIO shall notify PHS prior to the expenditure of any governmental funds and, whenever in the course of an ongoing PHS-funded research project, an Investigator who is new to participating in the Clinical Research discloses a Significant Financial Interest or an existing Investigator discloses a new Significant Financial Interest, the RIO will, within sixty (60) days, review the disclosure and determine whether a Conflict of Interest exists pursuant to the above process.

9. CONFLICT OF INTEREST VIOLATIONS

If the RIO has reasonable cause to believe that an Investigator has failed to disclose information on an actual or potential Conflict of Interest, the RIO shall immediately inform the Investigator of the basis for such belief and afford the Investigator an opportunity to explain the alleged failure to disclose or comply.

If the RIO determines that the Investigator has failed to disclose meaningful information on an actual or potential Conflict of Interest, then the RIO shall immediately notify the Institutional Official, and within the next sixty (60) days, convene a meeting to evaluate the presence of a Conflict of Interest.

If the RIO determines on evaluation that the Investigator has failed to comply with the instructions on Managing, reducing or eliminating the Conflict of Interest, the RIO shall:

- Immediately notify the Institutional Official, who shall take such administrative, contractual or personnel actions as are necessary to address the violation of this Policy, including suspension or termination of the conduct of the Clinical Study and/or any applicable contract;

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- Develop and implement, on an interim basis, a management plan that shall specify the action that has been or will be taken to Manage the Conflict of Interest going forward;
- Take such actions necessary to protect the integrity of the data and the safety of the human subjects participating in the Clinical Study in a manner consistent with this Policy; and
- Notify the PHS Awarding Component, if the Clinical Study is funded by PHS, or the Sponsor of the Clinical Study.
- If the RIO has reasonable cause to believe that (i) a Conflict of Interest has not been identified or managed in a timely manner, including failure by the Investigator to disclose a Significant Financial Interest that is determined to constitute a Conflict of Interest, or (ii) failure by the Investigator to comply with a Conflict of Interest management plan, St. Luke's shall:
 - Within one hundred twenty (120) days of the St. Luke's determination of noncompliance, complete a retrospective review of the Investigator's activities and the Clinical Study to determine whether the Clinical Study, or portion thereof, conducted during the time period of the noncompliance, was biased in the design, conduct, or reporting of such research.
 - Document the retrospective review, which shall include the following elements:
 - Project number;
 - Project title;
 - Name of the Principal Investigator of the Clinical Study;
 - Name of the Investigator with the Conflict of Interest,
 - Name of the entity with which the Investigator has a Conflict of Interest;
 - Reason(s) for the retrospective review;
 - Detailed methodology used for the retrospective review (e.g., methodology of the review process, composition of the review panel, documents reviewed),
 - Findings of the review; and
 - Based on the findings of the retrospective review, if appropriate, St. Luke's shall update any previously submitted FCOI Report, specifying the actions that will be taken to manage the Conflict of Interest going forward.
 - If bias is found and the Clinical Study is sponsored by PHS, St. Luke's will notify PHS promptly and submit a mitigation report to the PHS Awarding Component. The mitigation report must include, at a minimum, the key elements documented in the retrospective review above and a description of the impact of the bias on the Clinical Study and St. Luke's plan of action or actions taken to eliminate or mitigate the effect of the bias (e.g., impact on the research project; extent of harm done, including any qualitative and quantitative data to support any actual or future harm; analysis of whether the research project is salvageable).
 - For any FCOI Report previously reported by St. Luke's with regard to an ongoing PHS funded research project, St. Luke's shall submit to the PHS Awarding Component an annual FCOI Report that addresses the status of the identified Conflict of Interest and any changes to the management plan for the duration of the PHS-funded research project (including extensions with or without funds) in the time and manner specified by the PHS Awarding Component. The annual FCOI report shall specify whether the Conflict of Interest is still being managed or explain why the Conflict of Interest no longer exists.
 - Depending on the nature of the financial conflict of interest, St. Luke's may determine that additional interim measures are necessary with regard to the Investigator's participation in Clinical Study sponsored by PHS between the date that the Conflict of Interest or the Investigator's noncompliance is determined and the completion of the St. Luke's retrospective review.
 - Conclusions of the review.

10. SUBRECIPIENTS

St. Luke's will take reasonable steps to ensure that all Subrecipients and/or Subrecipient Investigators are held to the same requirements as Investigators. Written agreements with Subrecipients and/or Subrecipient Investigators will incorporate terms that establish their compliance with this policy and the applicable federal

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regulations. If the Subrecipients and/or Subrecipient Investigators cannot provide certification of this compliance, the applicable agreement will state that Subrecipients and/or Subrecipient Investigators are subject to this policy related to their work with St. Luke's.

11. REPORTING, RECORD-KEEPING, AND RECORD RETENTION

Prior to the Research Site expenditure of any funds under a PHS sponsored Clinical Study and, during the conduct of a Clinical Study, within sixty (60) days of determining that a Conflict of Interest exists, the RIO shall provide the PHS with a Conflict-of-Interest report, including any management plan. If the Clinical Research Integrity Committee identifies a Conflict of Interest and eliminates it prior to the expenditure of PHS sponsored funds, St. Luke's shall NOT submit a Conflict-of-Interest report to the PHS.

Prior to the commencement of any non-PHS sponsored Clinical Study, and, during the conduct of a Clinical Study, within sixty (60) days of determining that a Conflict of Interest exists, the RIO shall provide to the Sponsor a Conflict-of-Interest report and any management plan.

For a PHS sponsored Clinical Study, the RIO shall respond within five (5) business days to any public request for information about a Significant Financial Interest disclosed to St. Luke's by an Investigator that has been determined by the RIO to constitute a Financial Conflict of Interest. The written response shall note that the information provided is current as of the date of the correspondence and is subject to updates, on at least an annual basis and within 60 days of the Institution's identification of a new Financial Conflict of Interest. The information included in the written response shall include the following:

- Investigator's name;
- Investigator's title and role with respect to the Clinical Study;
- Name of the entity in which the Significant Financial Interest is held;
- Nature of the Significant Financial Interest;
- Approximate dollar value of the Significant Financial Interest (dollar ranges are permissible)
 - \$0-\$4,999;
 - \$5,000-\$9,999;
 - \$10,000-\$19,999;
 - amounts between \$20,000-\$100,000 by increments of \$20,000;
 - amounts above \$100,000 by increments of \$50,000): or
 - a statement that the interest is one whose value cannot be readily determined through reference to.
 - public prices or other reasonable measures of fair market value

The RIO shall maintain as confidential documents the originals and or copies of all Conflict-of-Interest Statements and any other documents submitted by the Investigator, and copies of other documents setting forth the determination and actions taken by the RIO. The RIO shall maintain these records as follows:

- Three years (3) years following the submission of the final expenditure report for PHS sponsored research, or, for awards that are renewed quarterly or annually, from the date of the submission of the quarterly or annual financial report, subject to the exception in subparagraph (c), below; or
- Two (2) years following the approval of the marketing application for FDA regulated Clinical Study, and all other Clinical Research, subject to the exception in subparagraph (c), below.
- If any litigation, claim, financial management review, or audit is started before the expiration of the three (3) year period set forth in subparagraph (a) or the two (2) year period set forth in subparagraph (b), the records shall be retained until all litigation, claims or audit findings involving the records have been resolved and final action taken.

PHS Awarding Components and the U.S. Department of Health and Human Services ("HHS"), the HHS Inspector General, the U.S. Comptroller General, the FDA, or any of their duly authorized representatives, have the right of timely and unrestricted access to any books, documents, papers, or other records of Institution that are pertinent to governmental awards, in order to make audits, examinations, excerpts, transcripts and copies of such documents. This right also includes timely and reasonable access to the Institution's personnel for the

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purpose of interview and discussion related to such documents. The rights of access are not limited to the required retention period set forth in paragraph 5, above, but shall last as long as the records are retained.

12. COMPLIANCE

In the event of an Investigator's non-compliance with this policy, St. Luke's may implement a range of enforcement mechanisms, including but are not limited to:

- suspension or termination of a Clinical Study;
- suspension or termination of research privileges;
- dismissal from IRB and other board or committee membership;
- discipline under St. Luke's employee disciplinary policies, if applicable; and/or
- termination for cause of any contract, agreement or award.

Violations of federal or state statutes and guidelines shall be handled consistent with federal and state laws and requirements.

13. REFERENCES

Conflict of Interest Board of Trustees Policy Manual (No. 25)

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Policy GA 104: Patient Consent for Use of Database Information

1. PURPOSE

To determine whether the use of database information constitutes research and requires IRB review and/or consent.

2. RESPONSIBILITIES for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO; Appointed / Elected IRB Members

3. POLICY STATEMENT

There has been much confusion in the research community regarding the use of information compiled in databases or contained in existing databases and whether IRB review and/or patient consent is required to access such information.

The following guidelines are to be used to determine whether the use of database information constitutes research and requires IRB review.

4. PROCEDURES

4.1: IRB Data Collection

If the collection of identifiable data is for a non-research use (e.g. quality assurance, outcome analysis, financial analysis), the act of collecting this information is not research and patient consent is not required.

If the investigator collects data with a specific intent to test a hypothesis or publish the information, and the collection involves data that identifies the patient, the activity is research and requires IRB approval. However, the consent requirement may be waived by the IRB if the protocol meets the criteria for waiver (45 CFR 46.116(d)). Those criteria are: 1) the research presents no more than minimal risk to the subjects; 2) the waiver will not adversely affect the subjects' rights and welfare; 3) the research could not practicably be carried out without the waiver; and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

If the investigator collects data with a specific intent to test a hypothesis or publish the information, and the collection is without identifiers or links to identifiable information, the activity is research and requires IRB approval. However, the consent requirement may be waived by IRB if the protocol meets the criteria for waiver. Additionally, the research may qualify for expedited review.

4.2: Retrospective Data Review

If the investigator has a specific intent to test a hypothesis or publish the information, and the review of existing data and the recording of that data occurs without identifiers or links to identifiable information, the activity is research, but qualifies as exempt from IRB review (45 CFR 46.101 (4)). Accordingly, subject consent is not required. ***However, the study must still be presented to the IRB to make the determination that the activity is exempt.***

The review of existing data and recording of data with identifiers or links to identifiable information with the specific intent to test a hypothesis or publish is research that is not exempt and requires IRB approval. The research may qualify for expedited review if the data was originally collected for non-research purposes and meets other criteria for expedited review (45 CFR 46.110). Additionally, consent may be waived by the IRB if protocol meets criteria for waiver.

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Policy GA 105: Roles and Responsibilities of Investigators and Department Chairs

1. PURPOSE

To describe the roles and responsibilities of the Principal Investigator, Sub-Investigator, Study Coordinator, Key Personnel, and the department chair and/or division head, in the responsible conduct of human subjects research.

2. RESPONSIBILITY for EXECUTING the POLICY

Principal Investigator (PI); Sub-Investigator(s) (Sub-I); Study Coordinator(s); Key Personnel; Department Chief/Chair/Division Head

3. DEFINITIONS

Principal Investigator (PI): Person primarily responsible for the conduct of the study and adherence to regulations. Studies to be conducted at SLUHN must be conducted by or under the supervision of SLUHN qualified medical or allied professional staff member(s). This means proposals for a research grant or clinical study must list such a faculty member as the Principal Investigator, thereby ensuring that an experienced professional, capable of assuming complete responsibility for the study, is directly involved and responsible for the procedures and/or treatments being undertaken as part of the research.

SLUHN personnel who are not medical or allied professional SLUHN staff members may, by virtue of training and expertise, serve as Principal Investigators for protocols involving human subjects. These will be considered on a case-by-case basis. In general, these individuals hold advanced degrees (Doctoral or Masters Level).

Individuals from other institutions who hold an adjunct appointment allowing limited activities at SLUHN are not eligible per SLUHN by-laws to be a Principal Investigator on a research grant or clinical study conducted at SLUHN.

Sub-Investigators (Sub-Is): For biomedical studies, qualified personnel other than the PI who are responsible for performing study-related procedures and making important study- related decisions, and who may be designated to take on PI responsibilities such as sign-off on regulatory documents in the absence of the PI are designated as Sub-I's. A Sub-I must be able to answer all study questions and conduct the study in the absence of the Principal Investigator.

The PI and Sub-I's must be qualified by degree and licensure to assume responsibility for the proper conduct of the research study. They should meet all the qualifications specified by the applicable regulatory requirements and should be able to provide these qualifications through a current Curriculum Vitae and appropriate licensure to the SLUHN IRB, if requested.

On some studies involving minimal risk, other personnel, such as non-faculty members and students may be designated as Sub-Investigators. Examples of this are chart reviews and database studies.

Study Coordinator: A research professional, such as a nurse, who works for and under the direction of the PI. The study coordinator is responsible for screening and recruiting of subjects, collecting and recording clinical data, maintaining clinical supplies, and if qualified, drawing blood and dispensing medication.

Key Personnel: Key Personnel are all other individuals contributing to the conduct of the study including, but not limited to, nurses, nurse practitioners, coordinators, residents, fellows, technicians, and students. Key Personnel must be listed on the Initial IRB Application Key Personnel list, submit a conflict of interest statement, and take all required human subjects training. Other individuals not listed as Key Personnel (i.e.,

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students and residents) may assist in protocol- related procedures only if they do so under the direct supervision of the Principal Investigator or a Sub-Investigator.

4. POLICY STATEMENT

The responsibilities delegated by the PI to the Sub-I and other key personnel must coincide with the experience and the training of that particular team member. The PI should document in writing the responsibilities delegated to all members of the team. Any change in Principal Investigator or other team member during the study must be promptly reported to the IRB as an amendment to the protocol using the SLUHN Adding/Removing Investigators Form.

IRB regulations, as well as the SLUHN IRB FWA, require that a SLUHN faculty member (salaried or volunteer) conducting clinical research involving human subjects using SLUHN facilities must use the SLUHN IRB for review and approval of clinical protocols.

Anyone proposing to conduct human subject research involving SLUHN patients, facilities or resources must submit a proposal to the IRB for review. This includes investigators that are not part of the St. Luke's Physician Group who intend to collaborate with a SLUHN Principal Investigator or involve SLUHN patients, facilities, or resources.

If the site of performance for a protocol is not a part of SLUHN, the SLUHN IRB must be contacted to arrange an appropriate IRB Authorization Agreement to assure compliance with 45 CFR Part 46. These documents must be reviewed and signed by all institutions participating in the project.

5. POLICY SPECIFICS

5.1: Procedures for investigators and department chairs

5.1.1: *Determination of human subject involvement:*

The SLUHN IRB relies on investigator and department chairmen to identify activities that will involve human subjects in research as defined in 45 CFR 46 and/or 21 CFR 50., and as per Policy GA102, or when it is not clear whether the activity involves human subjects in research as defined in 45 CFR 46 and/or 21 CFR 50, the investigator should contact the SLUHN IRB for a determination. The SLUHN IRB will make all final decisions regarding this matter.

5.1.2: *Requirement for a Sub-Investigator:*

It is preferred that human subjects research involving a drug, biologic, vaccine or device must have at least one Sub-Investigator. This is so the subject has an additional resource, other than the PI, to contact if needed. This may be required by the IRB on a case-by-case basis.

5.1.3: *Preparation of protocol:*

PIs shall prepare a protocol if not provided by the sponsor using the SLUHN Protocol Template, 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 subjects and ensure that pertinent laws and regulations are observed. This requirement is applicable even in cases where the research is exempt under 45 CFR 46. Investigators shall include the protocol, any investigator brochure, proposed informed consent form(s), any advertisements to recruit subjects and other pertinent information the IRB might need to make a proper determination.

5.1.4: *Scientific Merit and Ethical Consideration of Review:*

Department heads are responsible for reviewing research protocols for ethical considerations and scientific merit. Signature on the initial IRB Application from both the Department Chief/Chair and Service Line Administrator (if applicable) is required and is indicative of their review and approval of the protocol.

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Additionally, if the proposed protocol is led by a non-SLUHN employed physician, a separate meeting to discuss merit and resources is highly encouraged. This discussion should involve the SLUHN department Chair/Chief, the SLUHN Service Line Administrator, the SLUHN Director of Clinical Trials and Research, the SLUHN Medical Chair of Research and Innovation, and the non-SLUHN employed physician serving as the PI.

5.1.5 ***Submission of a protocol to the Institutional Review Board:***

Once it is determined that an investigator wants to initiate a research study and that it involves human subjects, 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. Investigators shall be responsible for promptly submitting a supplement and the revised protocol and/or consent form to the IRB when:

- It is proposed to involve human subjects, and the activity previously had only indefinite plans for the involvement of human subjects; or
- It is proposed to involve human subjects, and the activity previously had no plans for the involvement of human subjects; or
- It is proposed to change the involvement of human subjects and that involvement is significantly different from that which was initially approved by the IRB.

5.1.6: ***Complying with IRB decisions:***

Research investigators shall be responsible for complying with all IRB decisions, conditions, and requirements.

5.1.7: ***Obtaining informed consent:***

Investigators shall be responsible for obtaining informed consent in accordance with 45 CFR 46.116 and 21 CFR 50.23. The Principal Investigator may delegate a study team member (Sub-Investigator or key personnel) to conduct the consent interview. The original consent form, signed and dated by the subject, or the subject's authorized representative, and the person obtaining consent, and a witness if necessary, must be kept in the subject's study file and a photocopy provided to the subject.

Unless otherwise authorized by the IRB, legally effective informed consent shall:

- Be obtained from the subject or the subject's legally authorized representative;
- Be in a language understandable to the subject or the representative and allow sufficient time to consider participation; and
- Not include exculpatory language through which the subject or representative is made to waive any of the subject's legal rights, or releases the Research Investigator, the sponsor, the Institution or its agents from liability for negligence.

5.1.8: ***Submission of progress reports on the research:***

Research investigators are responsible for reporting the progress of the research to the SLUHN IRB using the Periodic Review Form, as often as, and in the manner prescribed, by the IRB, but no less than once per year [45 CFR 46.109(e) and 21 CFR 56.109(f)].

5.1.9: ***Submission of reports concerning serious adverse events, unanticipated problems, or risks:***

Research investigators are responsible for promptly reporting to the IRB any serious adverse events to human subjects. Research Investigators are also responsible for reporting promptly to the IRB any unanticipated problems which involve risks to the human research subjects or others.

5.1.10: ***Reporting changes in the research:***

Research Investigators are responsible for promptly reporting to the IRB any proposed changes in a research activity.

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

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5.1.11: ***Reporting of noncompliance:***

Research Investigators and department heads are responsible for promptly reporting to the IRB any serious or continuing noncompliance with the requirements of the SLUHN IRB FWA or the determinations of the IRB.

5.1.12: ***Attending IRB meetings:***

To facilitate the review of research and the protection of the rights and welfare of human subjects, research investigators, or approved representatives, are required to attend the IRB meeting at which their study is being discussed.

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Policy GA 106: Assigning Alternative Principal Investigator to Clinical Research Study

1. PURPOSE

To appoint an alternate Principal Investigator during a significant leave of absence of the primary Principal Investigator throughout a clinical research study.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair, HRPO

3. POLICY STATEMENT

The Principal Investigator is required by institutional policy to notify research administration about anticipated or unanticipated absence. A Principal Investigator whose absence warrants a substantial amount of time disengaged from a medical research study must formally appoint an alternate Principal Investigator. The alternate Principal Investigator should be approved for the position by the research administration and given all materials the primary Principal Investigator received or would have received, during the clinical study. The appointed member is to perform all functions of his/her appointer as a Principal Investigator for a specified period or indefinite period of absence. Only appointed person(s) may assume the role of Principal Investigator(s) during a research study.

4. THE APPOINTING PROCESS

The primary Principal Investigator shall provide a written letter of notification, explaining their change in status and complete description of any continuing investigation or research action plan. The letter submission should comply to research sponsor's guidelines and institutional guidelines to receive authorization for replacing the Principal Investigator of an investigational study. The convened IRB may approve, modify or disapprove the submission in agreement with compliance committees.

5. NOTIFICATION OF CHANGE IN STATUS

The research administration shall be responsible for notifying research sponsor and all clinical study staff of the chosen alternate Principal Investigator within 10 working days of approval. This ensures the welfare of humans participating in research by a convened IRB. The status of change should be reported to the following:

- The IRB
- The Researcher
- The Sponsor
- Department Chair or Dean as appropriate
- Other federal agencies when the research is subject to oversight by those agencies
- FDA when the research is FDA-regulated.

If federal agencies have received notification of the event(s) via other sources, such as the investigator, sponsor, or another organization, reporting to these agencies is not required of the SLUHN IRB.

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Policy GA 107: Signatory Authority

1. PURPOSE

To describe the signatory authority given to personnel of the SLUHN IRB.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO

3. POLICY STATEMENT

The IRB Medical Director; IRB Chair; and IRB Vice-Chair; HRPO are authorized to sign documents in connection with the review and approval of research involving human subjects, dependent on the level of review.

4. PROCEDURES

4.1: Authorization for Signatory Authority

Authorization to sign documents not described in this policy may be determined by the IRB Chairman and provided in writing to the individual.

4.2: Results of Reviews, Actions and Decisions by Convened Board

Results of reviews and actions taken by the IRB by a convened Board, may be signed by the IRB Chair, and IRB Vice-Chair.

4.3: Results of Reviews, Actions and Decisions by Expedited Review

Results of reviews and actions taken by the IRB by Expedited Review may be signed by The IRB Chair; IRB Vice-Chair; HRPO.

4.4: Routine Internal Correspondence

Routine internal correspondence is any written communication that does not imply or appear to imply IRB approval. This correspondence may be issued without signature.

4.5: 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 or their agents, whether public or private, will be signed by the IRB Chair, IRB Vice-Chair or other authorized personnel.

4.6: Decisions Made by Chairpersons of the Constituent IRBs

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

REFERENCES

45 CFR Part 46.103 (b) (5)

45CFR Part 46.115(a) (6)

21CFR Part 56.108(b)

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Policy GA 108: Emergent Use of a Drug, Biologic, or Medical Device

1. PURPOSE

To define emergent use of a test article (drug, biologic, or device) and to define the procedure for notifying the IRB of such use.

2. RESPONSIBILITY for EXECUTING the POLICY

Principal Investigators; Practicing Physicians; IRB Chair; IRB Vice-Chair; HRPO; Appointed/Elected IRB Members

3. POLICY STATEMENT

Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [(21CFR56.102(d))].

FDA regulations allow emergent use without prior IRB approval provided there is not sufficient time to call a meeting of the IRB (21 CFR 56.102(d)), and the emergency use is reported to the IRB within 5 working days after its initiation/administration.

Any subsequent use of the test article must have prior review by the full IRB (21 CFR 56.104). Under FDA regulations, emergency use of a test article is research, the patient is a subject, and the data obtained must be reported to the sponsor and the FDA for research purposes.

DHHS regulations require that all non-exempt research involving human subjects receive IRB review and approval. However, DHHS recognizes that physicians do have the authority to provide emergency medical care to their patients [45 CFR 46.116(f)]. Furthermore, DHHS guidance stipulates that, whenever emergent care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject and the outcome of such care may not be included in any report of a prospectively conceived research activity.

While FDA and DHHS regulations appear to be in direct opposition, the particulars allow for both to be satisfied.

4. POLICY SPECIFICS

When possible, contact the IRB Chair; Vice Chair; IRB Manager as soon as you contemplate emergent use of a study in order that they can determine that the circumstances would follow FDA regulations, and that the emergent use is not research as defined by HHS regulations.

4.1: Investigational Drugs and Biologicals

4.1.1: *Procedures to follow*

Determine if the proposed use meets the regulatory definition for emergency use of an investigational drug or biologic. Emergency uses must meet ALL of the following criteria:

- The subject has a disease or condition that is life threatening or severely debilitating;
- No generally acceptable alternative for treating the patient is available;
- The subject'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 follow as many subject protection procedures as possible. These include:

- Obtaining an independent assessment of necessity by an unininvolved physician;
- Obtaining informed consent from the participant or participant's legally authorized representative, in

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accordance with and to the extent required by FDA regulations, and appropriately documenting consent 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 6 below).

- Notifying the Institutional Review Board (IRB)

4.1.2: **Obtaining the drug/biologic**

The Investigator should contact the manufacturer of the drug/biologic to determine if it can be provided under an existing IND or, if not available through the manufacturer, the investigator should contact the FDA for an Emergency IND. If there is insufficient time for an IND, FDA may authorize shipment of the test article in advance of the IND application. Requests for authorization may be made by telephone or other rapid communication means (21 CFR 312.36). Investigator should consult with the Director of Clinical Trials and Research to assist with this process.

- www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm
- www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm597130.htm

Some manufacturers may require an “IRB approval letter” before releasing the test article. If it is not possible to convene a quorum of IRB members, the IRB Chair; will provide the sponsor a letter stating that the IRB is aware of the proposed use and considers the use to meet the emergent use category at 21 CFR 56.104(c). This does not represent IRB approval, but it may allow shipment to proceed.

4.2: **Investigational Medical Devices**

Requirements for emergency use of a medical device are similar to those for use of drugs and biologics. The investigator is referred to

<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#emergency> for specific instructions.

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;
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-796-5640) immediately after shipment is made. (Note: an unapproved device may not be shipped in anticipation of an emergency.) Nights and weekends, contact the FDA Office of Emergency Operations (HFA-615) 301-443-1240.

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

- Obtaining an independent assessment of necessity by an uninvolved physician;
- Obtaining informed consent from the participant or participant's legally authorized representative, in accordance with and to the extent required by FDA regulations, and appropriately documenting consent 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 6 below);
- Notifying the Institutional Review Board (IRB); and
- Obtaining authorization from the IDE holder, if an approved IDE for the device exists.

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5. PROCEDURES TO FOLLOW AFTER EMERGENT USE OF A TEST ARTICLE

Following the emergent use of a drug, biologic or device, the physician is expected to do the following: Submit an Emergency Use Notification in Cayuse Human Ethics to report the emergent use within five (5) working days of use:

- Justification for Emergency Use
- A brief medical history of the patient regarding emergency use of the test article, including why the condition is/was considered “life threatening” and what other options, if any, may have been employed
- Synopsis of patient outcome of the emergent use.
- Provide the IRB with a copy of the independent physician assessment
- Provide a copy of the signed Emergency Use consent form. If obtaining informed consent from the subject or a legally authorized representative is not possible, certify that the conditions for exception to the informed consent requirements are met (see section 6 below).
- Evaluate the likelihood of a similar need for recurring use of the test article, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IND or IDE for subsequent use.
- Provide copies of all paperwork related to the emergent use and a if applicable.

Based on this information, IRB Chair will determine whether the emergent use met FDA regulations and will ensure that the use is not research under HHS regulations (see Section 3 of this Policy).

The SLUHN IRB will maintain a record of each emergent use of a test article and record the following information: Investigator/physician; drug, biologic or device used; name of patient; use of agent; date of use; and number of times test article has been used at SLUHN.

The IRB Chair, or IRB Vice-Chair will present the emergent use to a convened Board. After Board review, the SLUHN IRB will notify the investigator in writing as to whether or not the circumstances met FDA criteria for emergent use and that the test article may not be used a second time without the submission of a protocol to the IRB for review and approval.

6. EXCEPTIONS TO THE INFORMED CONSENT REQUIREMENT

Although emergency use of a test article is permissible without prior IRB approval, every effort should be made to obtain informed consent from the subject or his/her legally authorized representative. The obtaining of informed consent shall be deemed feasible unless, before use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

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

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The documentation required in this section shall be submitted to the IRB within 5 working days after the use of

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the test article.

7. SUBSEQUENT EMERGENT USE OF A TEST ARTICLE

After an initial emergent use, FDA regulations require that any subsequent use of the test article must be subject to prospective 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.

The following are consistent with the policy:

7.1: 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 dose of a drug is required (e.g., daily or twice daily doses, or a course of chemotherapy) before the IRB can be convened and is consistent with the spirit of the "emergent use" doctrine. Accordingly, additional doses of a test article may be given to a patient only until the IRB is able to convene, provided that the above-stated procedures are followed and all of the conditions for emergency use continue to be met.

7.2: 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 of the above-stated procedures are followed and conditions for emergency use are met.

7.3: Recurrent Use of a Test Article Under Emergent Conditions

It is not permissible to administer a test article repeatedly as an emergent use and thereby avoid prospective IRB review. If a test article is administered a second time under the Emergent Use policy, the investigator should develop a new protocol or amend an existing one to cover future uses. The matter may also be referred to the convened IRB for resolution.

The physician/investigator will be required to take one of the following actions before any additional uses of the test article will be permitted:

- When there is an existing protocol covering the intended use of the test article, the protocol should be amended 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, a full protocol should be submitted to the IRB and should include at minimum completed IRB Application, Key Personnel Form, and consent forms.

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Policy GA 108 A: Humanitarian Use Devices – Off Label Use/Emergency Use

1. Purpose

This policy establishes requirements for the use of Humanitarian Use Devices (HUDs) at St. Luke's University Health Network (SLUHN), including routine, off-label, and emergency use, and defines the role of the Institutional Review Board (IRB) in reviewing such uses.

2. Policy Statement

A Humanitarian Use Device (HUD) is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States each year.

- Use of a HUD within its FDA-approved labeling does not constitute research.
- FDA regulations require IRB approval prior to any HUD use at SLUHN.
- Only HUDs with an approved Humanitarian Device Exemption (HDE) may be used at SLUHN.
- Investigators must obtain SLUHN IRB approval prior to HUD use, either:
 - Under an IRB-approved protocol, or
 - On a case-by-case basis.

3. RESPONSIBILITY for EXECUTING the POLICY

Principal Investigators; Practicing Physicians; IRB Chair; IRB Vice-Chair; Human Research Protection Office (HRPO)

4. Informed Consent Requirements

- FDA regulations **do not require** an IRB-approved consent form **when a HUD is used in accordance with its approved HDE labeling**.
- In **emergency situations** where informed consent cannot be obtained prior to use, the physician must:
 - Provide the patient with written information about the device following the procedure
 - **Notify the IRB of the emergency HUD use no later than 5 days of use.**

5. Off-Label Use of a HUD

The SLUHN IRB may approve of the **off-label, non-emergent** use of a HUD.

Requirements:

- The requesting physician is required to submit the request to the IRB for review and approval by the convened board.
- The patient must be informed that the HUD is being used in an investigational manner.
- The physician must use the Humanitarian Use Device (HUD) Consent/Authorization Template to obtain consent. [Humanitarian Use Device \(HUD\) Consent Authorization Template.docx](#)

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6. Continuing Review of HUD Approvals

- FDA guidance permits IRBs to conduct continuing review of HUD applications under expedited procedures.
- For HUDs used according to their approved labeling:
 - Expedited reviewers should consider:
 - Updated risk and benefit information
 - Any associated Medical Device Reporting (MDR) submissions
- For off-label HUD use:
 - Continuing review must be conducted by the full convened IRB.

7. Emergency Use of a HUD Without Prior IRB Approval

In an emergency situation, a HUD may be used **without prior SLUHN IRB approval or IRB Chair/Vice-Chair concurrence** if all of the following criteria are met:

- The patient has a life-threatening condition requiring immediate treatment.
- There is no generally acceptable alternative treatment that provides an equal or greater likelihood of saving the patient's life.
- There is insufficient time to obtain IRB approval or IRB Chair concurrence prior to use.

After the Emergency Use:

- The physician must submit an **Emergency Use Notification** in Cayuse Human Ethics within **5 days** of the HUD use.
- The notification must include:
 - Patient condition
 - Date of HUD use
 - Rationale for emergency use

Reference

FDA Guidance on Humanitarian Device Exemption (HDE) Program:

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program>).

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Policy GA 109: IRB Reporting Findings and Actions to Investigators

1. PURPOSE

To describe how the findings and actions concerning all research submitted to the IRB are to be communicated to investigators.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO

3. POLICY STATEMENT

It is imperative that the SLUHN IRB maintains open and frequent communication with the investigators and their research staffs.

4. PROCEDURES

4.1 Notifications

Initial New Submission:

The Principal Investigator and/or designee will be notified by email, SLUHN Cayuse IRB notification, or another means of communication of the IRB's review comments and study approval status in general within the week following the IRB meeting. The Analysts will specify the comments and requirements of the Board in the IRB correspondence.

In the case of a disapproval by the IRB, the reasons for the disapproval will be provided to the PI in writing. The notification will include the IRB's requirements for re-submission, along with information about how the PI may reply to the Boards' decision.

The IRB allows the PI a 30-day window to reply. If there are extenuating circumstances (e.g., sponsor delay, staff turnover) the PI may request additional time. If 30 days elapses without communication from the PI, the study will be administratively deactivated.

If the submission is incomplete, or if the PI (or designee) is not present at the convened meeting to present their protocol, the IRB may table their review until the following meeting. In such instances, the PI will be notified of this decision and the reason the study was tabled from review.

Renewals and Modifications:

The PI and/or designee will be notified by email, SLUHN Cayuse IRB notification, or another means of communication as soon as possible as to the actions taken by the IRB for any continuing review or amendment to the study.

Notification of Study Approval:

The Principal Investigator and/or designee will be provided with an approval letter and approved material once study is fully approved. The approval letter is generated in SLUHN Cayuse IRB and will be sent by email via SLUHN Cayuse IRB notification.

Closures:

Closures are received and handled by the HRPO for review. If there is no enrollment, they are approved by expedited review. If the study enrolled subjects, the closure will be discussed with the IRB Chairs at the Pre-IRB meeting and approved by expedited review. If the final report is satisfactory, the HRPO will issue a SLUHN

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Cayuse IRB notification to the PI acknowledging closure of the study.

4.2

Investigator Appeal of IRB Action

An investigator may appeal IRB-required revisions to the protocol and/or consent form. S/he may also appeal the IRB's decision to disapprove the study. All such appeals must be in writing and submitted to the IRB for review and consideration. An appeal to have the IRB review a disapproved study must be reviewed by the convened IRB, or in some instances, an assigned sub-committee of the full board. If the appeal is denied by the IRB, no institutional official may override the IRB's decision.

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Policy GA 110: Reporting of Unanticipated Problems, Terminations, Suspensions and Non-compliance to OHRP

1. PURPOSE

To describe the IRB actions and determinations that must be communicated to other entities within the University and with federal agencies.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair

3. POLICY STATEMENT

The IRB is required by federal regulations and institutional policy to communicate certain actions to entities that may have an interest in the status of the research being conducted. This policy defines the activities and the individuals and/or agencies that must be notified, if appropriate.

The DHHS and FDA regulations require prompt reporting of three situations

- any unanticipated problems involving risks to subjects or others
- any serious or continuing noncompliance with this policy or the requirements or determinations of the institutional review board (IRB); and
- any suspension or termination of IRB approval

4. THE REPORTING PROCESS

The IRB Chair; Vice-Chair will draft the report for submission to the convened IRB which may approve, modify or disapprove the report. The report will contain a complete description of the nature of the event, the findings related to the event, any actions taken by the IRB, the reasons such actions were taken, and description of any continuing investigation or corrective action plan.

5. DISTRIBUTION OF THE REPORT

The IRB Manager shall be responsible for distribution of the final report to the following within 10 working days of approval of the report by a convened IRB:

- The IRB
- The researcher
- SLUHN Legal Counsel
- Other federal agencies when the research is subject to oversight by those agencies, and they require reporting separate from that to OHRP
- FDA when the research is FDA-regulated.

If federal agencies have received reports of the event(s) via other sources, such as the investigator, sponsor, or another organization, reporting to these agencies is not required of the SLUHN IRB.

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Policy GA 111: Complaint Management

1. PURPOSE

To delineate the procedure whereby a research subject in a clinical trial, a relative of or advocate for a research subject, a member of a study team, government agency, or the Institution itself may report their concerns about any clinical trial.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair, IRB Vice-Chair, HRPO; Appointed/Elected IRB members.

3. POLICY STATEMENT

The SLUHN IRB has the responsibility to oversee the safety and welfare of human subjects participating in research, including compliance with applicable federal human subject regulations. This policy and procedure provides a means whereby any individual may report to the IRB any problem or issue of concern with on-going or completed clinical research, including potential noncompliance with federal human subject regulations.

4. PROCEDURES

IRB Chair, and/or IRB Vice-Chair will act as the initial reviewer for the complaint.

The reviewer will determine whether the complaint involves noncompliance or an unanticipated problem involving risks to participants or others as defined in the respective policies.

Complaints that involve non-compliance and/or unanticipated problems involving risks to participants or others will be handled according to Policy GA 109 and Policy GA 113.

The reviewer will be available by telephone or in person to the complainant in order to address the issue in a confidential manner. The complainant will have the opportunity to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan.

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Policy GA 112: Use of Students as Key Personnel and Subjects on Clinical Trials

1. PURPOSE

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

2. RESPONSIBILITIES for EXECUTING POLICY

IRB Chair, IRB Vice-Chair, IRB Manager, HRPO, and Appointed/Elected IRB members.

3. POLICY STATEMENT

Students 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 on clinical trials or research may specifically target students as subjects.

The principal controversy about the use of students as subjects in a research study involves whether or not the inducements to participate are considered coercive. 45 CFR 46.116 states that an investigator should seek consent “only under circumstances that provide the prospective subject sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence.” Considering that students exist in a subordinate role to their professors/mentors, some of whom may be principal investigators on the studies for which the students are being recruited, the potential for coercion, intentional or unintentional, does exist.

In addition to coercion, another major concern regarding student-participants is that of confidentiality. This applies particularly to the case where students are key personnel on a study that involves other students. Because of the close nature of the college environment, extra care must be taken to insure subject confidentiality. The 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.

4. PROCEDURE

The IRB shall carefully review recruiting inducements such as, but not limited to, allowing the enrollment of a student in the trial to count: 1) for participation in a course; 2) for course credit; 3) as writing a research paper, 4) as attendance at faculty research talks; 5) as direct payment for participation.

The IRB must discourage such recruiting methods and only approve methods that solicit student participants by less coercive means such as using sign-up sheets or general announcements, rather than direct solicitation of individual students from a class roster.

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Policy GA 113: Protocol Inclusion/Exclusion Waivers

1. PURPOSE

To delineate the procedures whereby sponsors and/or Principal Investigators may request IRB approval of an inclusion/exclusion waiver.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair

3. POLICY STATEMENT

It is not uncommon for a sponsor or the Principal Investigator to request or make allowances for certain subjects 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. In general, 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 him or her 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 subject

Typical examples of waiver requests include:

- Required imaging studies obtained days to weeks prior to that permitted by protocol
- Potential subject is slightly older or younger than specified in protocol
- Blood chemistries fall slightly outside the protocol permitted levels.

4. PROCEDURE

If the study is an IIT and the PI feels that a protocol inclusion/exclusion waiver is appropriate, the PI must submit a written request with a justification and risk assessment in sufficient detail to allow an informed decision on the part of the IRB.

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

If the study is a sponsored trial and the sponsor provides the PI with an inclusion/exclusion waiver for a subject, the PI will forward the notice of waiver along with a written request with a justification and risk assessment in sufficient detail to the IRB.

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

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Policy GA 114: Reporting and Reviewing SAEs and Unanticipated Problems Involving Risks to Subjects or Others

1. PURPOSE

The purpose of this policy is to ensure prompt reporting to the IRB of Serious Adverse Events (SAEs) and Unanticipated Problems (UAPs). Regulatory requirements of both DHHS (45 CFR 46.103(b)(5)) and FDA (21 CFR 56.108(b)(1)) require that “each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others.”

1. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; Principal and Sub-Investigators/Research Staff

2. DEFINITIONS

Adverse Event Grade refers to severity as per the Common Terminology Criteria for Adverse Events (CTCAE) created by the US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life-threatening or disabling

Grade 5 = Death

An **Adverse Event (AE)** is judged to be grade 1 or 2. It includes any unfavorable and unintended occurrence including an abnormal laboratory finding or symptom or disease, temporally associated with the use of a medical treatment or procedure that may or may not be considered to be related to the medical treatment or procedure and that is mild or moderate in severity and has a short duration of occurrence.

A **Serious Adverse Event (SAE)** is judged to be grades 3, 4 or 5 and is defined (21 CFR 314.80) as any serious adverse drug experience that results in any of the following:

- Death
- Life threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability /incapacity
- Congenital anomaly/birth defect

21 CFR 314.80 continues as follows: “Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

An **Emergency Department (ED) visit** should be reported as an AE or SAE if the PI determines the ED visit was possibly, probably, or definitely related to the study article or a study procedure. All ED visits that last more than 24 hours should be considered hospital admissions and be reported as SAEs whether or not related to study article or procedure.

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An **Unexpected adverse event** is defined as “Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.” For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., not included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.” (21 CFR 312.32).

An **Unanticipated Adverse Device Effect (UADE)** is any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with a device, if not identified in the device brochure, protocol, or consent form (21 CFR812.3(s)).

A **protocol deviation/violation** is a departure from the IRB-approved protocol. Any further definition beyond this is up for debate, as there continues to be national discussion about the use of these terms, and a consensus has not been reached on how these terms should be defined and distinguished from each other. A frequent differentiation is that a deviation does not place subjects at increased risk, whereas a violation does. Our current thinking on the topic is that we do not find the aforementioned differentiation useful because the assignment of risk to an event is a downstream decision. What is germane is that an event has occurred and needs to be assessed, first by the PI, and then by the IRB. Thus, for the current time, we will use the joint term deviation/violation, which will capture all events under these terms and will direct all of them to the appropriate reporting channel.

Unanticipated Problems posing risks to subjects or others (UAPs) are unforeseen given the information contained in the protocol and other study related documents and indicate that participants or others are at increased risk of harm (than was previously known or recognized) and are related or possibly related to the research. Examples include but are not limited to the following:

- An interim analysis of the data suggesting or indicating additional risk associated with a study procedure or test article.
- A report (journal article or abstract, etc.) that shows that 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 subject.
- Incarceration of a subject in a protocol not approved to enroll prisoners.
- An event that requires prompt reporting to the sponsor.
- Sponsor imposed suspension for risk.
- Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
- A change to a protocol or procedure that is not pre-approved by the IRB.
- Protocol violation (an accidental or unintentional change to the IRB-approved protocol) that may harm subjects or others or that indicates that subjects or others may be at increased risk of harm.
- Other unanticipated information that indicates participants or others might be at increased risk of harm.

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Some events do not qualify as AEs, SAEs or Unanticipated Problems posing risks to subjects or others. Most of these are events or circumstances encountered in the usual course of receiving medical attention. Examples of these are pain or minimal bleeding/bruising at the time of venipuncture, drowsiness after sedation, boredom while waiting for the scheduled visit or procedure, or other similar scenarios. Such events do not need to be reported.

Please note, protocol deviations/violations not posing risks to subjects or others are not considered unanticipated problems involving risk and **should not be reported to the IRB at the time they occur**. Additionally, non-serious AEs that are expected do not need to be reported to the IRB in real-time. Instead, for such events, a log of protocol deviations/violations and non-serious expected AEs should be maintained in the study file for inclusion in the continuing review submission or final report.

4. REVIEW OF SAEs AND UAPs

On-site SAE reports and UAPs are submitted to the IRB for expedited review, and when necessary, may be forwarded to the full convened board for discussion and further action if necessary. Immediate actions may be necessary to eliminate any immediate hazards to subjects or others. If this is the case, the IRB Chair; Vice Chair will notify the IRB of the actions taken.

If the unanticipated problem involves failure to follow federal or institutional human subjects regulations, further action will be initiated.

5. ACTIONS for CONSIDERATION BY THE CONVENED IRB

The convened IRB will consider the following actions during its deliberations:

- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to past subjects
- Notification of current subjects when such information might relate to their willingness to continue participation in the study
- Requirement that current subjects be re-consented
- Modification of the continuing review schedule
- Monitoring of the research and/or consent process by the Network Compliance Office
- Suspension of the research, Investigator, or research team
- Termination of the research
- Referral to other organizational entities for further investigation

6. REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND UNANTICIPATED PROBLEMS

AEs and SAEs are reportable from the time the patient consents to 30 days after the last study intervention, or as specified in the protocol (usually based on drug half-life). The IRB considers all observational and registry studies exempt from SAE reporting requirements. Additionally, non-medical (e.g., not involving pharmaceuticals or invasive procedures) interventional studies are also exempt from SAE reporting requirements unless otherwise specified by the protocol. If the protocol requires SAE reporting for non-medical (e.g., not involving pharmaceuticals or invasive procedures) interventional studies, protocol-specific guidelines should be followed, and reporting should occur according to the definition that is more protective of subject safety.

On-site Serious Adverse Events: On-site SAEs should be reported using the SLUHN Adverse Event Form, and should be reported within 10 days of learning of the event, except that death should be reported within 72 hours.

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Note: deaths from "natural causes" or underlying disease that occur more than 30 days following completion of the study interventions (i.e., events not temporally associated) need not be reported.

The occurrence of events that are clearly part of a disease process should be noted in the protocol and, if possible, specific SAE reporting requirements established.

SAEs that occur in device studies (e.g. UADEs) should be reported to the IRB if they are not identified in the device brochure, protocol, or consent form.

On-site Unexpected/Related AEs: On-site non-serious AEs that are unexpected and deemed to be at least possibly or definitely related to the study article should be reported within 15 working days of knowledge of the event using the UAP Form.

On-site Expected/Unrelated AEs: On-site AEs that are non-serious and are expected or unrelated to the study article do not need to be reported in real-time. Instead, such events shall be maintained on an ongoing log by the Clinical Trials Office and submitted at the time of continuing review. The Principal Investigator and/or Sub-Investigator is required to initial and date each event before submission to IRB.

"Off-site AEs/SAEs: Off-site AEs/SAEs or IND safety reports shall be maintained on an ongoing log by the Clinical Trials office and must be included with the continuing review for the study (if applicable)". The Principal Investigator's signature and date is required on the log and/or the last page of the log. The Principal Investigator's signature and date is also required on any sponsor INDSR summary reports and/or Clinical Study Reports from a Clinical Events Committee before submission to IRB.

Unanticipated Problems: Unanticipated problems that are serious adverse events should be reported to the IRB within 10 working days of the investigator becoming aware of the event using the Adverse Event Form, indicating that the SAE is unexpected within the form. Unanticipated problems (UAPs) that pose risk to subjects or others, and that are not AEs/SAEs should be reported within 15 working days of the investigator becoming aware of the problem using the UAP Report Form. For UAPs that do not pose risk to subjects or others shall be maintained on an ongoing log and submitted at the time of continuing review.

7. REFERENCES

OHRP Guidance: "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" January 15, 2007

21 CFR 312.64(b) Safety Reports

21 CFR 812.3 (s) Unanticipated adverse device effect

21 CFR 314.80 Post marketing reporting of adverse drug reactions

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Policy GA 115: Definition of Key Personnel in Research

1. PURPOSE

This policy defines key personnel for purposes of IRB oversight.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

Principal Investigators or designee

3. POLICY STATEMENT

Key Personnel in human subject research are those individuals who are substantially involved in the research and who must be listed on the IRB Key Personnel Form. Key Personnel must have taken CITI GCP and HSR training and must have completed the appropriate Financial Conflict of Interest (FCOI) disclosure and NIH Tutorial.

Examples of activities performed by key personnel include but are not limited to:

- Are involved in the conduct of study procedures
- Are able to view PHI
- Have access to study-related data that is not de-identified for statistical analysis or other study-related activities
- Interact with 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 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.

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Policy GA 116: Training for Investigators

1. PURPOSE

The purpose of this policy is to explain training requirements for new IRB members and for investigators and key personnel involved in the conduct of human subjects research.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; Principal and Sub-Investigators/Research Staff; IRB Manager, HRPO

3. POLICY STATEMENT

All IRB members and research staff are required to be trained in human subject research and have an understanding of the federal and local regulations governing such research.

All investigators and key personnel must complete required human research training prior to their involvement in the conduct of human research. Training status will be checked for all study personnel upon receipt of new study and subsequent continuing review submissions. If training is not complete for all personnel named on study, PI will be notified, and study will be held in suspension and will not be distributed for IRB review until training requirements are satisfied.

4. POLICY SPECIFICS

SLUHN uses the Collaborative Institutional Training Initiative (CITI), hosted by the University of Miami. CITI allows institutions to design training courses to their own specifications. The SLUHN IRB requires that all research personnel must complete the Good Clinical Practice (GCP) and Human Subject Research (HSR) Biomedical training modules prior to their involvement in the conduct of human subject research. GCP is renewed every 3 years and HSR is a onetime only training.

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Policy GA 117: IRB Fee Schedule and Payment Compliance

1. PURPOSE

To provide guidance regarding IRB fees, and to delineate the policy and procedure for the IRB fee schedule, as well as the protocol for IRB fee non-payment, for commercial/for-profit/externally sponsored studies.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

Institutional Review Board Leadership; IRB Chair; Vice-Chair; IRB Manager

3. INTRODUCTION AND POLICY STATEMENT

3.1: Application of IRB Fees

St Luke's University Health Network Institutional Review Board (SLUHN IRB) assesses administrative fees for commercial/for-profit/externally funded projects that involve human subjects. This policy and process also applies to external entities utilizing the SLUHN IRB to conduct human research review and approval.

The fee schedule* is as follows:

- **Convened New Study Initial Review = \$3000**
- **Expedited New Study Initial review - \$2500**
- **Convened Renewal (Continuing Review) - \$1500**
- **Expedited Continuing Review - \$1000**
- **Convened Amendment Review -\$750**
- **Expedited Amendment Review - \$250**
- **Reliance Agreement - \$1000**
- **Exemption - \$750**
- **Study Closure- \$500.00**

This practice is consistent with the policies and fees incurred at peer institutions and will be used to support the administrative costs associated with reviewing human subject research projects.

The volume of commercially/for-profit/externally funded research has grown substantially at SLUHN and while this increase is beneficial and a sign of the Health Network's growth as a premier research institution, the SLUHN IRB has experienced a concurrent increase in applications requiring review.

This increase has required the expansion of staffing in the SLUHN IRB –Department of Research & Innovation Research at SLUHN. Commercial/for-profit funded IRB applications represent some of the most complex and resource-demanding research reviewed by the SLUHN IRB. The collected IRB Fees will be used to continue staffing improvements, quality assurance efforts, and continuing education for staff and IRB Members.

IRB Applications for research studies that are funded by non-business/non-industry/external sponsors (e.g., Federal, State, non-profit foundations, or internal funds) may be exempt from the IRB Fee on case-by-case basis. Generally, if the study budget allows for IRB fees, they will be assessed as applicable.

When an IRB Application is received and is not designated as commercial/for-Profit funded, but is later determined by the IRB to be commercial/for-profit funded, appropriate IRB Fees will be assessed.

It is expected that Investigators or their staff incorporate applicable IRB Fees into the research proposal(s) and budget(s). Departments should incorporate the IRB Fee into the budget of all commercial/for-profit funded research projects.

To make the above research fees clear to research sponsors, departments/entities/investigators should refrain from referring to any other review fees they charge to sponsor's as "IRB Review Fees."

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The fees outlined above cover the cost of providing a specific service to the sponsor. IRB Members do not consider any potential financial benefit of the study to SLUHN when reviewing the application. Payment of the fee does not guarantee approval of the study protocol. The fees cover the cost of the service – which is why the fee must be paid even if the industry funding does not ultimately materialize.

3.2: Enforcement of Non-Compliance/Non-Payment

The overall review process for any particular study will remain on hold until the IRB fee is paid in full.

Exceptions, on case-by-case basis, can be considered when submitted in writing and are accompanied by a reasonable justification.

In order to avoid study conduct interruptions, the Principal Investigator / Department for a study that is at risk of suspension due to IRB fee non-payment will receive a warning letter if payment is not received within 30 calendar days. The Principal Investigator / Department will be given 30 additional days, for a total of 60 days from the due date for the specific missed payment, to produce the payment.

Separately Approved by: Convened IRB

Date: 2015-03-02

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100 General Administration (GA)

Policy GA 118: Use of a Central Institutional Review Board in Multi-Site Research Studies

The St. Luke's IRB/HRPO discourages the use of an outside IRB, but in rare circumstances an exception may be granted for compelling reasons.

1. PURPOSE

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

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; IRB/HRPO; Investigators

3. POLICY STATEMENT

The St. Luke's Institutional Review Board (IRB) and Human Research Protection Office (HRPO) discourages the use of external IRBs for the review and oversight of research conducted under its jurisdiction. **This policy is in place to ensure that all research activities adhere to St. Luke's high standards for ethical conduct, participant safety, and regulatory compliance.**

However, exceptions to this policy may be granted under certain circumstances. Compelling reasons for using an outside IRB **might include, but are not limited to:**

- 1. Multi-Site Studies:** When a research study involves multiple institutions, and a single IRB review is required to streamline the process and reduce redundancy.
- 2. Specialized Expertise:** If the external IRB possesses unique expertise or experience that is particularly relevant to the specific research project.
- 3. Conflict of Interest:** In cases where there is a potential conflict of interest that could affect the impartiality of St. Luke's IRB.
- 4. Regulatory Requirements:** When mandated by federal, state, or local regulations or guidelines.
- 5. Collaborative Agreements:** When there are pre-existing agreements or partnerships with other institutions that include provisions for IRB reliance.

Researchers seeking an exception must provide a **detailed justification for the use of an outside IRB**. This justification should address the specific reasons **why an external review is necessary and how it will benefit the research project**. The request will be reviewed by St. Luke's IRB/HRPO, which will make a determination based on the merits of the case.

3.1 Definitions

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

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- **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.

4. Procedure

4.1 Introduction As part of the St. Luke's Human Research Protection Program (HRPO), the St. Luke's IRB provides review and oversight of human subject's research conducted by St. Luke's 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 St. Luke's and the alternate IRB. St. Luke's HRPO 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:

- 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
- 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.

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5. References

Final NIH Policy on the Use of a sIRB for Multi-Site Research (effective January 25, 2018)

<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-076.html>

NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (effective January 20, 2020)

<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-058.html>

The Common Rule (45 CFR 46)

<https://www.ecfr.gov/current/title-45.subtitle-A/subchapter-A/part-46>

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200 IRB Organization (OP)

Policy OP 201: IRB Membership

1. PURPOSE

To establish a policy and procedure that will ensure that the membership of the SLUHN IRB conforms to the requirements of 45 CFR Part 46.107(c) and 21 CFR 56.107(c).

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair, HRPO

3. POLICY STATEMENT

The membership of the IRB will conform to the requirements of [45 CFR Part 46.107(c)], and will be comprised, at a minimum, of one or more nonscientist member(s) of varying backgrounds and experience, one or more unaffiliated non-scientist community member(s), and one or more faculty with expertise in medicine, basic science, and behavioral science.

4. PROCEDURES

Scientist/physician members of the IRB usually have formal appointments in one of the colleges of the University. Each IRB shall also have as a member one or more Pharmacists. Nurses may serve as members if they have specialty training and/or function as coordinators for clinical trials. Pharmacists and nurses will be employees of the SLUHN. Pharmacists are voting members unless there is a conflict of interest. Dispensing a study drug does not constitute a COI.

Non-scientist members may or may not be affiliated with SLUHN. Unaffiliated members may be non-scientists or scientists.

Unaffiliated members by definition may not be affiliated with SLUHN, nor have a family member (1st degree relative) who is affiliated with SLUHN. These members are tasked with representing the views and attitudes of the community at large. Such members may be assigned as primary reviewers depending on the nature of the protocol and their experience or training.

The IRB may have a legal representative whose function is to be knowledgeable about federal and state regulations, standards of professional conduct and conflict of interest on the part of investigators, key personnel, and IRB members. Counsel attending the IRBs are voting members and may count as either a scientist or non-scientist as per training or degrees.

In the absence of the Chair of an IRB, the Vice Chair, will assume the Chair.

Member Protections

IRB member information is not to be released. Sponsors may request such information; however, it is against internal policy to disclose information of IRB members' names.

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Policy OP 202: IRB Review of Protocols

1. PURPOSE

To establish the authority and composition of the IRB, and to describe the procedure for review and approval of an IRB submission.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO

3. POLICY STATEMENT

The IRB is a standing committee empowered to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the Institution. The IRB has full authority to approve, require modifications in, disapprove, 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, Part 46.107(c) and 21CFR 56.107(c), IRB membership shall consist of one or more nonscientist members, one or more unaffiliated lay members, and one or more faculty in each of the areas of medicine/basic science/behavioral science where it is anticipated that protocols will be submitted. The IRB shall also have as a member one or more Pharmacists. Generally, appointment to the IRB is voluntary, and all appointed members are voting members.

Except when an expedited or exempt review procedure is used, the IRB will review proposed research at a Pre-IRB meeting consisting of the Chair, Vice Chair, HRPO and Appointed IRB member. The full board IRB committee will meet monthly with a second meeting per month, if necessary, based on the number of items to be reviewed (45 CFR.103 (b) (4); 46.108).

4. PROCEDURES

New submissions for review will be checked by the IRB analyst for completion of all sections within Cayuse and for all relevant documents and required training and FCOI status for all participating personnel listed.

Incomplete submissions or those with personnel who are not current regarding training or FCOI requirements will not be accepted or distributed for review.

At least a week prior to the IRB meeting, the IRB analyst will assign reviewers to all new studies, modifications and renewals requiring full board review. Two primary reviewers are assigned for all full board reviews. Reviewers are expected to conduct an in-depth review of the study and make comments as necessary.

Submissions pertaining to studies (initial review, renewals, and modifications to approved studies) requiring review by the convened IRB will be distributed electronically via Cayuse IRB to the primary reviewers at least one week prior to the IRB meeting. Studies as listed above that qualify for expedited or exempt review, will be sent to the IRB Chair or Vice Chair.

4.1 Quorum:

A meeting cannot be convened until a quorum has been 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 8. If that same Board's voting membership is 15, the quorum would still be 8. Additionally, membership must meet the following requirements to meet quorum status:

- A quorum consists of regular and/or alternate members and must include at least one member whose primary concerns are in scientific areas and one non-scientist.
- When FDA-regulated research is reviewed, one member who is a physician must be present.

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- 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 OHRP- approved roster as the alternate for that member.
- The presence of a consultant may not be added towards 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. Voting members at a convened meeting must include a non-scientist, who represents the general perspective of subjects.

4.2 Meeting Minutes:

The Human Research Protections Coordinator 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;
- Meeting attendance, including status of any attendee who is not a regular member (alternate, consultant or invited guest)
- 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 disapproving the research;
- Summary of the discussion of controversial issues and their resolution;
- For initial and continuing review, the approval period if it is not one 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 women, human fetuses and neonates;
 - Research involving prisoners;
 - Research involving children;
- References to the rationale for the determination that a device poses significant or non-significant risk;
- 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 conflict of interest including conflict of interest as the reason for the absence.

An electronic copy of the final minutes will be retained on a secure server. In addition, the final minutes will be made available to Board members upon request.

4.3 Voting:

Members of the IRB 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 (minimal or greater than minimal), the length of the approval period (no greater than one year), and the necessity of monitoring of the investigative site. Unless otherwise determined by the members, the approval period will be one year.

Approval periods less than one year will be noted in the minutes.

A majority greater than half of the voting members present must vote in favor of a motion in order for that motion to carry. Only regular members or alternate members attending the meeting in place of their assigned regular member may vote. Any member with a conflict of interest with the study must absent themselves from the room during deliberation and voting on the study and this absence must be indicated in the minutes. This would include any member who will be involved in the conduct of the study.

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When voting on a proposal, the IRB has three options:

- Approved: A study may be approved without changes if it meets all approval criteria at 45 CFR 46.111 as well as other applicable regulatory requirements, and approved materials may be issued immediately.
- Conditionally Approved (Stipulations): A study may be approved with changes (or conditionally approved to be reviewed by expedited review by IRB Chair, Vice chair, HRPO and should be approved if the changes are made. If the revised materials are acceptable, the IRB HRPO will issue the approved materials.
- Not Approved/Tabled: A study falling into this category requires additional information, materials and/or responses to IRB questions and forms in order to move forward with review and consideration for approval. Because new information is required of the investigator, and/or considerable rewriting may be required, the submission must be revised, re-submitted in full and reviewed by the convened IRB.

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Policy OP 203: Duties of IRB Members

1. PURPOSE

This policy defines the duties required of the IRB member

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair

3. POLICY STATEMENT

The primary duty of each IRB member is to review human subject research applications with the purpose of assessing whether they are ethically and scientifically sound with regard to the participation of human subjects. The IRB member is expected to be knowledgeable about regulations governing human subject protection, biomedical and behavioral research ethics and SLUHN policies governing human subject research. The individual IRB member, as well as the convened IRB, must be, and must be perceived to be, fair and impartial in its deliberations, and immune from pressure either by institutional administration, the investigator whose study is being reviewed, or from other professional and nonprofessional sources.

4. POLICY SPECIFICS

4.1: Duty to the University

The IRB is an appointed Institutional Committee. As such, the IRB members serve SLUHN as a whole. Therefore, members must not allow their own interests, or that of their departments, to supersede their duty to protect the rights and welfare of research subjects.

4.2: Specific Duties

• Unaffiliated Members:

Unaffiliated members provide input regarding their knowledge about the local community and discuss issues and research from that perspective. They also review the informed consent document from a nonscientist point of view.

• Non-Scientist Members:

Nonscientist members are expected to provide input on areas germane to their knowledge, expertise and experience, professional and otherwise. For example, the legal member of the IRB should present the legal view of specific areas that may be discussed, such as exculpatory language or state requirements regarding consent. Nonscientist members should advise the Board when additional expertise in a nonscientific area is required to assess whether the protocol adequately protects the rights and welfare of subject, and to comment on whether the consent document is understandable.

• Scientist Members:

Scientist members are expected to contribute to the evaluation of a study on its scientific and statistical merits and standards of practice. These members should also be able to advise the Board whether additional expertise in a scientific or nonscientific area is required to determine whether the protocol adequately protects the rights and welfare of subjects.

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- *Chairperson/Vice Chairperson:*

In addition to the above responsibilities, the above roles have the authority to lead the meetings of the IRB, and may also perform, or delegate to an appropriate IRB member, the authority to perform expedited review when appropriate. The Chairpersons are empowered to suspend the conduct of a research project or clinical trial if the investigator is not following proper policies or procedures, or if it is deemed to place individuals at unacceptable risk pending IRB review.

- *Primary and Secondary Reviewers:*

In addition to the duties described above, both the primary and secondary reviewers are expected to perform an in-depth review of the research. The primary and secondary reviewers present his or her findings resulting from review of the submitted materials, provides an assessment of the soundness and safety of the protocol, and recommends specific actions to the full convened Board. Comments will also be provided in the electronic Cayuse IRB system.

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Policy OP 204: IRB Member Statement and Conflict of Interest

1. PURPOSE

This policy defines potential conflicts of interest that may be held by IRB members, and the means to document that no such conflicts exist amongst IRB members, as well as to document each IRB member's statement of compliance with all IRB Policies and Procedures as outlined in this manual.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO

3. POLICY STATEMENT

In accordance with FDA regulations at 21 CFR 56.107(e) and HHS regulations at 45 CFR 46.107(e), no Institutional Review Board (IRB) member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. St. Luke's University Health Network (SLUHN) interprets the regulations to prohibit IRB members from participating in the deliberative discussion or vote on any research in which they (i) participate in any way, including but not limited to study planning and design, conduct of the study, data analysis, subject recruitment, subject consent, and authorship; or (ii) have, or may appear to have, any personal, professional, or financial conflict.

4. DEFINITIONS

Professional Conflict of Interest: Exists when an IRB member or consultant is a key member of the research team for the protocol under review. This includes the Principal Investigator, Sub-Investigator and Study / Project coordinator and any individual that is listed on a grant application or FDA 1572 form.

Professional COI may also exist for IRB members or consultants who have a professional interest in a competing protocol; and

Individuals whose employment or job performance is contingent on successful approval of grants and contracts, who have an employment supervisory or reporting role to the person whose work the Committee is examining; or have a relationship with an entity that grants the member a non-financial benefit, such as a voluntary professional leadership role.

Personal Conflict of Interest: Occurs when an IRB member's or a consultant's immediate family has either financial or professional COI.

Immediate Family includes a spouse along with your and your spouse's parents, siblings, children, grandparents, and grandchildren.

Financial Conflict of Interest: Means financial interest in the sponsor, product or service being tested, or competitor of the sponsor or product or service being tested.

5. PROCEDURES

All voting IRB members must complete the below IRB Member Statement, along with the "Investigator or IRB Member Financial Conflict of Interests Disclosure Statement" in the Network Compliance System "Symplr". The IRB Statement and accompanying the "Investigator or IRB Member Financial Conflict of Interests Disclosure Statement" shall be completed once by each IRB member and shall be updated if any financial conflicts of interest change for themselves or their immediate family.

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Policy OP 205: IRB Document Storage and Archiving

1. PURPOSE

To delineate the criteria by which the IRB stores and archives documents. This defines the minimum requirement for retention of clinical research records to ensure compliance with applicable regulation, laws, and policies.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members HRPO

3. BACKGROUND

This policy conveys the regulatory requirements for clinical research record retention of clinical site operations as mandated by the Department of Health and Human Services (HHS) Federal Policy on Protection of Human Subjects at 45 CFR §46, the Food and Drug Administration (FDA) Investigational New Drug (IND) Application at 21 CFR §312 and the FDA Investigational Device Exemption (IDE) provisions at 21 CFR §812.

NOTE: This policy is not applicable to record retention of administrative and financial records related to funding.

3.1 SCOPE

This policy applies to clinical research records that are generated, stored, and retained at St. Luke's University Health Network and/ or sponsored clinical research sites. Such files include but are not limited to:

- IRB submission documents
- Research protocols
- Scientific evaluations
- Progress reports submitted by investigators
- Reports of injuries to participants
- Records of continuing review activities
- Correspondence between the IRB and the investigator
- Statements of significant new findings provided to participants
- Unless documented in the IRB minutes, determinations required by the regulations and protocol-specific findings supporting those determinations for:
- Waiver or alteration of consent process
- Research involving pregnant women, fetuses and neonates
- Research involving prisoners
- Research involving children
- Membership rosters
- Minutes
- Agendas

3. PROCEDURES

IRB records are stored in a manner that ensures privacy, confidentiality, security, and accessibility during the clinical research and after the research/ trial is concluded. Retention of multiple copies of documents is not required. The IRB will retain records on site in a locked file room or locked offices and are only available to IRB staff for three (3) years. Records relating to research will be kept for three (3) years after completion of the research. IRB documents then will be archived with GRM Document Management Company.

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4. REFERENCES

- 21 CFR §312.57, *Record Keeping and Record Retention*
- 21 CFR §312.62, *General Responsibilities of Investigators*
- 42 CFR §93, *Public Health Service Policies on Research Misconduct*
- 45 CFR §46.115, *IRB Records*
- 45 CFR §164, *Privacy and Security of Protected Health Information (HIPAA)*

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300 Quality Assurance (QA)

Policy QA 301: Audits by Regulatory Agencies

1. PURPOSE

This policy states the necessary preparations required for regulatory audits of the IRB and the appropriate actions of those individuals who might interact with the auditors.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; HRPO, Principal Investigators

3. POLICY STATEMENT

The policy pertains to all research submitted to the SLUHN IRB. Quality assurance and quality control of the daily operations of the SLUHN IRB is necessary to ensure that they support the IRB's mandates under federal and institutional regulations. Consequently, this policy provides a means for dealing with external auditing and accrediting agencies.

4. PROCEDURES

4.1 Preparing for an audit:

Certain regulatory and/or accrediting agencies have authority to audit the operations of IRBs. Such agencies include: FDA, OHRP, the Joint Council on Accreditation of Health Care Organizations (JCAHO), sponsors or funding agencies of research, and others who may be authorized by regulations or agreement with the Institution to audit specific documents and procedures.

For external audits involving the FDA or OHRP, the following individuals must be immediately notified:

- IRB Chair and Vice Chair
- IRB Manager and Human Research Protections Coordinator SLUHN Legal
- Network Compliance Officer
- Hospital Administration, if applicable

4.2 Participating in an audit:

The HRPO is expected to know and follow the procedures for the conduct of external and internal audit of specific studies.

Prior to being granted access to IRB documentation, inspectors or auditors should be asked to provide identification and proof of their authority or authorization to conduct the audit and have access to IRB documents. No entity other than those listed on the consent for the study may have access to any document that includes subject identifiers. SLUHN HRPO shall be responsible for redaction of such information from files prior to the audit, if required.

Auditors will be provided with an adequate working area to conduct the audit and the IRB staff shall make every reasonable effort to be available and to accommodate and expedite any auditor's request.

Documents may be copied and taken off-site only by individuals authorized in writing by the SLUHN Senior Counsel and/or Network Compliance Officer to do so.

4.3 Follow-up after an audit

Reports resulting from the audit requiring official response, either verbal or written, should be addressed by the Principal Investigator, the IRB Chair or Vice Chair, or other appropriate individuals, as soon as possible, but

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no later than 10 business days, after the completion of the audit.

For an FDA audit the IRB Manager should request an FDA Form 483 from the auditor at the completion of the exit interview.

The IRB will review the results of the audit to determine if any further action is required. If a PI was audited, the IRB may determine it necessary to implement a corrective action plan based on the audit results. If the audit showed continued deviation from protocol and/or IRB regulations, the IRB may find it necessary to initiate a non-compliance investigation. The SLUHN IRB will also use the audit results to evaluate the human research protection program to determine if any modifications are necessary.

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400 Research Review (RR)

Policy RR 401: Initial Review - Criteria for IRB Review and Approval

1. PURPOSE

This policy elaborates the criteria that the IRB must evaluate and approve before any study- related procedure involving human subjects can be initiated. The criteria are based on the ethical principles of the Belmont report and are the principles of autonomy, beneficence, and justice.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; IRB members; HRPO

4. POLICY SPECIFICS

4.1: Review of Studies by SLUHN IRB

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 proposal.

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 all appropriate approval recommendations for consideration by the convened IRB.

4.2: Review of Studies Involving Vulnerable Populations

If research involves vulnerable participants, the IRB Chair or Vice-Chair, the IRB Manager, will ensure that at least one reviewer (or consultant if necessary) has the knowledge and scientific expertise to perform in-depth review of the protocol. If consultants are employed, their comments and concerns will be duly noted in the minutes, but they may not vote on the protocol.

4.3 Criteria for IRB Approval for Research (45 CFR 46.111 and 21 CFR 56.111)

In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

- Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (***Note: 21 CFR 56.111 also includes "handicapped" as a vulnerable population category***)
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20.

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- 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 subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. ***(Note: 21 CFR 56.111 also includes "handicapped" as a vulnerable population category)***

5. REFERENCES

45 CFR 46.111(a) 1, 45 CFR 46.111(a) 2

21 CFR 56.111(a) 1, 21 CFR 56.111(a) 2

OHRP Compliance Activities: Common Findings and Guidance #3, #14, #15, #72

FDA Information Sheets: Frequently Asked Questions

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Policy RR 402: Renewal (Continuing Review) and Modification

1. PURPOSE

To elucidate the policy, procedures, and criteria for renewal of an approved human subject's study, and for the review of changes that may occur during the approved period of the study.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO

3. POLICY STATEMENT

The IRB will conduct renewal (continuing review) of a current approved study being conducted within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. The IRB has the authority to observe or have a third party observe the consent process and the research. The IRB delegates this activity to the administrative secretaries responsible for administration of the continuing review process and the quality assurance/quality improvement program that is conducted in conjunction with the continuing review process.

4. SPECIFIC POLICIES

4.1: IRB Approval Period and the Requirements for Renewal

A study must have active IRB approval as long as the following procedures are being conducted at the approved research site:

- Any research-related interventions
- Follow-up of participants, including long-term follow-up for survivorship
- Collection or analysis of private identifiable information or tissue

Once all the above procedures have been completed, renewal for a study is no longer required, and the study may be permanently closed with the IRB.

For research meeting the above criteria, the IRB must conduct renewal at intervals appropriate to the degree of risk, but not less than once per year. Research must be reviewed and approved by the IRB on or before the expiration date of the current IRB approval.

Investigators are required to submit a renewal and other required documents by the 20th of the month prior to the next IRB meeting. If the investigator fails to submit a continuing review to the IRB prior to the expiration date, the research activities must cease. If the investigator, in conjunction with the IRB, determines that the subjects on the study would suffer a hardship if 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 submission of a renewal of the study to the IRB. However, the data collected during this period of lapsed IRB approval may not be used for research purposes. Since a study not renewed by the expiration date automatically expires under federal regulations, the investigator must resubmit the complete study along with the renewal for approval by the convened IRB.

Alternatively, if a protocol lapses during the process of renewal (e.g. expires following the IRB's review while awaiting requested changes), it need not be re-submitted as a "new full review" since the continuing review is, by regulation, equivalent to a new full review. However, no subjects may be enrolled between the expiration date and the date of the new IRB stamped consent form.

4.2: Extension of IRB Approval Period

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval.

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Extensions beyond the expiration date will not be granted.

4.3: Withdrawal of IRB Approval of a Study

IRB approval for the conduct of a study may be withdrawn at any time if warranted by the conduct of the research and if the risks to the subjects are determined by the IRB to have increased to a point where they are determined to be unreasonably high. This might come about by a more than expected number of adverse events, unexpected serious adverse events or unanticipated problems, or evidence that the investigator is not conducting the research in compliance with IRB policies. Such findings may result in more frequent review of the study to determine if approval should be withdrawn, or enrollment stopped until corrective measures can be taken, or the study terminated.

4.4: Renewal

Renewal includes, but may not be limited to the following activities:

- *Site Visits and Third-Party Verification*

The IRB has the authority to observe, or have a third party observe, the consent process of research it has approved, and to verify that the study is being conducted as required by the IRB Policies and site-specific procedures as appropriate. IRB personnel may conduct a site visit.

- *Review of Serious and Unexpected AEs and UAPs*

Subject safety is of the greatest importance for the individual subjects and the clinical study. A serious adverse event or unanticipated problem involving risk must be promptly reported to the sponsor and the IRB. At the time of continuing review, the IRB should ensure that the criteria for the original IRB approval under 45 CFR 46.111 continue to be satisfied. Information regarding SAEs and unanticipated problems that have occurred since the previous IRB review, in most cases, will be pertinent to the IRB's determination of this at the time of continuing review. It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working.

A brief summary of any adverse events and/or unanticipated problems is to be included with the continuing review by submitting an AE and UAP log for the study. The summary should address whether there have been unanticipated problems and that adverse events have or have not occurred at the expected frequency and level of severity as documented in the research protocol, consent form and/or any investigator brochure.

- *Modifications*

Changes in a study during the period for which the study has IRB approval may not be initiated without prior IRB convened Board or expedited review and approval except when necessary to eliminate apparent immediate hazards to subjects.

If the change was initiated to eliminate apparent immediate hazards to a subject, it must be reported promptly (within 10 working days) to the IRB by submitting a modification for determination of whether the change was consistent with ensuring the subjects' welfare. If consistent, the modification will be reviewed by a convened Board or expedited review. If not, then the changes may be considered a deviation or a violation and shall be reported as such. The Board will be notified of the outcome.

All other changes requiring an amendment to the protocol and/or consent form must be submitted to the IRB by submitting a modification prior to their implementation.

- *Significant New Findings*

During the course of an approved study, the IRB may be required to review reports generated from data safety monitoring boards, adverse events, current literature and other sources to determine if: The status of the research has changed; the risk/benefit balance is still acceptable; new information needs to be conveyed

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to the subjects; if a segment of the population may be bearing an undue burden of research risk. Such significant new findings will be reviewed by the convened IRB or by expedited review where appropriate.

- *Reports from Employees, Staff and Faculty*

It is the responsibility of the investigative team, medical and nursing staff, or any other employees of SLUHN to promptly report to the IRB any findings, results, occurrence, or new information about an active study involving human subjects research that could affect the rights and welfare of the subjects. It is the responsibility of the IRB to act on any such information in order to protect the research subjects.

- *Reports of Alleged Non-Compliance*

All reports of inappropriate involvement of human subjects in research, or non-compliance with federal regulations involving human subjects, from any source, must be received and reviewed by the IRB Chair.

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 subjects or others. All such suspensions or terminations shall be reported by the IRB Chair to the Office of Human Research Protections and/or the FDA as appropriate.

4.5: Criteria for Renewal

The purpose of the renewal is to review the progress of the entire study, as well as the changes that occurred during the progression of the research. It may be only after the research has begun that the real risk can be determined, and the preliminary results used to compute the stated (IRB approved) risk/benefit balance can be evaluated. The IRB can, at this point, determine whether the study can be renewed with the same risk profile or if new information has changed that profile.

Renewal of a study at the time of expiration may not be conducted through an expedited review procedure unless: 1) the study is eligible for, and was initially reviewed by expedited review, or 2) the study has changed such that the only activities remaining are eligible for expedited review (e.g. the study is closed to enrollment and patients are on follow-up only).

Renewals are approved according to all applicable regulatory criteria. Proper completion of the renewal in Cayuse IRB, and submission of all required documents as part of the Renewal, will provide an appropriate review of the above issues.

4.6: Expedited Review

Generally, if a research study did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of Renewal except in limited circumstances. It is also possible that research activities that initially qualified for expedited review may have changed, or will change, such that expedited review would no longer be permitted for continuing review.

Renewals will be designated as expedited according to the Review Categorization Expedited Review Checklist in Cayuse IRB.

5. PROCEDURE for REVIEWERS – CONTINUING REVIEW

Renewals requiring full board review will be assigned to two Board members with appropriate expertise as primary reviewers for review and presentation to a convened Board.

Primary reviewer(s) will:

- Check that the Renewal is completed, and review all other required documents for completion and assessment of renewal under initial approval
- Check the date of the initial IRB approval and compare it to the date when the first subject was enrolled,
- Check the total number of subjects enrolled and compare to the target accrual for SLUHN and

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- compliance with the accrual policy
- Investigators must provide a detailed justification letter to continue the study if the study has not met 20% of the total accrual per year. This is not required for studies that are closed to accrual.
- Check for conflict-of-interest certification and training, and current CITI training
- Complete their review electronically and add comments as necessary.

The reviewers will present the full renewal for discussion and vote at a convened Board meeting. HRPO will receive the comments from the meeting and enter them into the appropriate minutes. If any minor clarifications or revisions are required of the investigator, the IRB Analyst will contact the investigator requesting the revisions.

Required revisions will be checked by HRPO for renewal and if satisfactory will be approved, and an approval letter issued.

6. EXPIRATION DATE

The expiration date for studies appears on first and last page of a stamped consent form and on the IRB approval letters. Except as noted above in section 4.1, all trial activity must cease by midnight on the date of expiration.

7. REFERENCES

45 CFR 46.109

21 §56.109

45 §46.110

21 §312.32(a), 21 CFR§314.80, 21CFR§600.80

45 §46.103(b)(5)(iii), 45 CFR§46.116(b)(5)

21 §50.25(b)(5), 21 CFR§56.108(b)(1), 21 CFR§812.150(a)(1) OHRP Guidance on Continuing Review, July 11, 2002

FDA Information Sheets: Continuing Review After Study Approval

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Policy RR 403: Review of Exempt Studies

1. PURPOSE

To delineate the requirements for classifying a study as exempt from IRB review, and the procedure for making the determination and conducting the review.

2. RESPONSIBILITY FOR EXECUTING THE POLICY:

IRB Chair; IRB Vice-Chair; HRPO and Appointed/Elected IRB Members; HRPO

3. POLICY STATEMENT

A new study may be designated as exempt from IRB review provided it meets one of the criteria cited in 45 CFR 46.101(b).

4. PROCEDURES

Exemption requests will be submitted using SLUHN Cayuse IRB. The IRB Chair, Vice Chair and/or designated IRB members will review all studies that potentially qualify for exempt status according to §46.101(b) and determine which of the six listed exemption categories is appropriate. Designated IRB members can obtain an authoritative decision about whether a research study is exempt and which category it falls under by asking the IRB Chair or Vice Chair. The title will also be entered onto the agenda for a convened Board meeting, and, subsequently, into the minutes for audit and record-keeping purposes.

Exempt studies, while not within the purview of federal human subject regulations, are held to the ethical standards of St. Luke's University Health Network. The following standards are evaluated based on review of information provided in the Application for Exemption from IRB Review:

- Selection of subjects is equitable
- Privacy of subjects is maintained
- Adequate provisions are in place to maintain all identifiable information confidential
- Consent process (if applicable) is adequate and based on IRB consent form templates

An exemption letter will be released directly from Cayuse IRB to the Principal Investigator via email for a study that is determined to be exempt and has no conditions for approval. However, any modifications to the study must be submitted as a modification to Cayuse IRB to determine that exemption status is still warranted. An administrative check-in date is assigned to check study status upon approaching one year.

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Policy RR 404: Expedited Review of New and Continuing Reviews

1. PURPOSE

To delineate the requirements for classifying the review of new studies and continuing reviews as expedited and the procedure for conducting the review.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members and IRB Appointed/Elected IRB Members; HRPO

3. POLICY STATEMENT

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 of the authorities of the IRB except that the reviewer(s) may not disapprove the study. If reviewers feel they cannot approve the study, then it should be forwarded to a convened Board for review.

The convened IRB will be notified, for informational purposes, of all research proposals that have been approved by the expedited procedure.

4. PROCEDURES

4.1 Determination and Processing of Expedited Review

All new studies will be received by HRPO via the SLUHN Cayuse IRB computerized system. The IRB analyst will review the submission and documents, and that each new study is in relation to the federal criteria for expedited studies as stated in 45 CFR 46.110, 21 CFR 56.11, and as outlined in the IRB document, "Expedited Review Categories and Determination" to determine if any of the categories are applicable. They will then enter each proposal into the agenda for the next IRB meeting.

Once assigned to the IRB Chair/Vice Chair they will review the new study and ensure it is in relation to the federal criteria for expedited studies as stated in 45 CFR 46.110, 21 CFR 56.11, and as outlined in the IRB document, "Expedited Review Categories and Determination" to determine if any of the categories are applicable.

All expedited studies are entered into the minutes of the appropriate meeting. However, per federal regulations, the Board is not required to vote on these items. They are documented for information, auditing and record-keeping purposes only. As soon as the expedited study is approved, an approval acknowledgement notification, and stamped materials (if applicable) may be released to the Principal Investigator, and the study may begin.

4.2 Expedited Criteria

The expedited review criteria as outlined in the IRB document, "Expedited Review Categories and Determination" are as follows:

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

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- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

1. Clinical studies of drugs and medical devices only when one of the below conditions are met:
 - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.
 - a. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from:
 - a. healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
 - b. other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means.
Examples include: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review,

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including studies of cleared medical devices for new indications.)

Examples include: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject=s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects [[45 CFR 46.101\(b\)\(4\)](#)]. This listing refers only to research that is not exempt.

6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects [[45 CFR 46.101\(b\)\(2\) and \(b\)\(3\)](#)]. This listing refers only to research that is not exempt.

8. Continuing review of research previously approved by the convened IRB as follows:
 - a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects;
 - b. where no subjects have been enrolled and no additional risks have been identified;
 - c. where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

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Policy RR 405: Suspension or Termination of Human Subjects Research

1. PURPOSE

To provide information to the individuals conducting human subjects research as to how the IRB may take action to suspend or terminate previously approved research.

2. FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO; and appointed/Elected IRB Members

3. DEFINITIONS

Suspension of IRB Approval: An action that temporarily stops some or all research activities of an approved protocol.

Termination of IRB Approval: An action initiated by the convened IRB to permanently close a research study.

4. POLICY STATEMENT

Federal Regulations require that the IRB have the authority to suspend or terminate approval of research that is not being conducted in accordance with IRB requirements or that has been associated with unexpected serious harm to research participants. Suspensions and terminations are actions that may be temporary or permanent and that may affect some or all research procedures. Suspensions and terminations may be ordered by a convened IRB, the IRB Chair or Vice Chair. If suspension or termination is not ordered by a convened IRB, the action will be reported for review to a convened IRB.

Examples of situations that may result in suspension or termination include but are not limited to:

- Research not being conducted in accordance with IRB requirements;
- Unexpected serious harm to research subjects;
- Non-compliance with federal or local regulations;
- Research misconduct issues;
- Sponsor or PI decision to suspend or terminate the trial.

Before deliberating on issuing a suspension or termination, the IRB may require additional information about the study. At this point, the IRB may initiate a fact-gathering review by a subcommittee of IRB members, or a third party not involved with the research study and who has expertise in the type of research being conducted or expertise in the specific area of concern. The findings of this fact-gathering review will be reported to the IRB, and the IRB will make its deliberations based on this information.

The IRB will notify the Investigator in writing of its decision to suspend or terminate a study and provide a rationale for its actions. This letter will include an opportunity for the PI to respond to the IRB's determination and to attend an IRB meeting to discuss the suspension or termination and provide clarification of issues.

4.1 Procedures to Follow Regarding Subjects Participating in Suspended or Terminated Trials

When a study is suspended or terminated the PI must devise a corrective action plan that is submitted to the IRB for approval. The plan must address the following issues:

- PI notification of current subjects, and the means by which, and the timeframe in which, they must be notified
- Consideration of actions the PI will take to protect the rights and welfare of currently enrolled subjects by:
 - Transferring subjects to another investigator;
 - Making arrangements for clinical care outside of the research setting;

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- Allowing continuation of some research activities under the supervision of an independent monitor;
- Requiring or permitting follow-up of participants for safety reasons;
- Withdrawal from the trial in an orderly fashion including any appropriate clinical testing related to safety;
- Notifying (if appropriate) subjects of adverse events or outcomes.

4.2 Reporting Suspensions and Terminations

All terminations or suspensions of human subject research will be reported to federal or other agencies, as applicable, within 10 working days of the IRB determination.

5. REFERENCES

45 CFR 46.113
21 CFR 56.113

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Policy RR 406: Review of Modifications

1. PURPOSE

This policy elaborates the process of IRB review of modifications to IRB-approved human subject research.

2. RESPONSIBILITY FOR EXECUTING THIS POLICY

IRB Chair; IRB Vice-Chair; IRB Members, IRB Manager; HRPO and Appointed/Elected IRB Members

3. POLICY STATEMENT

Changes in a study during the period for which the study has IRB approval may not be initiated without prior IRB approval of a modification to the protocol and/or consent form except where necessary to eliminate immediate apparent hazards to subjects. If such an exception to the rule is utilized, a modification must be submitted to the IRB as soon as possible (see SLUHN Policy RR402).

4. PROCEDURES

4.1: Submission of Modifications

An modification to a study protocol and/or the informed consent document is to be submitted to the IRB using the SLUHN Cayuse IRB computerized system. The required protocol and/or consent form changes, if any, must be clearly indicated in tracked change format for ease of review. Clean copies of the revised protocol, consent form, and other amended materials must also be included for IRB stamping.

Modifications 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 subject
- Consent form
- Advertising and other recruitment materials

4.2: Receipt of Modifications

Modifications for research studies are received by the HRPO via the SLUHN Cayuse IRB computerized system, which then will be manually added to the agenda for the appropriate IRB meeting. Designated IRB analysts will preview the modification and make a determination as to category of review.

4.3: Review of Modifications

Modifications requiring convened Board review will be assigned two reviewers. In so far as possible, the chosen reviewers will be one of the original reviewers of the study.

The Primary Reviewer(s) will present and discuss the modification at the convened meeting of the Board. The modification will be handled by the Board as is done for new studies (SLUHN Policy RR 401) and renewals (SLUHN Policy RR 402).

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4.4: Approval of Modifications

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.

4.5: Expedited Review of Modifications

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 of the authorities of the IRB except that the reviewer(s) may not disapprove an expedited amendment. Only the convened IRB may do this. If a reviewer feels that s/he cannot approve an amendment, it should be forwarded to the convened IRB for review.

The IRB Analysts will preview each amendment to determine the level of IRB review required.

The following categories of amendment must receive convened IRB review:

- Amendment changes risk/benefit ratio of study
- Amendment substantially alters science of study
- Amendment requires special expertise for review
- Amendment provides new information that may affect a subject's decision to continue participation

Also to be considered when making determination:

- Is enrollment open or closed?
- Are subjects currently receiving treatment?
- Is the amendment to be implemented at SLUHN, or is it being submitted for administrative purposes only?

Modifications that are minor exclude 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. Consequently, minor modification can be reviewed using an expedited review procedure. Examples of minor modification include but are not limited to:

- The addition of research activities that qualify for exemption or fall under an expedited review category
- Advertising
- A minor 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 university committees with jurisdiction over research

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The amendment will be given expedited review by the IRB Analysts.

All expedited modification will be entered onto the agenda and minutes for information, auditing and record-keeping purposes only.

As soon as an expedited amendment is approved an electronic approval acknowledgement notification and stamped materials (if applicable) may be released to the Principal Investigator, and the amendment may be implemented.

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Policy RR 407: Closure for 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.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB chair and IRB vice chair, Principal Investigator; Study Team Members; HRPO

3. POLICY STATEMENT

This policy describes the procedure whereby an investigator must notify the IRB when a human subject research project has been completed.

4. PROCEDURES

4.1: Studies Involving Subjects

Study completion means that all activities involving subject 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 Principal Investigator must submit a closure to the IRB using the SLUHN Cayuse IRB computerized system. The investigator must complete enrollment Information, the Progress Report (Interventional Studies) section which should include a brief summary describing what has or has not occurred in the study, plus data related to subject responses to intervention, including the reason for study's permanent closure (termination of IRB oversight). Explain any withdrawals, subjects lost to follow-up, or deaths. Describe any subject grievances or complaints. Any serious adverse events, unanticipated problems and monitoring visits not previously reported. Data & Safety Monitoring Board (DSMB) interim findings. If drug or device trial, was there any changes in FDA status. Site Close Out Letter. Provide a synopsis of results so far and describe any data analysis that has taken place. Has any publications or presentations resulted from the research. Final Study Impact and Future Plans.

If all requested information and documentation has been submitted, the IRB Analyst will review the IRB submission for completeness and place the closure on the agenda for the next appropriate meeting of the convened IRB. The closure will be assigned to an IRB Analyst. If the closure is considered to be complete and approved by the reviewer, the IRB will be so informed for information only at its meeting and the information recorded in the minutes of the meeting.

4.2: Studies Declared Exempt

Exempt studies will be given a yearly administrative check-in date. An IRB Analyst will follow-up with an email to check the status of the study. If the study is ongoing, the admin check-in will be extended for another year, if the study has been completed it will be administratively closed.

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Policy RR 408: Review of Advertisements

1. PURPOSE

Provide direction for the review and approval of advertisements

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, IRB Manager; HRPO; Appointed/ Elected IRB Members

3. PROCEDURES

The IRB will review advertising that is intended to be seen or heard by a prospective subject to solicit their participation in the study, 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; and how to contact the site for further information. The IRB must approve the information contained in the advertisement, and the mode of communication before use of the advertising material.

Any review of an advertisement should assure that the advertisement does not:

- State or imply a favorable outcome/benefit beyond what is stated in the consent form and protocol;
- Make claims that the drug, biologic or device is safe or effective for the purposes under investigation;
- Make claims 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";
- Inappropriately emphasize payment for participation (e.g., no money amounts, inappropriate wording)
- Include any exculpatory language.

Advertisements to recruit subjects should be limited to the information necessary for potential subjects 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 subject;
- The location of study and the person or office to contact to volunteer or for further information.

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Policy RR 409: Payment of Subjects for Participation

1. PURPOSE

The Policy will define the criteria to be used by a reviewer and the IRB when reviewing proposed payments to subjects, and the procedures to be followed.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; IRB Manager; HRPO; Appointed/Elected IRB Members

3. PROCEDURES

The IRB should assure that payment is appropriately presented for what it is, recruitment incentive and compensation for participation, by assigning it to the Payment section of the consent form. No reference to payments should be made in the Benefits section. All information about the amount and schedule of payments for participation should be included in the consent form.

The IRB must assure that the amount and schedule of payments are neither coercive nor present undue influence. The payment amount should be neither excessive, thereby potentially presenting undue influence on the subject to participate, or exceedingly small, thereby undervaluing the subject's commitment of time and effort to the study.

Furthermore, the payment schedule should not be structured in such a way that the subject's voluntariness in participating might be coerced by the desire to obtain the payment. Payment for participation should not be contingent upon completion of the entire study but prorated to include payment for each visit or test, as appropriate. Payment of a small portion as an incentive to complete the study is acceptable provided that the amount is not coercive or so large as to unduly induce subjects to remain in the study when they would otherwise have withdrawn. Payment to participants who have withdrawn from the study may be made at the time they would have completed the study.

Compensation for participation in a trial offered by a commercial sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing, because this unduly implies that market approval of the test article is guaranteed.

Special attention should be paid to payments in pediatric studies, as in many cases, the payment goes to the parent and not the child. In these situations, the IRB needs to assure that the parent is not being unduly influenced by the payment to enroll the child, especially since the child is subservient to the parent's decision. Children are federally designated as a vulnerable subject population, but they also can be vulnerable to coerced decision-making on the part of their parents.

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Policy RR 410: Recruiting Methods and Enrollment Incentives

1. PURPOSE

To delineate the criteria by which the recruitment of subjects will be evaluated.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO; Appointed/Elected IRB Members

3. PROCEDURES

Recruiting methods, including advertising and payment arrangements to subjects, can affect the equitable selection of subjects and an appropriate informed consent process. Consequently, the IRB will systematically review proposed recruitment processes to judge whether they fulfill the regulatory requirements of informed consent.

3.1: Procedures applicable to the research subject:

When assessing whether recruitment of subjects is both ethical and equitable and follows federal regulations and IRB policy, the IRB must take the following criteria into consideration:

- The inclusion/exclusion criteria
- Venues in which advertising about the study will appear
- The setting in which the potential subject is approached for recruitment
- The intended populations of potential subjects to be approached for recruitment
- Whether potential subjects are vulnerable to coercion or undue influence, by nature of their situation, social status, level of education, health status, cognitive ability, etc.
- Whether any payment or non-monetary incentive to subject seems disproportionate to the procedures the subject will undergo
- That a sponsor compensating participants by offering a coupon good for a discount on the purchase price of the product once it receives marketing approval is prohibited
- Whether information concerning the amount and schedule of payments is clearly set forth in the consent document and the amount is reasonable and not excessive

The IRB may decide that certain recruitment procedures need to be eliminated or modified to avoid the possibility of the subject feeling coerced into participating in the research. The IRB may also require changes to the recruitment process to make the recruitment of potential subjects more equitable.

3.2: Procedures applicable to the Institution, investigators and key personnel:

In order for SLUHN and its investigators and key personnel to remain unbiased in the conduct of human subject research and protect against undue influence or inequitable selection of subjects, the following payments to researchers or SLUHN are not permitted under this policy:

- Entering into a human subject research agreement that contains an enrollment incentive provision.
- Acceptance of, or a request for, an enrollment incentive by SLUHN, its investigators, or subcontractors.
- Fees paid to the researcher that exceed the actual costs for recruiting human subjects.
- Extra-contractual benefits that allow the researcher or SLUHN secondary gain, or financial incentives beyond the scope of work performed

3.3: Recruitment of Subjects through Private Medical Information (Recruiting from a Practice for another Investigator's Research)

The health care provider (personal physician or physician director of a practice) must 1) approve contacting his/her or the practice's patients for research purposes, 2) introduce the study to the patient, and 3) obtain the

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patient's permission to be contacted by the study staff.

The health care provider may introduce the study either verbally during the course of medical care delivery, or through a recruitment letter.

The recruitment letter must be signed by the practitioner, or the practitioner and the investigator. In some cases, the letter may be signed by a physician representative on behalf of the entire practice (Department or Division head or clinical practice director).

The recruitment letter must contain the following:

- Introduction of the researcher and the topic of the research
- Purpose of the research
- Brief description of what the subject's involvement (may be simply a telephone interview to determine if inclusion criteria are met)
- An "opt in" or "opt out" mechanism such as a number to call or a postcard to return within a specified time period (e.g., 10 days)
- A statement that if there is no response indicating "opt out" within the specified time period, a research staff person may call.

Researchers may not contact potential subjects unless an "opt in" response has been received or an "opt out" decision has not been received within the specified time period. All recruitment letters must be approved by the IRB.

3.4: IRB Review of Advertisements

- The IRB will consider the following when reviewing advertisements:
- The information contained in the advertisement.
- The mode of its communication.
- The final copy of printed advertisements.
- The final audio or video taped advertisements.

The IRB will also ensure that advertisements do not:

State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.

- Include exculpatory language.
- Emphasize the payment or the amount to be paid, by such means as larger or bold type.
- Promise "free treatment" when the intent is only to say subjects 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 FDA labeling (When following FDA regulations).
- Use terms, such as "new treatment," "new medication," or "new drug," without explaining that the test article is investigational (When following FDA regulations).

The IRB will review advertisements to ensure they are limited to the information prospective subjects need to determine their eligibility and interest, such as:

- The name and address of the investigator or research facility.
- The purpose of the research or the condition under study.
- In summary form, the criteria that will be used to determine eligibility for the study.
- A brief list of benefits to subjects, if any.
- The time or other commitment required of the subjects.
- The location of the research and the person or office to contact for further information.

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Policy RR 411: Review of Research Employing Investigational Drugs or Devices

1. PURPOSE

To delineate the criteria by which the IRB determines that research employing drugs or devices meets all FDA requirements.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members

3. PROCEDURES

If research involves an investigational drug or device the Principal Investigator will confirm that the IND or IDE numbers are valid by providing the IRB with one of the following:

- The sponsor protocol imprinted with the IND or IDE number
- A written communication from the sponsor documenting the IND or IDE number
- A written communication from the FDA documenting the IND or IDE number (required if an investigator listed on the protocol holds the IND or IDE)

If a study involves an FDA-regulated product, but no IND or IDE number is provided by the sponsor, the PI must confirm that the research meets one of the following IND or IDE exemptions:

3.1: IND Exemptions

Exemption 1

- The drug product is lawfully marketed in the United States.
- 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.
- If the drug that is undergoing investigation is lawfully marketed as a prescription product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
- The investigation is conducted in compliance with 21 CFR 50 and 56.
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

Exemption 2

- The clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
 - Blood grouping serum
 - Reagent red blood cells
 - Anti-human globulin
 - The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made
 - by another, medically established, diagnostic product or procedure.
 - The diagnostic test is shipped in compliance with 21 CFR 312.160.

Exemption 3

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

*****If none of these exceptions are met then the sponsor must obtain an IND NUMBER*****

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3.2: IDE Exemptions

*****Also see SLUHN Policy SC 501 regarding significant and non-significant risk devices*****

- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - Is noninvasive.
 - Does not require an invasive sampling procedure that presents significant risk.
 - Does not, by design or intention, introduce energy into a subject.
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

*****If the IDE exceptions are not met, the sponsor must obtain an IDE# from the FDA*****

- If the sponsor determines that a device involves non-significant risk and does not meet the above requirements, then the investigator will ensure that the research will be conducted in accordance with the following abbreviated IDE requirements:
 - Consent will be obtained from each subject under the investigator's care in accordance with 21 CFR 50
 - The PI will document the consent accordingly, unless documentation is waived.
 - The device is not a banned device.
 - The sponsor labels the device in accordance with 21 CFR 812.5.
 - The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device was not a significant risk device and maintains such approval.
 - The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation was waived.
 - The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
 - The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10).
 - The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
 - The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

3.3: Submission to the IRB

Complete all required information regarding investigational drugs or devices in the Cayuse IRB Initial submission, and attach any FDA correspondence regarding IND or IDE applications.

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500 Reviews Requiring Special Consideration (SC)

Policy SC 501: Determining Whether a Device Study Involves a Significant Risk or Non-significant Risk

1. PURPOSE

To distinguish between a significant risk (SR) device and a non-significant risk (NSR) device and to indicate the procedure the IRB must follow when reviewing studies involving such devices.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO and Appointed/Elected IRB Members

3. POLICY STATEMENT

The Investigational Device Exemption (IDE) regulations (21 CFR Part 812) describe two 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 which therefore 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 that are determined to be SR devices are governed by IDE regulations at 21 CFR 812.3. Investigational devices that are 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 and in record keeping and reporting requirements. NSR device studies do not require an IDE application to be submitted to and approved by the FDA. Furthermore, sponsors and IRBs do not have to report the IRB approval of a NSR device study to the FDA. In the instance of NSR studies, the IRB serves an essential function for the FDA by acting as its surrogate with respect to the review, approval and continuing review of a NSR device study.

Investigators employing investigational devices will certify on the Cayuse IRB Subission that they will observe their responsibilities regarding such use (21 CFR 812 subpart E).

4. PROCEDURES

4.1: The IRB decision process for a device study

The January 2006 FDA “Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Non-significant Risk Medical Device Studies,” provides guidance on how to determine the differences between significant risk and non-significant risk medical device studies. It also contains an updated list of examples of significant and non-significant risk devices.

4.1.1: *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 subject;
- 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 subject;
- 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 subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

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4.1.2: *What is a Non-significant Risk Device?*

An NSR device is one that does not meet the definition for a SR device.

4.2 IRB Review

4.2.1 *Non-significant 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 [(21 CFR 812.150(b)(10)];
- a description of the device;
- reports of prior investigations with the device;
- information about other IRBs and their determinations;
- a risk assessment and the rationale for the determination of risk;
- 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 (21 CFR 56.111). Generally, NSR studies require review at a convened meeting of the IRB. In some cases, a study involving a NSR device may qualify as minimal risk, in which case, the IRB may review the study under its expedited review procedure (21 CFR 56.110).

4.2.2 *Significant Risk Device Studies:*

In deciding if a device 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 subjects could be life threatening, result in permanent impairment of a bodily function or permanent damage to a body structure or necessitate medical or surgical intervention to preclude permanent damage to body structure, should be considered a SR device. If the subject 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.

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4.3 IRB Responsibilities following SR/NSR Determination

Following determination of SR/NSR status, the IRB will:

- Notify the sponsor and investigator of a SR decision.
- Review the study according to the requisite criteria (21 CFR 56.111). If the study received SR designation, review will occur only after the sponsor obtains the IDE.
- 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.

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Policy SC 502: Review of Cancer Trials Approved Under NCI Central IRB Program

1. PURPOSE

To describe the procedures by which SLUHN participates in the National Cancer Institute (NCI) Central IRB (CIRB) review of multicenter oncology trials conducted by NCI-established cooperative groups.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO

POLICY STATEMENT

The SLUHN IRB has agreed to participate in the NCI CIRB program by transferring IRB oversight responsibilities to the NCI CIRB for oncology studies opened through the NCI CIRB. In participating in this NCI program, the SLUHN IRB, pursuant to a fully executed IRB Authorization Agreement (IAA), agrees that the full scope of IRB oversight responsibilities as outlined in the IAA will lie with the NCI CIRB. In this model, the signatory institution, SLUHN, agrees to provide the CIRB with local context considerations including but not limited to the following:

- State and local laws
- Conflict of Interest policies
- Boilerplate language for inclusion in the consent document

4. PROCEDURES

Prior to activating an NCI CIRB-approved study at SLUHN, the study must be reviewed by the SLUHN Clinical Trials Office for overall feasibility, and the PI must electronically “sign-off” on the study via the NCI CIRB IRB Manager system, acknowledging his/her agreement to conduct the study in compliance with Federal regulations and take responsibility for overall oversight of the study.

Once the NCI CIRB approval letter is received, the Clinical Trials Office shall stamp the NCI CIRB-approved Informed consent and the trial may commence at SLUHN.

The IRB will be notified of all NCI CIRB-approved studies on a quarterly basis.

Responsibilities of the signatory institution include but are not limited to the following:

Report to the CIRB potential unanticipated problems or serious or continuing noncompliance.

- Merge the CIRB-approved local boilerplate text into the CIRB-approved consent document when necessary.

SLUHN reserves the right to independently audit and conduct investigations into alleged noncompliance in accordance with SLUHN IRB policy and to review and act upon reports of unanticipated problems in accordance with SLUHN IRB policy.

If there is a decision to send a CIRB-approved study to a convened IRB for review, the IRB will follow the usual procedures for review and approval of a new study and will assume oversight for the study. The IRB may choose to use the CIRB documents in its consideration of the protocol and consent form.

The responsibilities of the NCI CIRB and the Signatory Institution are provided in detail in the attachment to the fully executed IAA which is kept on file in the Clinical Trials Office.

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Policy SC 503: Review and Approval of a Humanitarian Device Exemption

1. PURPOSE

To delineate the policy and procedure for IRB review, approval, and supervision of a proposal involving a Humanitarian Device Exemption (HDE).

2. INTRODUCTION

The provisions of the FDA Safe Medical Devices Act of 1990 regarding Humanitarian Use Devices (HUDs) became effective on October 26, 1996. HUDs are devices that are intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. The Office of Orphan Products Development (OOPD) determines if a device meets specific requirements including scientific rationale and population prevalence, for designation as a HUD. The manufacturer's research and development costs for bringing such a device to market could exceed its market returns for diseases or conditions affecting small populations. The FDA developed and published this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To be considered for HUD status the sponsor must complete a Humanitarian Device Exemption (HDE). An HDE is similar in both form and content to a premarket approval (PMA) application but is exempt from the effectiveness requirements of a PMA. Because of the impractical cost of conducting large-scale clinical trials for devices designed for potentially small user populations, the HDE application is not considered research and thus the applicant is not required to present the results of scientifically valid clinical investigations that demonstrate that the device is effective for its intended purpose. The application must, however, contain sufficient information for the FDA to determine 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. Additionally, the applicant must demonstrate that no comparable devices are available for that purpose and that they could not otherwise bring the device to market without receiving HUD status.

If a HUD is being used in a clinical investigation (e.g. if collection of safety and effectiveness data is performed), regardless if the HUD is being used for its HDE-approved indication(s) or for a different indication, then this would be considered investigational use and would be subject to the same requirements that apply to all FDA-regulated clinical studies, including 21 CFR Parts 50 and 56. Additionally, if the HUD is being used for a use other than its approved indication(s), the Investigation Device Exemption (IDE) regulations (21 CFR Part 812) apply, and if the device is a significant risk device, an FDA-approved IDE is required.

3. RESPONSIBILITY FOR EXECUTING THE POLICY

Institutional Review Board Leadership, including the Chair, and Vice-Chair

4. POLICY STATEMENT

An approved HDE authorizes marketing of the HUD pending IRB approval and supervision of the clinical testing of the HUD. The labeling for the HUD must state that the device is a HUD and that, although federal law authorizes the device, the effectiveness of the device for the specific indication has not been demonstrated. HDE applications must demonstrate that no comparable device, other than another HUD-approved under the HDE regulation or a device being studied under an approved IDE, is available to treat and/or diagnose the disease or condition. HDE applications do not have to be renewed 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.

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5. PROCEDURES

5.1: General IRB Responsibilities

The IRB has a unique role in the HUD setting. All IRB regulations and guidance documents are written from the point of regulation of human subjects research. In approving an HDE application, the IRB must operate without guidance from a federal system designed to regulate only human subjects research. This is the only situation where federal regulations require the IRB to approve and monitor an activity that clearly is not research. An HDE application approved by the FDA and an IRB authorizes marketing of the HUD.

Consequently, when evaluating a request to use such a device for medical treatment or diagnosis, the IRB is left to its own discretion to establish criteria for IRB approval of the device.

This policy requires the IRBs, when evaluating a request to use a HUD, to consider the following items that are generally included in the HDE application:

- The generic and trade name of the device
- The FDA HDE number (6 digits)
- The date of the HUD designation
- Indications for the use of the device
- Description of the device
- Consideration of whether the sponsor has determined 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 the specific purpose/indication being requested and that they could not otherwise bring the device to market without receiving HUD status.
- Any contraindications, warnings, and precautions for the use of the device
- Adverse effects (known and possible) 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. Approval may be granted for a maximum one year or less depending on the perceived risk levels. There is no time limit on the FDA approval of an HDE.

5.2: 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 rather may approve the use of the device without any restrictions, use of the device under protocol, or use of the device on a case-by-case basis on a protocol basis. The use of the device should, however, not exceed the scope of the FDA-approved indication.

While the regulations do not require a consent form as the device will be used outside a research setting, the IRB will make a determination as to whether it would be prudent to require a consent form, particularly to indicate the unproven status of the device. Alternatively, the IRB may require that both the investigator and the subject sign the Device Brochure to indicate that the subject and the investigator have had a discussion about the HUD and that the subject has understood what the device is and why an IRB is required to monitor its use.

Items to be submitted and reviewed by the convened IRB for initial approval of the HDE are as follows:

- Copy of the FDA HDE Approval Order
- A description of the device
- The product labeling

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- The patient information packet
- A sample consent form (if required)
- A summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, test, or procedures
- A statement from the investigator that the HUD is not being used as a part of a research project or clinical investigation designed to collect data to support an FDA pre-market approval application.

The HDE Approval Order, product labeling, and HUD patient information packets can be found at:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2>

The IRB shall ensure that the physicians distribute the patient information packet to patients prior to receiving their HUD.

5.3: Continuing Review

The IRB will approve the device for a period of time not to exceed one year. In the case of a HUD with higher risk, the IRB may approve the device for a specific number of patients with a summary report required before approving the device for additional patients.

Continuing review must follow the requirement found at 21 CFR Part 56. The FDA has determined that it is appropriate to conduct the review using expedited review procedures if the IRB so determines since the initial review was performed by a convened IRB and the use of the HUD within its approved labeling

5.4: Medical Device Reporting

The IRB shall receive and review all Medical Device Reporting (MDR) reports that are submitted to the FDA in accordance with 21 CFR Part 803.

5.5: Device Use Tracking

All HUD device use should be recorded in real-time (or within 5 days in emergency situations) in a standardized logbook. Required information should be logged on the form provided by the IRB, and must include the following:

- Date and time of device placement
- Name, age, and medical record of patient receiving the device
- Unique device identification number
- Documentation of procedure consent process, with evidence of discussion regarding the device being used classified as "Humanitarian Use Device"; If separate consent not required, the nature of HUD must be disclosed under routine consenting process and documented as such
- Name(s) of individual(s) involved in the consent process, as well as evidence of information materials (i.e., product brochures) being given to the patient

The original copy of the log should be kept in the Department / Clinical Unit performing the procedure. A copy of the log should be sent to the IRB / Clinical Trials Office for regulatory record-keeping.

5.6: Emergency Use

If a physician in an emergency situation determines that IRB approval for the use of the HUD cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The physician must report the emergency use within five (5) days by providing written notification of the use to the IRB Chair, including identification of the patient involved, the date of the use, and the reason for the use.

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6. REFERENCES

FDA Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Frequently Asked Questions about Medical Devices (January 2006)

FDA Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff (July 2010)

Code of Federal Regulations: 21 CFR 50, 21 CFR 56, 21 CFR 812, 21 CFR 814

Approved by: Fully Convened Institutional Review Board – Nov Session 2014

Date: 2014-11-17

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Policy SC 504: Pregnant Women and Women of Childbearing Potential as Subjects in Clinical Research

1. PURPOSE

To describe the policy and procedures for IRB review of the enrollment of pregnant women and non-pregnant women of childbearing potential as subjects in clinical research.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO and Appointed/Elected IRB Members

3. POLICY STATEMENT

Research involving pregnant women raises multiple ethical and regulatory issues. The Department of Health and Human Service (DHHS) amendment to 45 CFR Part 46, Subpart B, 201-21, "Additional Protections for Pregnant Women and Human Fetuses involved in Research" became effective March 19, 2001. The rule supports all of the special protections for pregnant women and fetuses involved in research that have been in force since 1975.

Pregnancy encompasses the period of time from implantation to delivery. A woman shall be assumed to be pregnant if she exhibits any of the presumptive signs of pregnancy such as missed menses, until the results of a pregnancy test are negative or until delivery [45 CFR 46, Part B, 202(e)].

A major distinction is that the original rule did not permit inclusion of a pregnant woman as a research subject unless the purpose was to attend to the health needs of the mother, and the fetus was placed at risk only to the degree necessary to treat the mother and required the permission of both parents. The amended rule aims to promote a policy of presumed inclusion of pregnant women in clinical trials. This inclusion was accomplished by the removal of the previous requirement for paternal consent which led to the exclusion of many women from protocols that were expected to have direct benefit for pregnant women. Thus, the pregnant woman became the sole decision maker as to participation.

3.1: Inclusion of Pregnant Women

Federal regulations concerning research on women who are pregnant specify that no pregnant woman can be involved as a subject unless the purpose of the research is to meet the health needs of the mother, the fetus will be placed at risk only to the minimum extent necessary to meet such needs, and the research presents minimal risk to the fetus.

3.2: Inclusion of Non-pregnant Women of Childbearing Potential

It must be assumed that pregnancies will occur as a result of the inclusion of non-pregnant women of childbearing potential as subjects in clinical trials. This presents problems for IRBs regardless of advice to use precautions. The IRB must evaluate the various safeguards that might be proposed that would afford some increase in subject safety such as frequent pregnancy tests, reliable means of contraception, and abstinence.

4. PROCEDURES

The consent document should include a clear statement about risks to the subject and the embryo or fetus and the potential for birth defects if pregnancy were to occur.

Generally, women of childbearing potential should not be included in a trial if teratogenicity (malformations of development) is likely, since the risk of malformation of the fetus far outweighs any societal benefit. The IRB should also be aware that the risks of a teratogenic compound might be transferred between the sexes. A drug with the potential to affect an individual's DNA may be given to a man who may impregnate a woman who is unaware of the risk.

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4.1: Duties of IRB when research involves pregnant women, or fetuses, prior to delivery

The Investigator Brochure should be carefully reviewed by a physician reviewer to ensure that appropriate animal studies have been completed that have not indicated fetal loss, birth deformities, low birth weight, and reduced survival as well as mutagenicity.

The protocol should be carefully reviewed for opportunities to reduce the risk benefit ratio for both the mother and the fetus, and the minutes of the convened IRB meeting should reflect the discussion regarding the protection of the mother and the fetus. The risks to the mother and the fetus should be considered separately. If the risk to the fetus is increased by enrollment of the mother in the study, then the father, if available, should be a participant in the consent process. The protocol should have clear plans for follow-up of the pregnant woman up to and after delivery.

When the IRB considers such research, it must satisfy all of the conditions specified in 45 CFR, Subpart B, sec 203, 204, as cited below:

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus is not greater than minimal, or any risk to the fetus that is greater than minimal is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus.
- Any risk is the least possible for achieving the objectives of the research.
- The woman's consent or the consent of her legally authorized representative is obtained in accord with the informed consent provisions of 45 CFR Part 46, subpart A, unless legally waived or altered.
- The woman or her legally authorized representative, as appropriate, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child.
- For children, as defined in 45 CFR 46.402(a), assent and permission must be obtained in accord with the provisions of 45 CFR 46, subpart D.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- Individuals involved in the research will have no part in determining the viability of fetus.

5. REFERENCE

45 CFR 46, Part B, sec 202,203

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Policy SC 505: Prisoners as Human Subjects in Research

1. PURPOSE

To define the requirements for the review of research involving prisoners as subjects in human research.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, IRB Manager; HRPO; Appointed/Elected IRB Members

3. POLICY STATEMENT

The IRB shall apply additional protection as necessary to protect research subjects that are potentially vulnerable to coercion in regard to autonomy, conditions that may affect risk/benefit determinations, or unequal burden in research (Belmont Report; 45 CFR 46.111(b); 21 CFR 56.111(b)).

When an IRB regularly reviews research involving a vulnerable population, at least one individual, whether a member or a consultant, who is knowledgeable about, and experienced in working with, such subjects, should be present at the meeting when the study is discussed.

If an investigator indicates to the IRB that prisoners will participate in his/her research, or if a subject(s) enrolled on a research protocol may reasonably be expected to be or is incarcerated at some time during his/her enrollment, additional requirements will apply to IRB review of the study (45 C FR 46 Subpart C).

A majority of IRB members will have no association with the prison(s) involved. At least one member of the IRB shall be a prisoner or a prisoner advocate with appropriate background and experience to serve in that capacity.

- The IRB may approve research only if it finds that the following conditions have been met:
 - The IRB will certify to DHHS through the Office for Human Research Protections (OHRP) that the IRB has reviewed the research under the conditions required by the federal regulations and that the research falls within the permissible categories.
 - The research will not begin until OHRP verifies that the research falls into one of the following permissible categories:
 - The projected research involves practices which have the intent and reasonable probability of improving the health and well-being of the subjects. The IRB may approve studies where some prisoners are assigned to a control group, and thus may not benefit from participation. The FDA has published notice in the Federal Register of its intent to permit such research.
 - Research on conditions affecting prisoners as a class (e.g. vaccine trials on hepatitis or HIV) provided that the Secretary, DHHS, has published notice of its intent to approve such research.
 - Any possible advantages accruing to the prisoner through participation in the research, when compared to general living conditions, medical care, quality of food, amenities, and opportunities for earnings in prison, should not be of such a magnitude that the prisoner's ability to weigh the risk(s) and potential benefit of the research in the limited-choice environment of the prison is unduly influenced.
 - The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers.
 - Selection procedures within the prison or prison population are fair to all prisoners and not subject to arbitrary intervention by prison authorities or other prisoners.
 - Prisoners selected as control subjects must be selected randomly from the group of eligible prisoners unless the Principal Investigator provides justification to the IRB in writing for employing some other procedure.

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- Information provided to prisoner subjects is presented in language that is appropriate for the subject population.
- Adequate assurance has been obtained that the Parole Board(s) will not take into account the prisoner's participation in the research when making decisions regarding parole. Each prisoner will be informed in advance that participation in the research study will have no effect on his/her parole.
- At the end of the prisoner- subject's participation in the research, adequate provision has been made for follow-up examination or care that takes into account the varying lengths of prisoner sentences, and of ways for informing participant of this fact.

3.1: When a subject becomes a prisoner during a research study

If a subject in a research study becomes incarcerated after enrollment in an on-going study, the Principal Investigator must immediately inform the IRB in writing of this situation. This is necessary because it is unlikely that the IRB's review of the research and the consent document contemplated the potential constraints imposed by incarceration of a subject. After receiving the Principal Investigator's notification of prisoner status for one of the subjects, the IRB must review the protocol again at its earliest opportunity with a prisoner or prisoner advocate as a member of the convened Board.

Upon review, the IRB can either approve the involvement of the prisoner subject in the research in accordance with this policy or determine that the subject be withdrawn from the study. In addition, the IRB should assure, when appropriate, that the consent document stipulates that any subsequent incarceration of a research subject may result in the termination of the subject's participation by the investigator without the subject's consent.

The OHRP has provided the following clarification regarding Part C 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) prisoners living within the community and sentenced to court-supervised monitoring or treatment regardless of whether they are described as parolees or probationers are not considered prisoners; (3) prisoners 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 subject population.

4. PROCEDURES

4.1: IRB Responsibilities for Review of Research Involving Prisoners

The IRB must review the proposed research taking into consideration all applicable federal and institutional policies, as well as the additional requirements for prisoners to participate in research as described in 45 CFR 46, Subpart C.

The IRB may not review or make determinations regarding studies involving prisoners as a target population unless the Board has a member who is a prisoner advocate with a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner. The prisoner advocate will serve as an ad hoc member with voting privilege only at the time of review of a protocol involving a prisoner.

Documentation of the expertise of the prisoner advocate will be provided by a curriculum vita.

Studies involving prisoners will be reviewed according to standard IRB procedures to assure that the research meets the criteria for approval expressed in 45 CFR 46.111 and 21 CFR 56.111.

- When a research participant becomes a prisoner, and the IRB has not previously reviewed the proposal for prisoner populations, the IRB will conduct a review of the research proposal in accordance with Subpart C and determine one of the following:
 - IRB review and approval is not required if the research interactions and interventions or the obtaining of identifiable private information will not occur during the incarceration period;

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- Withdrawal of the participant from the study is not necessary if the participant will not be placed at undue harm or risk;
- Approve research participation for non-prisoner participants but approve participation of prisoner-participants as pending [if the seven required findings in 45 CFR 46.305(a) have been met] and the IRB is awaiting confirmation from OHRP that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2). All interactions and interventions with, including obtaining identifiable private information, must cease for these prisoner-participants until the requirements of Subpart C have been satisfied with respect to the relevant protocol.
- Approve research participation for non-prisoner participants but defer participation for prisoner-participants if the seven required findings in 45 CFR 46.305(a) have not been met to the satisfaction of the IRB. All interactions and interventions with, including obtaining identifiable private information, must cease for these prisoner-participants until the requirements of Subpart C have been satisfied with respect to the relevant protocol.

NOTE: OHRP has allowed one important exception. In special circumstances in which the Principal Investigator 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 subject may continue to participate in the research until the requirements of Subpart C are satisfied.

For studies that were not intended to include prisoners, the IRB must determine which of the following situations applies:

- Non-prison study (not previously reviewed and certified under Subpart C) in which participant has become incarcerated (or otherwise fits the definition of prisoner in 45 CFR 46.303(c)) and the PI wishes to continue the individual's participation in the study.
- Non-prison study with at-risk population (i.e., probationers, substance abusers).
- Non-prison study, majority of study population are non-prisoners but PI seeks to enroll some prisoners (as defined in 45 CFR 46.303(c)).
- Minimal risk DHHS conducted or supported epidemiologic research, majority of study population are non-prisoners but PI seeks to enroll some prisoners (prisoners are not the focus of the study) and the sole purpose of the study is either:
 - to describe the prevalence or incidence of a disease by identifying all cases;
 - to study potential risk factor associations for a disease;
 - initial Subpart C review of study designed to be conducted in a prison or using prisoners as defined in 45 CFR 46.303(c), the PI seeks to enroll already incarcerated subjects.

For DHHS-supported research, SLUHN must certify to the Secretary (through OHRP) that an IRB designated under its Federalwide Assurance has made the seven findings required under 45 CFR 46.305(a), and a statement indicating that the IRB chose one of the four permissible categories of research in 45 CFR 46.306(a)(2). OHRP does not require that the prisoner letter include a specific listing or rationale behind the IRB findings. The institution may wish to include a brief, protocol-specific explanation of the IRB's rationale for each finding.

The institution must indicate in the certification letter which of the four categories of permissible research involving prisoners in 45 CFR 46.306(a)(2) is applicable to the proposed research. Research involving prisoners can proceed only if the research fits under a category of permitted research under 45 CFR 46.306(a)(2). OHRP will make its own determination, based on the information in the prisoner certification letter, the protocol materials and the grant application as to whether any of the four categories apply to the proposed research.

SLUHN must include a statement that indicates that the IRB was constituted as per requirements in 45 CFR 46.304. OHRP does not require that the prisoner certification letter include information about the manner in which the IRB fulfills the requirements of 45 CFR 46.304. The institution may wish to provide the name of the

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prisoner representative.

The following information must also be sent to OHRP: the protocol application (which includes the protocol and any IRB submission material; the grant application (including any grant award updates); and the prisoner certification letter containing the following information:

- FWA number
- IRB number for the designated reviewing IRB
- Site(s) where research involving prisoners will be conducted
- If prisoner research site is "engaged in research", provide FWA #
- DHHS Grant Award number
- DHHS Funding Agency Name
- Funding Agency Grants/Program Officer Name and Telephone #
- Title of DHHS Grant
- Title of Protocol (if the same as the title of the grant, indicate as such)
- Version date of the informed consent document to be used with prisoners
- Date(s) of IRB Meeting(s) in which the protocol was considered
- Chronology of the following: Date of initial IRB review; and/or Date of Subpart C reviews including: type of IRB review (initial, amendment, addendum, continuing review); and special IRB review for prisoner issues
- Name of Principal Investigator
- Justification for the use of prisoners in the study. If applicable, delineate the protocol to be conducted in the prison from the overall project described in the grant application
- Study objectives or study aims
- Brief summary of study procedures
- Customary treatment or services at the prison (or alternative to incarceration) research site(s) for the condition being studied
- Description of how risks specific to a prison (or alternative to incarceration) setting are minimized; Whether the prison site(s) are "engaged in research" and whether they have obtained an assurance with OHRP
- Whether a Certificate of Confidentiality was obtained by the PI for the study
- Description of recruitment procedures in the specific prison (or alternative to incarceration) setting and/or description of how the consent form was altered for use with a prison population or specific prisoner, and whether the subsequently incarcerated participant will be reconsented.

All prisoner research certification letters will be mailed to:

OHRP Prisoner Research Coordinator
Office for Human Research Protections (OHRP) Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

4. Non-prisoner participants

The IRB may approve the research for non-prisoner participants only if all the criteria in Subpart C are satisfied.

The IRB must inform the Investigator in writing that no prisoner-subjects can be enrolled or involved until the IRB/institution receives a letter from OHRP that acknowledges receipt of the prisoner certification and indicates the Secretary's (through OHRP) determination that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

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5. REFERENCE

OHRP Guidance on the Involvement of Prisoners in Research, May 23, 2003

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Policy SC 506: Enrollment of Children and Neonates in Research

1. PURPOSE

This Policy presents the federal regulations governing the enrollment of children and neonates in clinical research and the procedures that investigators must follow in proposing a protocol involving this class of subjects, as well as the procedures that the IRB must adhere to in reviewing and approving such a protocol.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; IRB Manager; HRPO; Appointed/Elected IRB Members and Investigators

3. POLICY STATEMENT

The Children's Health Act of 2000 requires that all research involving children that is supported or regulated by the Department of Health and Human Services be in compliance with Subpart D of 45 CFR Part 46. 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. The additional safeguards of Subpart D require the IRB to determine the level of risk, and the prospect of direct benefit presented to the child by the proposed research.

Although enrollment of children in clinical trials presents difficult considerations for IRBs, such enrollment is important to the children because children differ markedly from both animals and adults and thus research using these as models cannot substitute as alternatives for testing agents in children. The lack of appropriate testing of agents in children will potentially increase their risk of harm from exposure to practices or treatments untested in children. Furthermore, new therapies or useful general knowledge concerning diseases or conditions specifically affecting children could not be developed.

Research in children requires that the IRB carefully consider the degree of risk, and possible benefit to the child involved in the research, for this is at the core of the concept of beneficence when considering research in a pediatric population and must be considered before the Board can realize that it has the authority to approve the study.

This Policy is to be considered in connection with SLUHN Policy IC 603, *Policy and Procedures for Parental Permission and Child Assent to Participate in a Research Protocol*, and Policy IC 604, *Child Assent*.

4. PROCEDURES

4.1: Minimization of Risks

The IRB must ascertain whether the risks to children can be minimized and must consider the risks from the prospective subject's point of view. The IRB members should be familiar with the ways in which research can be modified to minimize risks to children in particular. The investigators conducting the study should be properly trained and experienced in conducting research with the pediatric population and in the evaluation and management of adverse events in this population.

In addition to fulfilling the criteria stated in 45 CFR 46.111, the IRB can approve research involving children only if the research proposed falls into one of the following categories:

- The research presents no more than minimal risk to the child (§46.404).
- Research involving an intervention or procedure presenting greater than minimal risk to children but offers the prospect of direct benefit or may contribute to the well-being of the individual child (§46.405).
- Research involving an intervention or procedure that presents only a minor increase over minimal risk yet does not offer any prospect of direct benefit or contribute to the well-being of the individual child.

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If the IRB cannot determine that the research falls into one of the above categories, it must disapprove the study.

Under 45 CFR 46.407, if it is felt that the research, not otherwise approvable, presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the study may be referred to the Secretary of the DHHS for review.

4.2: Research Presenting Greater Than Minimal Risk

The IRB can approve research on children that presents greater than minimal risk only if the risk is justified by the anticipated benefit to the subject, or the risk is only a minor increase over minimal risk and there is anticipation that the study is likely to yield generalizable knowledge about the subjects' disorder or disease. Such knowledge must be considered essential for the understanding or amelioration of the subjects' disorder or condition.

For the IRB to approve research under 45 CFR 46.405, it must be able to justify that not only is there a balance of risk and anticipated benefit, but the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by the available alternatives. There must be "research equipoise" between two or more arms of a concurrently controlled trial, where one arm represents currently accepted practice, or between a single arm study and the alternatives available off study.

"Research equipoise" is a conceptual state where there is honest professional disagreement among experts about whether the experimental or the control treatment should be considered the preferred treatment or practice, i.e. there is genuine uncertainty about which intervention is better. Research equipoise does not require numeric equality of intervention risks and benefits, but only approximate equality. For example, an experimental intervention may pose more risk to subjects than accepted practice as long as it also offers the prospect of greater direct benefit to the subjects and the risk to potential benefit is within generally accepted practice guidelines.

4.3: Child Assent (Also see SLUHN Policy IC 604)

An important part of research on children is the provision for obtaining and documenting child assent. In determining whether children are capable of assenting, the IRB shall take into account the age, maturity, and psychological state of the children in the study population. This may apply to all of the children or on a case by case basis as determined by the IRB. A child's assent to participate in a clinical trial protocol implies that he/she has agreed to participate after being fully informed about the study in lay language geared to the level of the child's comprehension of the procedures involved and the attendant risks and benefits. Mere failure to object should not be construed as assent.

How the assent process will be carried out must be clearly stated in the protocol. It is the presumption in Pennsylvania that an individual 18 years of age is of legal age and can sign for him/herself. While there is no specific age where assent is required under Pennsylvania law, in concurrence with the practice of other institutions, the SLUHN IRB requires that children age 7 to 17 be asked to indicate their assent on the assent form, or, if a child's level of understanding and maturity permit, understanding and signing the parental permission form.

It is important to note that a pregnant female under the age of 18 is considered emancipated and thus is permitted to make decisions independent of parents. The same applies to an individual under the age of 18 that is living on his/her own and financially supporting them.

In addition to the child's assent, one or more parents must give permission for the child's participation in the study depending on the risk involved and whether a benefit is expected. If the risk is minimal, or if the risk is greater than minimal with the prospect of a direct benefit, the assent of the child and the permission of one parent are sufficient. If the risk is greater than minimal, but there is no prospect of a benefit, the child's assent

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as well as the permission of both parents is required unless this is not possible for reasons stated in SLUHN Policy IC 603.

5. CHILDREN AS WARDS OF THE STATE OR OTHER AGENCY

Under §46.409, children who are wards of the State or other agency can be included in research approved under § 46.404 or § 46.405 and may also be included in research approved under § 46.406 or § 46.40. if such research is: 1) Related to their status as wards; 2) conducted in schools, camps, hospitals, institutions where the majority of the children involved as subjects are not wards. If the research is approved under such conditions, the IRB shall require the appointment of an advocate for each child who is a ward, in addition to any other individual acting as guardian or in loco parentis. One individual may serve as an advocate for more than one child. The advocate must be an individual who has the appropriate background and experience and who agrees to act in the best interests of the child. This individual must not be associated in any way with the research, the investigator, or the guardian organization.

6. RESEARCH INVOLVING NEONATES (45 CFR 46.205)

6.1: Viable Neonates

A neonate after delivery that has been determined to be viable may be included in research only if the extent permitted by and in accord with the requirements of 45 CFR 46 Subparts A and D.

6.2: Neonates of Uncertain Viability and Nonviable Neonates

Individuals engaged in research will have no part in determining the viability of a neonate. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

6.3: Neonates of Uncertain Viability

- Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this Subpart B unless the following additional conditions have been met. The IRB determines that:
 - The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
 - The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means, and there will be no added risk to the neonate resulting from the research.
 - The IRB will accept the consent of either parent or her legally authorized representative

6.4: Nonviable Neonates

- After delivery a nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:
 - Vital functions of the neonate will not be artificially maintained;
 - No research procedure will terminate the heartbeat or respiration of the neonate;
 - There will be no added risk to the neonate resulting from the research;
 - The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

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The IRB will require the consent of both parents unless one parent is unable to consent due to unavailability, incompetence or incapacity. The IRB will not permit consent by a legally authorized individual for research involving a nonviable neonate.

7. TOOLS

DHHS requirements in 45 CFR Part 46, Subpart D for *Research involving Children*, as illustrated in the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research".

45 CFR 46.205, Research Involving Neonates

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Policy SC 507: Differences in State and Federal Law and Reporting Requirements Affecting the Protection of Privacy Interests of Research Subjects

1. PURPOSE

Differences in state and federal law pertaining to research should be clarified.

2. DEFINITIONS

Policies set forth the Federal definitions applicable to research and the laws of the Commonwealth of Pennsylvania. Specific policies should be consulted to ensure legal compliance.

3. APPLICATIONS

Consistent with specific IRB policies, if the principal investigator has questions concerning the application of Federal and state laws related to research, the principal investigator is responsible for securing clarification. Recognizing that state laws may differ with respect to the Federal laws and the laws of states other than the Commonwealth of Pennsylvania, the principal investigator and the IRB shall contact the , General Counsel who will refer the question(s) regarding the laws to the Network Compliance Office/Officer for clarification to ensure appropriate application in research.

4. SPECIAL CONSIDERATIONS CONCERNING CONFIDENTIALITY RELATED TO REQUIRED DISEASE, ABUSE AND HIV REPORTING

4.1 Confidentiality of Records [See 45 CFR 46.116(a)(5); 21 CFR 50.25(a)(5)]

Consent forms must explain the extent to which information obtained in connection with the research and that could identify the subject will remain confidential and will not be disclosed without the subject's permission. Limits on confidentiality, including the Commonwealth of Pennsylvania's requirement for reporting of suspected child abuse or neglect, 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." Note: Where a research study involves sensitive topics, researchers should consider applying for a Certificate of Confidentiality. (These certificates should not be used to attempt to avoid reporting of suspected abuse or neglect, however.)

4.2 Mandatory Reporting of Disease, Infections and Conditions

Researchers and subjects should be aware that the laws of the Commonwealth of Pennsylvania (See, 28 Pa. Code § 27 and (35 P.S. § 7607) require health care professionals and health care facilities to report to the Pennsylvania Department of Health (Department) all diseases, infections and conditions listed in the table below.

WITHIN 24 HOURS	WITHIN 5 DAYS
Anthrax	AIDS (Only physicians and hospitals are required to report cases of AIDS)
Arboviruses	Amebiasis
Botulism	Brucellosis
Cholera	CD4 T-lymphocyte test result with a count of less than 200 cells/ μ L or a CD4 T-lymphocyte percentage of less than 14% of total lymphocytes
Diphtheria	
Enterohemorrhagic E. coli	
Food poisoning outbreak	
Haemophilus influenzae invasive disease	

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<p>Hantavirus pulmonary syndrome</p> <p>Hemorrhagic fever</p> <p>Lead poisoning</p> <p>Legionellosis</p> <p>Measles (rubeola)</p> <p>Meningococcal invasive disease</p> <p>Plague Poliomyelitis</p> <p>Rabies Smallpox</p>	<p>Campylobacteriosis</p> <p>Cancer</p> <p>Chancroid</p> <p>Chickenpox (varicella)</p> <p>Chlamydia trachomatis infections</p> <p>Congenital adrenal hyperplasia (CAH) in children under 5 years of age</p> <p>Creutzfeldt-Jakob Disease</p> <p>Cryptosporidiosis</p> <p>Encephalitis</p> <p>Galactosemia in children under 5 years of age</p> <p>Giardiasis</p> <p>Gonococcal infections</p> <p>Granuloma inguinale</p> <p>Guillain-Barre syndrome</p> <p>HIV (Human Immunodeficiency Virus)</p> <p>Hepatitis, viral, acute and chronic cases</p> <p>Histoplasmosis</p> <p>Influenza</p> <p>Leprosy (Hansen's disease)</p> <p>Leptospirosis</p> <p>Listeriosis</p> <p>Lyme disease</p> <p>Lymphogranuloma venereum</p> <p>Malaria</p> <p>Maple syrup urine disease (MSUD) in children under 5 years of age</p> <p>Meningitis</p> <p>Mumps</p> <p>Perinatal exposure of a newborn to HIV</p> <p>Pertussis (whooping cough)</p> <p>Phenylketonuria (PKU) in children under 5 years of age</p> <p>Primary congenital hypothyroidism in children under 5 years of age</p> <p>Pitacosis (ornithosis)</p> <p>Rickettsial diseases</p> <p>Rubella (German measles) and congenital rubella syndrome</p> <p>Salmonellosis</p> <p>Shigellosis</p> <p>Sickle cell disease in children under 5 years of age</p> <p>Staph infections</p> <p>Streptococcal invasive disease (group A).</p> <p>Streptococcus pneumoniae, drug- resistant invasive disease</p> <p>Syphilis (all stages)</p> <p>Tetanus</p> <p>Toxic shock syndrome</p>
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	Toxoplasmosis Trichinosis Tuberculosis, suspected or confirmed active disease Tularemia
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4.3: Other Reporting Requirements

Healthcare providers in Pennsylvania are also required to report:

- serious or imminent plans to harm oneself or another
- child neglect or abuse
- child sexual abuse

Child abuse or suspected child abuse reporting requirements extend to abuse committed by a parent, a person responsible for the welfare of the child (i.e., anyone who provides care or supervises the child), an individual living in the same house, or a paramour of the child's parent.

4.4: HIV/AIDS-Related Considerations

No HIV-related test shall be performed without first obtaining the informed written consent of the subject or legally authorized representative. 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 subject is not known and may not be retrieved by the researcher is prohibited, unless reviewed and approved by the IRB established by the PA Department of Health. Consent requirements for HIV-related tests shall not apply to the following:

- the performance of an HIV-related test on a cadaver by a health care provider which 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
- the performance of an HIV-related test for the purpose of medical research if the testing is not prohibited by the Department and is performed in a manner by which the identity of the test subject is not known and may not be retrieved by the researcher. (35 P.S. §7605)

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600 Informed Consent (IC)

Policy IC 601: Informed Consent and HIPAA Authorization: General Requirements

1. PURPOSE

This policy describes the general requirements for obtaining and documenting informed consent.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

Investigators; IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed Elected IRB Members

3. POLICY STATEMENT

This policy pertains to all research submitted to the IRBs. Informed consent must be legally effective and prospectively obtained (45 CFR 46.116; 21 CFR 50.20). Except as delineated in SLUHN Policy IC 606, *Waiver of Informed Consent and HIPAA Authorization*, no investigator may enroll a human being as a research subject unless s/he has obtained legally effective informed consent from the subject or the subject's legally authorized representative (LAR). Consent shall be sought only under circumstances that provide the prospective subject or the LAR sufficient opportunity to consider whether or not to participate in the study, and that minimize the possibility of coercion or undue influence.

Subject authorization also must be obtained for prospective use or disclosure of protected health information (PHI) for research conducted within the University or the University Hospital. Except as described in SLUHN Policy IC 606 no investigator may prospectively collect PHI unless s/he has obtained legally effective authorization of the subject or the subject's legally authorized representative.

The IRB requires documentation of informed consent by use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR. Authorization to collect PHI will also be obtained by the use of the IRB-approved consent form that contains a federally compliant HIPAA Confidentiality Section or, as appropriate, a separate HIPAA Authorization document.

4. PROCEDURES

The consent form document may be either of the following:

- A written consent document that encompasses the elements of informed consent and the required elements of a HIPAA authorization. This form may be read to the subject or the subject's LAR. The investigator shall give the subject or the LAR adequate opportunity to read it before it is signed. The subject or LAR shall receive a copy of the signed and dated consent document.
- A "short form" written consent document stating that the elements of informed consent as required have been presented orally to the subject or the subject's LAR. When this method is used, there shall be an impartial witness to the oral presentation. The IRB must approve a written summary of what is to be said to the subject or representative. The subject or the LAR will sign the short form. The witness shall sign both the short form and a copy of the summary, and the person actually obtaining the informed consent shall sign the summary. A copy of the signed and dated summary and the signed and dated short form shall be given to the subject or the LAR.

4.1: Required Elements of Informed Consent

- The Common Rule 45 CFR 46.116 (a) (5) (i) indicates, Informed Consent begin with a concise and focused summary of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reason why one might or might not want to participate in the research.

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- 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 subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental or investigational.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that the subject can pursue outside of the study.
- A statement describing the extent to which, if any, the confidentiality of records identifying the subject will be maintained and that states the possibility that the Food and Drug Administration (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 subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- Informed consent documents may not contain any exculpatory language through which the subject is made to waive or appear to waive legal rights or releases or appears to release the investigator, the sponsor, or the university from liability for negligence.

4.2: Additional Elements of Informed Consent

- When appropriate, one 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 subject (or to the embryo or fetus if the subject is or may become pregnant) which are currently unforeseeable.
- Anticipated circumstances in which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study at St. Luke's University Health Network and nationally if a multi-site study.

4.3: Elements of HIPAA Authorization

The following elements are required in a federally compliant HIPAA Authorization. These elements should be part of the Confidentiality Statement in the SLUHN Informed Consent Document template:

- A description of the health information to be collected as part of the research.
- A description of the person or classes of persons authorized to use or disclose the protected health information.
- A description of the person or classes of persons who may receive the information, and the purpose(s)

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for each disclosure.

- An expiration date or the extent of the authorization for use or disclosure if any
- A statement of the subject's right to revoke authorization and person to contact to revoke
- Reference to the covered entities Notice of Privacy Practices
- Notice that disclosure of protected health information to non-HIPAA compliant entities may result in subsequent loss of protection of PHI.
- Limitations, if any, on a subject's access to their records during the study.

4.4: Documentation of Informed Consent

At some point in the consent process, an interview or session is held with the prospective subject and/or LAR so that all of the subject's/LAR's questions and concerns are answered before s/he makes the final decision on participation. This interview can be conducted by the PI, a Sub-I, or any key personnel designated by the PI. When the subject or LAR signs the consent form, this is referred to as "obtaining informed consent."

The ultimate responsibility for ensuring that informed consent is obtained, and that the consent interview is conducted in such a way that all of the subject's/LAR's questions and concerns are answered rests with the PI. However, because consenting situations are so varied, the IRB will only make specific determinations as to who can and cannot obtain informed consent on a case-by-case basis.

Whomever is designated to conduct the consent interview must describe the research study to the potential subject/LAR, discuss appropriate alternatives, and answer any questions regarding the research, and obtain the subject's/LAR's consent to participate prior to initiating any research procedure.

If the consent interview is conducted by key personnel other than the PI (or Sub-I if the PI is unavailable), the PI or Sub-I must be reachable by phone if the subject should have questions that cannot be answered by the person conducting the interview. If the research poses greater than minimal risk, the PI or a Sub-I should make every effort to be present at some time during the consent interview.

When the subject signs and dates the consent form, the person conducting the consent interview will also sign and date

The original consent form, signed and dated by the subject, or the subject's authorized representative, and the person obtaining consent, and a witness, if necessary, must be kept in the subject's study file and a photocopy provided to the subject.

4.5: Other Requirements

Second Person: The consent document should use the second person (You/your) style so the consent form conveys a dialogue with information being provided and that there is a choice to be made by the subject rather than presumption of the subject's consent with the use of the first person style (I/mine).

Simple Language: The information provided in the informed consent documents must be in language understandable to the subject. The informed consent document should not use complex language that would not be understandable to all subjects. Technical and scientific terms should be adequately explained using common or lay terminology (See SLUHN Guidance Document G 703).

FDA-Regulated Test Articles: For research involving test articles regulated by the U.S. Food and Drug Administration (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 subject's medical records.

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4.6: IRB Review of Consent Process

The IRB will take the following into consideration when reviewing the protocol and consent document:

- Person(s) who will conduct the informed consent process.
- Matters of timing of obtaining informed consent and the waiting period between informing the subject and obtaining consent.
- Ensuring that the process provides ample time for the person conducting the consent interview and the prospective subject to exchange information and ask questions.

5. TOOLS

SLUHN Informed Consent Document Template

SLUHN Policies IC 601, Informed Consent and HIPAA, and IC 602, IC documentation

SLUHN Guidance G 703, Lay terminology

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Policy IC 602: Documentation, Waiver and Alteration of Informed Consent

1. PURPOSE

This policy describes the requirements for documenting informed consent and the circumstances when the IRB may waive or alter the requirement to document informed consent.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members; Investigators; Study Personnel

3. POLICY STATEMENT

This policy pertains to all research submitted to the IRBs. Unless specifically waived by the IRB, informed consent for all subjects, or their legally authorized representatives, must be documented. SLUHN provides for waiver or alteration of consent, and waiver of written documentation under certain conditions. FDA- regulated studies have no such provision because the types of research that qualify for waiver are not regulated by FDA or are covered by the emergency treatment regulations at 21CFR.50.23.

4. PROCEDURES

4.1: Documentation of Informed Consent (45 CFR 46.117; 21 CFR 50.27)

Each subject or his/her legally authorized representative (LAR) must sign and date a copy of the current IRB-approved consent form prior to enrollment or any participation in any phase of the study, unless the requirement is waived by the IRB, and be given a copy of the signed document that has also been signed by the person obtaining informed consent.

The IRB may approve procedures for documentation of informed consent that involve: (1) a written consent form signed by the subject; (2) a short form written consent form with oral presentation; or (3) in limited circumstances a waiver or alteration of a written consent form. Each of these three options is described in detail below. It is the responsibility of the IRB to determine which of the procedures described below is appropriate for documenting informed consent.

4.1.1 Written Consent Form Signed by Subject or 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 subject or the LAR as well as by the person obtaining informed consent. The person obtaining informed consent should allow the subject or the LAR adequate opportunity to read the consent document before it is signed. A signed and dated copy of the document must be provided to the person signing the form.

Some studies involving subjects 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 subject's continued involvement is informed and voluntary. Additionally, the IRB should consider whether and when to require a reassessment of subject's decision-making capacity.

The written informed consent document should contain, in a language understandable to the subjects of the study, all the elements necessary for legally effective informed consent. Subjects who do not understand English should be presented with an informed consent document written in a language understandable to them.

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4.1.2 *Research Data Retention*

In accordance with FDA guidance:

- When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- The investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject 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 subject's information.
- The Researcher must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, a researcher may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

4.1.3 *Short Form Consent (45 CFR 46.117(b); 21 CFR 50.27)*

As an alternative to standard written informed consent documents, oral presentation of informed consent information may be used with a short form consent document. In such cases, the subject must be provided with *a*) a short form informed consent document stating that the elements of consent have been presented orally to the subject or the subject's LAR; and *b*) a written summary of the information that is presented orally.

A witness to the oral presentation is required. When this method is used the IRB must review the written summary. The subject or the LAR must sign the short form written consent document.

The person obtaining consent must sign a copy of the written summary of the information that is presented orally. The person obtaining consent may not be the witness to the consent.

For potential subjects who do not speak English (SLUHN Policy IC 605), where informed consent is documented using this short form procedure, the written informed consent document should contain, in language understandable to the subject, all the elements necessary for legally effective informed consent. When this procedure is used with subjects who do not speak English:

- The oral presentation and the short form written informed consent document should be in a language understandable to the subject;
- The IRB-approved English language informed consent document may serve as the summary; and
- For those subjects who are consented using a foreign language consent document, the witness should be fluent in both English and the language of the subject. For those studies, the IRB will receive all foreign language versions of the short form as a condition of approval. The information in the protocol must match the information in the informed consent document.
- Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

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4.1.4 Research Not Regulated by the FDA

The IRB may waive the requirement to obtain written consent from some or all subjects (see SLUHN Policy IC 606) if the IRB finds that:

- The only record linking the subject and the research is the consent document, and the harm resulting from a possible breach of confidentiality is the principal risk to the subject. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement of written consent is waived, the IRB will request a script of information to be provided verbally to subject. The IRB also may require the PI to provide subjects with a written statement regarding the research. The script and/or written statement must be approved by the IRB.

4.1.5 Use of Facsimile or Mail to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the subject or LAR, and to conduct the consent interview by telephone or video conference.

Consent may also be obtained by mail. When using this procedure, the subject or LAR will sign and date the consent form and mail it to the investigator, and the investigator will then sign and date the consent form and mail a copy of this form to the subject or LAR.

5. RECONSENTING

Reconsent of research subjects is required when there is new information about a trial that could affect the subject's willingness to continue in the trial. Examples include increased or new risks and changes in the protocol that materially affect the subject, such as additional study visits, increased length of visits, new questionnaires or changes in treatment modalities. If the updates are no longer relevant to patients, because of the patients' current participation requirements in a study, then reconsenting is not required, for example, if the patient is in a survival tracking phase of a protocol. The IRB does not require consent changes to be submitted if the study is closed to accrual and the subjects have completed their active participation in the study, or if subjects who are still actively participating and the change does not affect their participation. Subjects should be presented with the amended IRB-approved consent form with added and/or deleted content denoted appropriately (e.g., hi-lighted or underlined). The changes also should be explained verbally to the subject. The subject should initial and date the pages containing the changes and also sign and date the signature page of the consent form. The subject should receive a complete copy of the signed and dated amended consent form.

6. REFERENCES

SLUHN Policy IC 605, *Informed Consent for Illiterate and Non-English-Speaking Subjects*.

FDA Guide to Informed Consent, Information Sheets, 1998 pp. 34-35.

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Policy IC 603: Parental Permission for a Child to Participate in a Research Protocol

1. PURPOSE

To provide information regarding the requirements for parental permission for a child's participation in a research study. This policy is to be used in conjunction with SLUHN Policy IC 604, *Child Assent to be a Subject in Research*.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members; Investigators

3. DEFINITIONS

Children: Both HHS and FDA define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research (or clinical investigations in the case of FDA), under the applicable law of the jurisdiction in which the research will be conducted." [(45 CFR 46.402 (a) and 21 CFR 50.3(o)]

Assent: Both HHS and FDA define assent as "a child's affirmative agreement to participate in research (or clinical investigation in the case of FDA). Mere failure to object should not, absent affirmative agreement, be construed as assent." [45 CFR 46.402(b) and 2a CFR 50.3(n)]

Permission: Both HHS and FDA define Permission as "the agreement of parent(s) or guardian to the participation of their child or ward in research (or clinical investigation in the case of FDA)" [45 CFR 46.402(c) and 21 CFR 50.3(r)]

Parent: Both HHS and FDA define Parent as "a child's biological or adoptive parent." [45 CFR 46.402(d) and 21 CFR 50.3(p)]

Guardian: HHS defines guardian as "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care." [45 CFR 46.402(e)]. FDA defines Guardian as "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research." [21 CFR 50.3(s)]

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

Ward: FDA defines ward as "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." [21 CFR 50.3(q)]

4. POLICY STATEMENT

4.1: Parental Permission for Enrollment of a Child in a Study

Children generally have not reached their full intellectual and emotional capacities and thus are legally unable to give valid consent. Consequently, when children or minors are involved in research, federal regulations require the assent of the child or minor and the permission of the parent(s). No individual can consent for someone else; s/he can only give permission. In the case of a parent wishing to enroll a child/adolescent in a research study, the parent must sign a parental permission that is similar to the adult consent form except that the parent gives permission for his/her child/adolescent to participate in the research. Parental permission is treated the same as informed consent apart from some additional provisions found in 45 CFR 46.408. Parental

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permission along with child assent meets federal requirements for enrollment of a child in a research study.

While the default for parental permission is that both parents sign permission, federal regulations provide that an IRB may find that the permission of one parent is sufficient for research to be conducted if the research represents no more than minimal risk, or if the research involves greater than minimal risk, but presents the prospect of direct benefit to individual subjects. Where research is covered by 45 CFR 46.406 and 46.407 of the HHS regulations and 21 CFR 50.53 and 50.54 of the FDA regulations, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

4.2: Waiver of Parental Permission

Under the regulations at 45 CFR 46.408 (c), in addition to the provisions for waiver contained in 45 CFR 46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in 45 CFR 46.116 (c) and (d), provided an appropriate mechanism for protecting the children who will participate as subjects 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 subjects, and their age, maturity, status, and condition.

4.3 Child Assent for Participation in a Research Study

As defined in SLUHN Policy IC 604, Child Assent for Participation in Research, "assent" means a child's affirmative agreement to participate in research. Failure to object without affirmative agreement cannot be construed as assent. The child must actively show his or her willingness to participate in the research rather than just complying with directions to participate and not resisting in any way. The IRB shall make certain that adequate provisions are made for soliciting the assent of the child when in the judgment of the IRB the child is capable of giving it. When the child is judged intellectually capable of understanding the parental permission form, the child should read the parental permission form and sign it rather than signing the Child Assent form. The child's signature on the parental permission will then indicate his/her assent.

5. TOOLS

SLUHN Parental Permission Form, including Child Assent Form
SLUHN Policy IC 604, *Child Assent to be a Subject in a Research*
SLUHN Policy SC 507, Differences in State and Federal Law

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Policy IC 604: Child Assent for Participation in Research

1. PURPOSE

This policy describes the Federal and state laws, and the requirements for assent of children, for participation in research. The purpose of the policy is to ensure that the Principal Investigators and Institutional Review Boards ("IRB") members comply with all federal regulations and state and local laws regarding participation of children in research.

2. RESPONSIBILITY FOR EXECUTING POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Investigators

3. POLICY STATEMENT

Federal regulations at 45 CFR, Part 46 Subpart D (Additional Protections for Children Involved as Subjects of Research) and FDA regulations at 21 CFR, Part 50, Subpart D for the Protection of Human Subjects set standards for the informed consent process and assign the IRB with the responsibility for ensuring that any research involving children adheres to federal and state regulations.

The principle of respect for persons requires that the decision of an autonomous person be respected. However, as children are not fully autonomous individuals and have not developed full cognitive ability, the permission of the parent or parents (or legally authorized representative) is required (See, SLUHN Policy IC 603, *Parental Permission for a Child to Participate in a Research Protocol*.)

4. DEFINITIONS

Assent: Consistent with the U.S. Department of Health and Human Services ("DHHS") and the Food and Drug Administration ("FDA"), "assent" means a child's affirmative agreement to participate in research (or clinical investigation in the case of FDA). Mere failure to object should not, absent affirmative agreement, be construed as assent. [See, 45 CFR Sections 46.402(b) and 2a CFR 50.3(n)]

Children: DHSS regulations define "children" as persons who have not attained the legal age for consent to medical or dental treatments or procedures involved in research under the applicable law of the jurisdiction in which the research will be conducted. [See, 45 CFR Section 46.402(a)]

The FDA defines children as persons who have "not attained the legal age of consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." [See, 21 CFR Section 50.3 (o)].

Under the laws of the Commonwealth of Pennsylvania, persons under the age of eighteen (18) generally meet the definition of children and will be considered children for purposes of this policy, with the exceptions set forth below. As a result, permission of the child's parent(s) or guardian(s) must generally be obtained prior to the participation of that child in research.

The following exceptions to the general rule noted above apply, where a person under the age of eighteen (18) does not meet the federal definition of "child" and may provide legally effective consent to participate in research if either:

- 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 been graduated from high school may give effective consent and the consent of no other person shall be necessary.
- The person is an emancipated minor. A minor may be determined by a court of competent jurisdiction to

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be emancipated (i.e., is self-supporting, does not live with parents). To demonstrate emancipation, such minor will be required to present appropriate documentation.

If an emancipated minor provides consent for him/herself, the court order should be copied and included in the research records with the consent document.

Parent: Consistent with the DHHS and FDA regulations and the Commonwealth of Pennsylvania, a “parent” for purposes of this policy means either a child's biological (natural or birth parent) or a person(s) adjudicated as an adoptive parent(s). [See, 45 CFR Section 46.402(d) and 21 CFR Section 50.3(p)]

Legally Authorized Representative (“LAR”): DHHS regulation defines a LAR as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.” [See, 45 CFR Section 46.102(c)]. FDA regulation defines a LAR in the same way. [See, 21 CFR Section 50.3(l)].

For purposes of this policy and consistent with the laws of the Commonwealth of Pennsylvania and Federal regulations, a “LAR” capable of providing consent on behalf of a child to participate in research studies is either a parent as defined in Section 4.3 above or a guardian as defined in Section 4.5 below.

Guardian: FDA defines guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. [21 CFR Section 50.3(s)].

DHHS defines guardian as “an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.” [45 CFR Section 46.402(e)]

Consistent with the laws of the Commonwealth of Pennsylvania, a legal custodian may provide the effective consent on behalf of a child to general medical care. 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. (See, 20 P.S. Section 5521). 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.

Ward: FDA defines ward as 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. [See 21 CFR Section 50.3 (q)]. 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.

5. PERSONS NOT MEETING THE DEFINITION OF CHILDREN

All individuals defined as “children” will be afforded the protections under federal laws cited above and additional protections for enrollment of children in research as delineated in IRB policies. Subpart D protections are not applicable for persons who do not meet the definition of children. (See exceptions listed in Section 4.2 above). The IRB may consider these subjects potentially vulnerable and may choose to apply additional protections.

When a research protocol involves persons who do not meet the definition of children, the IRB will carefully balance the potential risks and benefits of the proposed research and will consult with SLUHN legal as deemed necessary. For children, as defined above, parental permission as set forth in Section 6 below and assent as noted in Section 7 below shall be required.

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6. PARENTAL PERMISSION REQUIREMENTS

For children who are not legally capable of consenting to medical treatment as defined above, Federal regulations require parental permission for a child's participation in any medical research study except where parental permission is waived. The regulations divide medical research involving children into four categories. In the first two categories (45 CFR Sections 46.404 and 46.405), permission of only one parent or legal guardian is required. In the third and fourth categories, (45 CFR Sections 46.406 and 46.407), permission of both parents, if legally possible, is required.

Both parents should provide permission, however, permission of only one parent may suffice for:

- Research not involving greater than minimal risk (45 CFR Section 46.404); or
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject (45 CFR Section 46.405).
- Unless one parent is deceased, unknown, incompetent, or not reasonably available, or only one parent has legal responsibility for the child, permission from both parents is required for:
- Research that has a greater than minimal risk and no prospect of direct benefit to the child (45 C.F.R. Section 46.406); or
- Research approved by the Secretary of DHHS that does not fit the above criteria, but presents an opportunity to understand, prevent or alleviate a serious problem affecting children's health (45 C.F.R. Section 46.407).

See also SLUHN Policy IC 603: *Parental Permission for a Child to Participate in a Research Protocol*.

7. ASSENT PROCEDURES

7.1: Soliciting Assent

In instances where a child may not be capable of giving informed consent, the IRB must find that adequate provisions are made for soliciting the assent of the child subject when, in the judgment of the IRB, the subject is or has become capable of providing assent, unless assent has been waived by the IRB (45 CFR Section 46.408).

7.2: Determining Capability of Assent

IRBs have wide discretion in determining whether a child is capable of assent. In determining whether children are capable of assenting, the investigator and the IRB shall take into account the age, maturity, and psychological state of the child involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. The IRB will determine for each protocol, depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects, whether all or some of the children are capable of assenting to participation. Where appropriate, the IRB may choose to review on a case-by-case basis whether assent should be sought from certain individual subjects.

7.3: IRB Assessment of Risks and Benefits

Federal regulations divide medical research involving children into four (4) categories (refer to Section 6 above). The IRB shall classify research involving children into one (1) of the four (4) categories and consider the risks and benefits of the research study.

- In the first category, 45 CFR Section 46.404, research is considered research not involving greater than minimal risk.
- The second category, 45 CFR Section 46.405, research involves greater than minimal risk but presents the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject and (b) the relationship of risk to benefit is at

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least as favorable as any available alternative approach.

- The third category, 45 CFR Section 46.406, concerns research involving greater than minimal risk with no prospect of benefit to individual subjects, but likely to yield generalized knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational settings; and (c) the intervention or procedure is likely to yield generalized knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.
- The fourth category set forth at 45 CFR Section 46.407, is research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

7.4: Assent Not Necessary

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the subject and is available only in the context of the research, the assent of the subject is not a necessary condition for proceeding with the research. When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary.

7.5: Child's Dissent

In circumstances where a child might dissent, a child's dissent, which should normally be respected, may be overruled by the child's parent(s) at the IRBs' discretion if the research may provide direct benefit for the child.

7.6: Waiving Assent

The IRB may waive parental permission and/or child assent under the following circumstances:

- If the child is not capable of assent.
- If the research offers a prospect of direct benefit not available outside of the research [See Section 7.4 above and 45 CFR Section 46.408(a) waiver of assent of child].
- If the same conditions are present under which parental permission may be waived. [See, 45 CFR Section 46.408 (a through c) and 45 CFR Section 46.116(d)].

Even where the IRB determines that the children are capable of assenting, the IRB may still waive the assent requirement under specific circumstances in which consent may be waived. [See, 21 CFR Section 50.55 (b) and 45 CFR Section 46.408(c)].

7.7: Parental Permission Inappropriate

In certain research (e.g. research involving abuse or neglect), serious doubts as to whether parents' interest adequately reflect the child's interests may occur. In these cases, the IRB may devise alternative procedures for protecting the rights and interests of the children asked to participate, including seeking a court appointment of a special guardian.

7.8: Documenting Child Assent

7.8.1: *IRB Determination:*

When the IRB determines that assent is required, it shall also determine whether and how child assent must be documented. [See, 45 C.F.R. Section 46.408 (e)]. When children as defined in Section 4.2 above are involved in research, (1) the assent of the child, and (2) the permission of the parent(s) in place of the consent of the subjects are required.

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7.8.2: *Child's Decision:*

When assent is required, the decision of the child to assent or dissent should be respected and documented.

7.8.3: *Use of Assent Form:*

The IRB requires the use of a SLUHN Child Assent signature to serve as their affirmation to the Parental Permission form for children ages 7 through 17 who wish to participate in a research study.

7.8.4: *Use of Parental Permission Form for Child:*

It is acknowledged that some children who are adolescents (15-17 years of age) should be able to adequately comprehend the information in the Parental Permission Form for the study, and so with the concurrence of the parent(s) may also sign and date that document. The child's signature and date on the parental permission would then indicate his/her assent.

8. RESEARCH INVOLVING CHILDREN BEING CONDUCTED IN STATES OTHER THAN PENNSYLVANIA

If the research includes enrollment of participants in other states or countries, the principal investigator is responsible for providing the IRB with sufficient information to (a) verify the age at which participants in such jurisdictions have the ability to consent to participation in research, including any medical treatments or procedures, if applicable and/or (b) verify the requirements for determining who may serve as a LAR, including a guardian for a child to participate in research.

The principal investigator must also provide information on any state specific regulations on privacy requirements and genetic research. The principal investigator may consult with the SLUHN Legal Counsel for advice or direction. Recognizing that state laws differ with respect to the definition of children, age of majority and what constitutes "emancipation", or what constitutes a LAR including guardian, for research involving children conducted in states other than the Commonwealth of Pennsylvania, the principal investigator and the IRB shall contact the IRB Medical Director or Associate Directors, who will refer the question(s) regarding children to the SLUHN Legal Counsel. The IRB may, if it appears advisable, require the submission of an opinion rendered by an attorney from any applicable jurisdiction on age at which an individual can consent to participation in research and/or who may serve as a LAR including a guardian with regard to a child's participation in research.

9. REFERENCES

45 CFR PART 46.408 (Subpart D)

21 CFR Part 50.55 (Subpart D)

Parental Permission Form and Child Assent Form

SLUHN Policy IC 603: *Parental Permission for a Child to Participate in a Research Protocol.*

SLUHN Policy SC 506: *Enrollment of Children, Neonates and Minors in Research*

SLUHN Policy SC 507: *Differences in State and Federal Law*

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Policy IC 605: Illiterate, Non-English Speaking Subjects, and Subjects Physically Unable to Sign

1. PURPOSE

To delineate the policy and procedures for conducting the informed consent process when a potential subject cannot read English, is non-English speaking, or is physically unable to sign a consent form.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members, HRPO; Appointed/Elected IRB Members; Investigators

3. POLICY STATEMENT

Department of Health and Human Subjects (DHHS) regulations require that informed consent information be presented in "language understandable to the subject" and that, in most instances, informed consent be documented in writing unless appropriate waiver criteria are met (45 CFR §46.116 and §46.117). If a potential subject is non-English speaking, the consent form must be translated into the subjects' language. In the translation, particular attention must be paid to meanings and cultural nuances surrounding words and phrases as they may have different meanings or connotations in the potential subjects' own language. If the translation is not accurate, the subject could be misinformed, and this would undermine the ability of the subject to give truly informed consent.

4. PROCEDURES

4.1 Persons Illiterate in English

An individual who understands but does not read English may have the consent form read to him/her and s/he may "make his/her mark". The signature of an impartial witness to the consent process and that of the person conducting the consent interview are required [21 CFR §50.27(b)(2)]. ***Ideally, the witness should be a relative of the subject, but the witness cannot be study personnel.***

4.2: Individual Does Not Understand or Speak English

Having a translator present during the consent interview to do an ad hoc translation of the consent form is not permitted under federal regulations. If an individual meets the inclusion/exclusion criteria for the study, but does not speak English, s/he cannot be denied participation on the study but must be offered the opportunity to read and understand a consent form translated into his/her native language. Federal regulations do not elaborate on who is qualified to translate the consent form into the required language. In situations where time does not permit a full translation to be prepared, the provisions for the short form consent process, as per 45 CFR 46.117(b)(2), are permitted.

However, the research summary and short form consent required by this regulation must be translated into the native language of the subject by CryaCom International. A certificate of authenticity will be included with the translated document by CryaCom. A translator must be present at the consent interview. The translator may serve as the witness for the short form consent process. The short form documents must be approved by the IRB prior to being used.

The above procedure is allowable in circumstances where a non-native speaker who is not part of a targeted non-English speaking subject population presents as a potential research subject. When an investigator is specifically targeting particular non-English speaking populations for enrollment in a study, appropriately translated consent forms must be approved by the IRB prior to enrolling members of these populations.

4.3: Individuals Physically Unable to Sign a Consent Form

If a subject is cognitively capable of consent but is physically unable to sign the consent form (e.g. paralyzed),

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the subject's power of attorney or an impartial witness must be present for the entire consent interview. Ideally, the witness should be a relative of the subject and cannot be study personnel. After the subject has indicated the intention to consent, the subject's name and the current date may be written in the appropriate places on the consent form signature page.

If able, the subject will make his/her mark on the signature line. The witness will initial and date each page of the consent form and complete the witness section of the signature page.

4.4: Translation of the Consent Form

For translation of the consent form, the investigator must use a professional translator. Companies providing translation services will provide certification that the translation is an accurate representation of the original English consent form.

4.5: Presence of a Translator

A translator should be present during the consent interview for a non-English speaker. The translator must be someone who can accurately translate between spoken English and the subject's native language and who understands the cultural nuances of the language. The translator may be a member of the subject's family or someone else who can adequately fulfill the duty. A translator should also be available during the full course of the non-English speaker's participation in the study, so that the subject can always communicate reliably with the research team, which is a right of any research subject. The principal investigator should assume responsibility for assuring that appropriate arrangements with the translator or translation service can be made before the non-English speaker is enrolled.

4.6: Short Form Consent

All foreign language versions of short form consent documents must be approved by the IRB under the provisions of §46.117(b)(2). Review of the foreign language versions of the documents may be carried out by expedited review, but only if the protocol and full English language informed consent document have been given prior approval by a convened IRB.

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Policy IC 606: Waiver of Informed Consent and HIPAA Authorization

1. PURPOSE

To describe the procedures by which an IRB may waive documentation of informed consent or authorization to use and/or disclose protected health information.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members

3. POLICY STATEMENT

The IRB has the authority to waive the requirement for the investigator to document the informed consent process with an IRB-approved signed consent form. The IRB also has the authority to waive authorization for the use and/or disclosure of protected health information.

4. PROCEDURE

4.1: Waiver of Informed Consent

- 45 CFR 46.116(c) states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
 - The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
 - The research could not practicably be carried out without the waiver or alteration.
 - Or that [45 CFR 46.116(d)]:
 - The research involves no more than minimal risk to the subjects;
 - The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - The research could not practicably be carried out without the waiver or alteration; and
 - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

When the IRB waives the requirement for informed consent, the IRB must document the specific criteria required by federal regulations in the minutes of the appropriate convened IRB meeting. This is not required for exempt studies.

If the research protocol meets the requirements for expedited review, the same documentation requirement holds when the waiver is granted through the expedited procedure.

FDA regulations have no provision for the waiver of informed consent, the alteration of the elements of informed consent, or the waiver of written consent. Therefore, if a study is FDA-regulated, these waivers are not permitted.

4.2: Waiver of Authorization to Use and/or Disclose Protected Health Information

Investigators at SLUHN may use and/or disclose protected health information of the covered entity for research purposes without prospective authorization, provided that they request such a waiver from the IRB by completion of a Request for Waiver of Subject Authorization.

The following criteria must be adequately addressed:

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- The use or disclosure of the protected health information 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 protected health information 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 protected health information.

4.3: Documentation of Waiver of HIPAA Authorization

- The IRB shall provide the following documentation for all waivers of HIPAA Authorization approved under Section 4.2 above:
 - Identification of the IRB and the date on which the alteration or waiver was approved;
 - Statement that the IRB determined that the alteration or waiver of HIPAA Authorization, in whole or in part, satisfied the criteria of Section 4.2 of this policy;
 - Brief description of the protected health information for which use or access was determined to be necessary by the IRB;
 - Statement that the alteration or waiver of HIPAA Authorization was reviewed and approved under expedited or full IRB review procedures; and
 - Signature of the Director/Associate Director of the DHSP or other designated authority of the IRB as described in Policy GA 110.

5. TOOLS

SLUHN Request for Waiver of Subject Authorization

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Policy IC 607: Surrogate Consent

1. PURPOSE

To describe procedures to be followed in order to allow certain populations of patients (other than children who are covered under SLUHN Policy IC 604: *Child Assent for Participation in Research* and Policy IC 603, *Parental Permission for a Child to Participate in a Research Protocol*), otherwise incapable of making autonomous choices, to participate as subjects in research where the potential for direct benefits exceeds the risk of harm.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members; Investigators

3. DEFINITION OF LEGALLY AUTHORIZED REPRESENTATIVE ("LAR")

Both the FDA and DHHS define a Legally Authorized Representative as "...an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." [45 CFR Section 46.102(c); 21 CFR Section 50.3(l)].

For purposes of this policy, the following individuals may be considered a LAR of the subject and capable of providing surrogate consent:

- a court appointed guardian authorized to consent to the subject's participation in the protocol in a current court order issued within the subject's jurisdiction;
- a health care proxy appointed by the subject in a power of attorney; or
- where there has been no guardian appointed by a court or a health care power of attorney designated by the patient/subject, certain individuals may provide consent. Such individuals must be at least 18 years of age. There is a priority of order of individuals who may provide consent, which is noted below in Section 5. (See, 8 PA Code Section 103.22).

4. POLICY STATEMENT

4.1: Background

Federal regulations require that the researcher obtain the legally effective informed consent of the subject or the subject's legally authorized representative prior to medical research. Federal law defers to state law to determine which individuals are legally authorized to provide surrogate consent for the research subject. Pennsylvania law requires the informed consent of the patient or the patient's authorized representative before the administration of an experimental medication, the use of an experimental device, or the use of an approved medication or device in an experimental manner.

By statute, Pennsylvania authorizes surrogate consent for an experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment by the subject's court-appointed guardian pursuant to a court order issued after fact finding. Pennsylvania statutory law further authorizes a person named in the patient's power of attorney to consent to medical, therapeutic and surgical procedures for the subject.

While Pennsylvania statutory law does not explicitly authorize surrogate consent in the absence of a power of attorney or court-appointed guardian, case law strongly supports substituted consent by close family members when patients lack capacity to make medical decisions [see *In re Fiori*, 543 Pa. 592, 673 A.2d 905 (1996)]. When the patient is unable to give informed consent, the patient's close family member is in the best position to determine the wishes of the patient regarding participation in therapeutic research.

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4.2: Policy

The IRB recognizes the research subject's right to autonomy. The IRB also recognizes, however, that individuals with diminished capacity for decision-making require the consent of a surrogate decision maker (surrogate consent) in order to participate in research where the potential for direct benefit exceeds the risk of harm.

This policy pertains to individuals with diminished capacity for making decisions including:

- Individuals under sedation
- Individuals who are semi-conscious or unconscious
- Individuals who are experiencing overwhelming stress or pain (e.g., women during childbirth, individuals presenting to the ER with acutely painful conditions, such as Sickle Cell crisis, etc.)
- Cognitively impaired individuals
- Decision ally impaired individuals
- Individuals who are inebriated or under the influence of drugs

Only studies given IRB approval specifically to enroll decisionally impaired individuals with use of the surrogate consent form may do so. An investigator may not decide on an ad hoc basis to enroll a decisionally impaired individual without prior IRB approval.

When evaluating studies that may involve individuals with decisional impairments, the IRB must evaluate whether: 1) the proposed plan for the assessment of capacity of the individual to consent is adequate, and 2) assent of participant is required, and if so, whether the plan for assent is adequate.

With regard to surrogate authorization in abuse, neglect and endangerment situations, notwithstanding state law or any requirement of this policy or the HIPAA privacy regulations to the contrary, the IRB may elect not to treat a person as the LAR of an individual for surrogate if they have a reasonable belief that:

- the individual research subject has been or may be subjected to domestic violence, abuse, or neglect by such person; or
- considering such person the LAR could endanger the individual; and, the Investigator, in the exercise of professional judgment, decides that it is not in the best interest of the individual to consider the person the individual's LAR.

If such a decision is made not to treat a person as the patient's LAR for these reasons, documentation of the factual basis for such decision should be noted in the medical and research record with the report or any other documentation of suspected domestic violence, abuse, or neglect.

5. PROCEDURE

First, the investigator will determine whether a person who meets the study's eligibility criteria is unable to provide informed consent due to one or more of the above-stated criteria. The investigator may consult with a psychiatrist in determining the patient's capacity to make medical decisions. Secondly, the investigator will determine whether the risk of harm posed by the research to this patient is reasonable in relation to the potential for direct benefit to the subject. If both of these criteria are met, the investigator should seek surrogate consent for that person. The investigator will complete the form "*SLUHN Surrogate Consent*" by documenting as thoroughly as possible the reason for the subject's inability to provide informed consent.

The following individuals may be considered legally responsible surrogates capable of providing substituted consent:

- a court-appointed guardian
- a health care proxy appointed by the subject to execute "power of attorney"

In the absence of a court order or a duly appointed health care proxy, the investigator will obtain the surrogate informed consent from one of the following individuals health care representatives in priority order:

- spouse

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- natural or adoptive parent
- adult child (individual over the age of 18 years)
- adult brother or sister
- any other available adult relative related through blood or marriage

This list is ordered according to legal preference and is congruent with SLUHN policy for permission to administer medical care. The investigator should always seek out the available relative who is highest on the list.

The consent process will comply with the policies and procedures set forth by the IRB, and by state and federal law. The surrogate should base his or her decision on the subject's expressed wishes or, if unknown, what the surrogate believes the subject would have desired in light of his or her prognosis, values, and beliefs. When a surrogate provides consent, it is advised that s/he should remain the responsible party for all research decisions throughout the duration of the subject's participation in the research.

In the event of a disagreement among potential patient surrogates, an attempt to reach consensus shall be made. If consensus cannot be reached, the subject cannot be enrolled in the study, unless further mediation is sought out for the parties in disagreement.

Subsequent to obtaining the surrogate consent, the investigator should obtain the assent of the subject once it is determined that the subject is capable of understanding that permission for his/ her inclusion in a research study has been granted.

If the subject's condition improves and he/ she regains the capacity to provide informed consent after he/she has been enrolled in the study and undergone some or all study procedures, the investigator shall inform the subject of his/her participation in a research study and seek informed consent from the subject for continued participation in the research. If the subject agrees to continue participation, informed consent should be obtained. If the subject declines to participate, the subject will be withdrawn from the study, and the data obtained thus far will not be used in the research study, unless the subject agrees to allow the data already collected to be used. This agreement should be confirmed in writing with the subject's signature.

If, on the other hand, the subject is capable initially of providing informed consent, but it is likely that the subject will lose this capacity during the study, the subject should be encouraged at the beginning of the study to appoint a surrogate who will have the authority to consent to continuing participation, modification to the study, and withdrawal from the study if the subject loses capacity.

6. APPLICABILITY OF THE LAWS OF OTHER STATES

If the research includes enrollment of participants in other states or countries, the principal investigator is responsible for providing the IRB with sufficient information to verify the circumstances under which surrogate consent is allowable within in such jurisdictions. The IRB may, if it appears advisable, require the submission of an opinion rendered by an attorney or consultant from any applicable jurisdiction.

If the research is being conducted in jurisdictions outside of Pennsylvania, the Principal Investigator should contact the IRB Medical Director or Associate Directors, who will enlist SLUHN Legal counsel in determining the laws regarding priority of legally authorized representatives in the relevant states.

7. TOOLS

SLUHN Surrogate Consent

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Policy IC 608: Research in Emergency Settings (Prospective Review)

1. PURPOSE

To describe the exception from informed consent requirements for emergency research and the requirement for prospective review.

PLEASE NOTE: This policy does NOT apply Emergent Use of a Drug, Biologic, or Medical Device. That is addressed in SLUHN Policy GA 107.

2. RESPONSIBILITY FOR EXECUTING THE POLICY

IRB Chair; IRB Vice-Chair; IRB Members; IRB Manager; HRPO; Appointed/Elected IRB Members

3. POLICY STATEMENT

21 CFR Part 50.24 permits an IRB, with the concurrence of a licensed physician who is not participating in the research being reviewed, to approve emergency research, and in certain instances to waive the requirement for informed consent.

In order to waive informed consent under these conditions, the IRB must find and document that:
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.

Obtaining informed consent is not feasible because:

- The subjects 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 from the subjects' legally authorized representatives is feasible; and
- There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

Participation in the research holds out the prospect of direct benefit to the subjects because:

- Subjects are facing a life-threatening situation that necessitates intervention;
- Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
- Risks associated with the investigation are reasonable in relation to what is known about the medical condition of potential subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The clinical investigation could not practicably be carried out without the waiver.
- The proposed research plan defines the length of the potential therapeutic window based on scientific evidence.
- The investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time; and if feasible, to ask the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representative(s) and make this information available to the IRB at the time of continuing review.
- 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 subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.
- The IRB has reviewed and approved procedures and information to be used when providing an

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opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (i) (v) of this section.

Additional protections of the rights and welfare of the subjects will be provided, including at least:

- Consultation carried out by the IRB with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
- Public disclosure to the communities in which the clinical investigation will be conducted, and from which the subjects 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 a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact, within the therapeutic window, the subject's family member who is not a legally authorized representative and asking whether he/she objects to the subject'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 assure that, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, will be informed of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

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

If the IRB determines that 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.

4. REFERENCE

Federal Register 61(192): 51531-51533.

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Policy IC 609: Re-consenting

1. PURPOSE

Re-consenting of research subjects is required when there is new information about a trial that could affect the subject's willingness to continue in the trial. Examples include changes in risk levels or new risks and protocol modifications that materially affect the subject, such as additional study visits, increased length of visits, new questionnaires or changes in treatment modalities. Other instances requiring re-consent could include patients who were improperly consented out of compliance with local, state, and/or federal regulations, as well as institutional policies. If the updates in question are no longer relevant to patients, because of the patients' current participation requirements in a study, then re-consenting is not required, for example, if the patient is in a survival tracking/observational phase of a protocol or has completed relevant study procedures.

2. RESPONSIBILITY for EXECUTING the POLICY

IRB Chair; IRB Vice-Chair; IRB Committee; Appointed/Elected IRB Members.

3. DEFINITIONS

3.1 Informed Consent: is an individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to participate in research either for themselves or for a child for whom they are the parent or guardian.

3.2 Re-consent: is an individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to continue to participate in research either for themselves or for a child for whom they are the parent or guardian.

4. POLICY STATEMENT

All subjects must be made aware of new information about a trial that could affect their willingness to continue on the protocol. This is done through a process of re-consenting. If the updates are no longer relevant to patients, because of the patients' current participation requirements in a study, then re-consenting is not required (i.e., the patient is in a purely observational, survival tracking phase of a protocol).

It is standard practice that critical information is released immediately from the study sponsor for timely reporting to the IRB in the form of a dear doctor letter, DSMB results, updated IBs, or other form of memoranda. However, the formal ICF amendment is not always released until a later date. It is the SLUHN IRB's expectation that such new information be communicated verbally to enrolled subjects in a timely manner in the interim of the formal ICF amendment being released and IRB approved. This expectation is to ensure all subjects are made aware of new information that may affect their continued participation on a research study. Any communication of new findings or risks with the patient must be clearly documented in study records.

5. PROCEDURES

Should new information be released via other means outside of a revised Informed Consent Form (ICF), for example, via an updated IB changing risks, dear doctor letters, DSMB reports, or other memoranda, it is the responsibility of the investigator and/or appropriate study staff delegated the informed consent task, to inform the subject of this new information at their next study visit verbally and adequately document this discussion and their agreement to continue their participation in the patient study records in the interim of the formally revised ICF being released and approved by the IRB for use. Once the revised ICF is IRB approved, the subjects must be formally re-consented as outlined above.

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Subjects should be presented with the amended IRB-approved consent form with added and/or deleted content denoted appropriately (e.g., highlighted or underlined). The changes also should be explained verbally to the subject. The subject should sign and date the signature page of the consent form and complete the re-consent teach-back section to confirm understanding of the changes. The subject should receive a complete copy of the signed and dated amended consent form.

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700 Guidance (G)

Guidance G 701: Definition of Key Personnel in Human Subjects Research

1. PURPOSE

This policy defines key personnel as listed on the SLUHN IRB Application and Key Personnel Form for purposes of IRB oversight.

2. RESPONSIBILITY FOR UNDERSTANDING THE GUIDANCE:

IRB Chair; IRB Vice-Chair; IRB Members; Appointed/Elected IRB Members.

3. POLICY STATEMENT:

Key Personnel in human subject research are those individuals who are substantially involved in the research and who must be listed on the IRB Application. Key Personnel must have taken CITI Good Clinical Practice (GCP); Human Subject Research (HSR) Biomedical Researcher and FCOI NIH training, and must have completed the appropriate Financial Conflicts of Interest (FCOI) Disclosure.

Examples of activities performed by key personnel include but are not limited to:

- Involvement in the conduct of study procedures
- Ability to view PHI
- Have access to 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 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, case report form templates, etc.

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Guidance G 702: Reporting Adverse Events and Unanticipated Problems involving Risks to Subjects or Others – Guidance for Problem Issues

1. PURPOSE

This guidance addresses specific situations pertaining to reporting of adverse events (AEs) and Unanticipated Problems Involving Risks to Subjects or Others (UAPs).

2. RESPONSIBILITY FOR UNDERSTANDING THE GUIDANCE

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed Elected IRB Members.

3. GUIDANCE FOR REPORTING ADVERSE EVENTS:

Due to lack of federal guidance on many of the specifics of what needs to be reported as an adverse event, the SLUHN IRB provides the following recommendations for particularly problematic reporting issues. This guidance represents our current thinking on this topic but may change as a result of new federal guidance.

- Multiple causes for hospitalization – Many cooperative group studies (NRG, ECOG-ACRIN, etc.) require that in situations where a hospitalization has many contributing causes, the cause of highest severity (as per NCI's grading system) should be reported as the primary cause. For these studies, this requirement should be followed. For non- NCI funded studies, the IRB recommends that the cause of highest severity, as per the PI's opinion, should be reported as the primary cause. Secondary causes may be described in the body of the report.
- Multiple hospitalizations for the same cause – Because each hospitalization is a separate event, each should be reported as a separate adverse event.
 - Emergency Department visits should be reported as SAEs if:
 - The subject is admitted to the hospital
 - The subject is kept in the ED for more than 24 hours
 - The ED visit is probably or definitely related to the study drug
 - The ED visit is probably or definitely related to a study device and the problem is not listed in the device brochure, protocol or consent form
- Protocol-specific AE reporting guidelines – If the adverse event reporting guidelines in a commercially sponsored or cooperative group protocol are more specific than those of the SLUHN IRB, the investigator should follow the protocol-specific guidelines and should report according to the definition that is more protective of subject safety.
- Reporting deaths – Subject deaths that occur 30 days or more after study treatment has ended **do not** require individual reporting unless it is believed that the death is study-related. Deaths of subjects on long-term follow-up who are not receiving experimental intervention should be reported in aggregate at the time of continuing review. The IRB Final Report Form also includes a question pertaining to number of deaths.
- Laboratory or other test abnormalities should be logged as AEs and reported at the time of continuing review or reported as SAEs according to severity. In order to avoid unnecessary reporting, it is best to define laboratory abnormalities with respect to SAEs in the study protocol. For example, if a study is being done on patients undergoing major surgery but the major surgery is not part of the protocol, then events that are related to the surgery need not be reported as SAEs even if they meet criteria for grade 3 or above. Examples include:

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- Laboratory abnormalities that are clearly expected during the recovery period from the surgery (especially relevant to those patients being monitored in the ICU after surgery)
- Expected ECG abnormalities after cardiac surgery
- Return to the OR for surgical complications, or events related to recovery from anesthesia.

Similarly, an expected event of hypotension need not be reported if it is grade 3 [defined in CTCAE as sustained (up to or >24 hours without persisting physiologic consequences)] but should be reported as an SAE if grade 4 [shock (e.g., acidemia, impairment of vital organ function)].

4. HOW TO DETERMINE IF AN ADVERSE EVENT IS ALSO AN UNANTICIPATED PROBLEM THAT MUST BE REPORTED TO THE IRB:

In most instances, adverse events should be considered unanticipated problems involving risk to human subjects and reported to the IRB only if they are unexpected, serious, and have implications for the conduct of the study (e.g., requiring a significant or safety-related change to the protocol). An isolated unanticipated event that is serious and involves risk should be reported as such but may not require modification to the protocol or consent until a pattern is established.

Examples of adverse events that should be considered UAPs and reported to the IRB include:

- A serious unexpected (not in consent form) event that is uncommon and strongly associated with drug exposure such as angioedema, agranulocytosis, liver injury/failure, Stevens-Johnson syndrome, etc.
- A serious unexpected event that may occur once or a few times that is not commonly associated with drug exposure or found in the patient population under study, such as tendon rupture or progressive multifocal leukoencephalopathy.
- An event that occurs multiple times at a study site or is found on aggregate analysis of data from a multi-site study suggesting that these are not isolated occurrences but do pose risk to subjects.

An adverse event described in the consent or other study document that occurs at a rate or severity that is inconsistent with prior observations. Examples include:

- Mild kidney function test abnormalities are expected to occur in about 5% of subjects but are being noted in 15% of subjects.
- Abnormal liver function tests are described as a risk in the consent, protocol, and Investigator Brochure, but hepatic necrosis is observed in a study subject in whom causality is at least possibly related, in the investigator's opinion. (Here, the severity of the event is not reflected in the study documents.)
- Serious risk as described in the consent form occurs at a rate significantly greater than expected (e.g., noted as occurring at 1% but found in 10%).
- Any other event that requires modification of risks as listed in the Investigator Brochure.

Adverse events that are expected (listed in the Investigator Brochure, protocol and consent form) generally do not require reporting to the IRB as unanticipated problems but may require reporting as SAEs. Examples of adverse events that do not represent unanticipated problems and do not need to be reported to the IRB as such include the following:

- Known complications of standard chemotherapy regimens in subjects participating in a study adding an experimental chemotherapy drug or placebo to standard of care with the known risks of chemotherapy listed in the consent form. An example would be a patient having severe neutropenia with development of sepsis and subsequent multi-organ failure and death. Since this clinical scenario in terms of the nature, severity, and frequency is expected, it need not be reported to the IRB as an UAP. However, the hospitalization would, under SLUHN rules, be reported as a SAE.

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- A person in a multi-center study of a new non-steroidal anti-inflammatory drug (NSAID) for osteoarthritis develops abdominal pain and nausea and the work-up demonstrates gastric ulcers. The consent indicates that abdominal pain and nausea occur in about 10% of individuals taking NSAIDS, and gastric ulceration develops in about 20% of these patients. Medical review indicates that subjects across the study are experiencing nausea, abdominal pain and gastric ulceration at the expected frequency. This clinical scenario is not unexpected and therefore does not have to be reported as a UAP.

5. REFERENCE

IRB Policy GA 113 "Policy and Procedure for Reporting and Reviewing Unanticipated Problems Involving Risks to Subjects or Others"

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Guidance G 703: Guidance on Lay Terminology

1. PURPOSE

The language of medical science is precise but contains terms that may be incomprehensible to the general public. The ability to convey these complex ideas to prospective study participants or to lay members of IRBs is an art that is difficult to master, yet it lies at the heart of informed consent. The following is a glossary of technical terms to suggest terminology more easily understood by lay people.

2. RESPONSIBILITIES FOR UNDERSTANDING THE GUIDANCE:

IRB Chair; IRB Vice-Chair; IRB Members; HRPO.

3. INFORMED CONSENT GLOSSARY

- *Abdomen* – belly, stomach
- *Ablation* – removal
- *Abstain from* – avoid
- *Acute* – short-term, sudden onset
- *Adverse Event* – side effect
- *Alopecia* – hair loss
- *Amnesia* – loss of memory; inability to remember
- *Analgesic* – pain-relieving medication
- *Anaphylaxis* – a severe allergic reaction that could result in injury or death
- *Anesthetize* – make numb; put to sleep
- *Angioplasty* – operation to open clogged blood vessels
- *Anorexia* – loss of appetite
- *Antibodies* – cells or substances in the body that fight infection
- *Anus* – rectum
- *Artery* – blood vessel
- *Arrhythmia* – irregular or “skipped” heartbeat
- *Arthralgia* – joint pain
- *Aspiration* – inhalation; sucking in; removal of fluid from [location] through a tube or needle
- *Asthenia* – loss of energy; weakness
- *Asymptomatic* – without signs or symptoms of disease
- *Ataxia* –unsteady movement
- *Bacteria* – germs
- *Benign* – not cancerous
- *Biopsy* – removal and examination of a small part of [a tissue or organ]
- *Bone density* – bone thickness; hardness of bone
- *Bradycardia* – slow heart rate
- *Cardiac* – involving the heart
- *Cardiac catheterization* – procedure in which a small tube, called a catheter, is inserted through the blood vessels into the heart and a doctor uses a special fluid to look at the blood vessels in the heart
- *Cardioversion* – procedure that uses electricity to stimulate the heart and to make it return to its normal rhythm
- *Catheter* – flexible plastic tube that is inserted into the [location]
- *Central nervous system* – the brain and spinal cord
- *Chronic* – long-term
- *Coerced* – pressured; forced
- *Cognitive status* – levels of awareness and thinking
- *Colon* – large intestine; bowel
- *Colonoscopy* – procedure that uses a special camera at the end of a long tube
- *Confidentiality will not be compromised* – the staff protects your privacy

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- *Consent* – agreement
- *Contrast material* – fluid put into blood vessels or an area of the body to highlight the blood vessel or area for an x-ray picture
- *Convulsions* – seizures
- *Coronary* – involving the heart
- *Creatinine clearance* – a test of kidney function
- *Computed tomography (CT) scan* – computer enhanced x-ray; a special type of x-ray
- *Culture* – a test for the presence of germs
- *Defecate* – to have a bowel movement; to pass stools
- *Defibrillation* – a procedure that uses electricity to stimulate the heart and to make it return to its normal rhythm
- *De novo* – new
- *Deteriorate* – to get worse; to lose function
- *Diastolic blood pressure* – pressure when the heart rests between beats; the bottom number of a blood pressure reading
- *Diplopia* – double vision
- *Distended* – bloated; swollen; inflated
- *Double-blind* – neither the subject nor the doctor will know what drug the subject is taking
- *Duodenum* – beginning of the small intestine which is attached to the stomach
- *Dyspepsia* – gas; upset stomach
- *Dyspnea* – difficulty breathing; shortness of breath
- *Dysrhythmia* – abnormal or irregular heartbeat
- *ECG, EKG, or electrocardiogram* – picture and measurement of a heartbeat
- *Echocardiogram* – procedure using sound waves to take pictures of the heart chambers and measure of its pumping strength
- *EEG* – measurement of electrical activity of the brain
- *Edema* – swelling
- *Efficacy* – effectiveness; usefulness
- *Electrode* – wire
- *Electrophysiology study* – heart rhythm study
- *Elucidate* – to make clear; to determine; to find out
- *Embryo* – animal in the earliest stages of development
- *Enema* – medication given through the rectum that cleans out the bowel
- *Enzyme abnormality* – blood test result that suggests abnormal organ function or injured cells
- *Exclusion criteria* – reasons that one cannot be included
- *Excreted* – made; given off; put out
- *Fast* – do not eat or drink
- *Fatigue* – tire; tiredness
- *Fetus* – developing human
- *Flatulence* – gas passed through the anus/rectum
- *Flushing* – to become red in the face or other part of the body because of rush or blood to the skin; blushing of the skin
- *Fracture* – break
- *Gastric* – relating to the stomach
- *Gastrointestinal* – relating to the stomach and intestines
- *Glucose* – sugar
- *Hematoma* – a bruise; bleeding into the body tissue around a blood vessel
- *Hemodynamic measurement* – test to measure blood flow
- *Hepatic* – relating to liver
- *Hepatitis* – inflammation or swelling of the liver
- *Holter monitor* – a machine, the size of a pocket radio that records the beats of a heart
- *Hypertension* – high blood pressure

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- *Hypotension* – low blood pressure
- *Hysterectomy* – removal of the womb
- *Immobilization* – making something unable to move
- *Immobilized* – unable to move
- *Immunological* – relating to the body's ability to fight infection *Implantation* – operation to place a [device] inside the body
- *Incision* – cut
- *Indicated* – suggested; necessary
- *Induce* – cause
- *Inert* – not active
- *Inert substance* – has no known effect on this disease
- *Inflamed* – swollen, red and warm
- *Inflammation* – swelling and redness
- *Inflation* – filling with air
- *Infused* – dripped in; put in
- *Ingest* – swallow eat or drink
- *Inject* – to put into by way of a needle (or other device)
- *Insomnia* – unable to sleep *Instilled* – put into; dripped into
- *Intensity* – degree; amount
- *Intramuscular injection* – putting something into muscle with a needle
- *Intravenous* – in a blood vessel
- *Intravenous infusion* – putting something into a blood vessel through a plastic tube and needle
- *Isolated* – separated; closed off
- *Lactating* – making breast milk; breastfeeding
- *Lesion* – site of an injury; site of a disease *Leukocyte* – blood cell that fights infection
- *Libido* – sexual desire; sex drive
- *Local anesthetic* – medicine to numb an area of the body
- *Lumbar puncture* – a needle inserted between the bones of the spine to put in a drug or to take a sample of the spinal fluid
- *Lumbosacral* – lower back
- *Maintenance dose* – one's usual daily dose
- *Malignancy* – tumor; cancer
- *Manifested* – showed
- *Meningitis* – infection or irritation around the brain
- *Metabolism* – process by which food is used to supply energy for the body; the energy the body uses when it works; the way the body breaks down food or a drug
- *Metastasize* – spread
- *Magnetic Resonance Imaging (MRI)* – pictures of the inside of the body taken with large magnet and radio waves (radiation is not used)
- *Mucosa* – the lining inside [an organ]
- *Myocardial infarction* – heart attack
- *Nasal congestion* – stuffiness of the nose
- *Nasal* – relating to the nose
- *Nasogastric (NG) tube* – a flexible plastic tube that is inserted through the nose or mouth into the stomach
- *Nausea* – feeling sick to one's stomach
- *Negative finding* – a normal result; the usual result for a healthy person
- *Neurological examination* – test of the brain, spinal cord and reflexes
- *New indication* – new use
- *Occult blood test* – a test for small amounts of blood in the stool
- *Open-label* – a scientific study in which the identity of the drug, device or procedure is known to both

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the subject and to the doctor; the subject will know which drug she or he is taking

- *Optimum or optimal* – best
- *Oral* – spoken; by mouth
- *Osteoarthritis* – bone and joint pain
- *Over-the-counter drugs* – drugs that one can buy without a doctor's prescription
- *Overnight fast* – nothing eaten or drunk after [time] p.m.
- *Palpitation* – irregular or "skipped" heartbeat that one can feel
- *Paresthesia* – tingling in the [location]
- *Perception* – one's view; one opinion
- *Perforation* – hole; tear
- *Pharmacological* – relating to the drug
- *Physiologically capable* – able to function
- *Plasma* – blood
- *Pneumonia* – lung infection
- *Pneumothorax* – collapsed lung
- *Polyps* – abnormal lumps that can sometimes be cancerous
- *Positive history* – in one's past history; condition that one ever had
- *Positron Emission Tomography (PET)* – special camera that uses energy rays to show how well the internal parts of the body are working
- *Predictive value* – expected value
- *Prognosis* – expected course of a disease
- *Prone* – lying flat facing down; lying on one's stomach
- *Prorated compensation* – less if one does not complete the study
- *Protocol* – study plan
- *Psychological test* – test of one's behavior
- *Pulmonary* – relating to the lung
- *Puncture* – to make a hole
- *Pyelogram* – a series of x-ray pictures of the kidneys
- *Quantify* – measure
- *Radioactive isotope* – a chemical or substance that gives off radiant energy or rays similar to x-rays
- *Randomly* – like picking numbers out of a hat; like flipping a coin; indicates the chance of being assigned to each group)
- *Recuperate* – to get better; to heal
- *Reliable method of contraception* – a way to prevent pregnancy such as using birth control pills; Norplant or Depo-Provera; using an intrauterine device (IUD); or using a condom or diaphragm with a sperm-killing jelly
- *Renal* – relating to the kidney
- *Render one ineligible* – make one unable to participate
- *Respiratory* – relating to breathing
- *Saline* – salt water
- *Secretion* – one of the fluids made by the body
- *Sedation* – making drowsy or sleepy
- *Somnolence* – sleepiness; drowsiness
- *Sputum* – thick saliva; spittle
- *Standard of care* – the usual treatment for a disease
- *Stent* – a small tube that keeps a blood vessel open
- *Subcutaneous* – under the skin
- *Subsequent* – later; following; or as a result
- *Superficial* – near the surface
- *Supine* – lying flat facing up; lying on the back
- *Sutures* – stitches

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- *Symptoms* – signs or symptoms
- *Syncope* – fainting or lightheadedness
- *Systemic* – involving the whole body
- *Systolic blood pressure* – the blood pressure during a heartbeat; top number of a blood pressure reading
- *Tachycardia* – fast heartbeat
- *Telemetry* – monitoring the [organ or location] from a distance
- *Therapeutic dose* – the amount of medication needed to treat a condition
- *Third party payors* – health insurance; Medicare or Medicaid
- *Tinnitus* – ringing in the ears
- *Titration* – adjusting the amount of drug one should take
- *Topical* – applied to the surface of the skin
- *Triglyceride* – fat in the blood
- *Tubal ligation* – tying the Fallopian tubes to prevent pregnancy
- *Unable to comply with* – unable to follow study directions or the study requirements
- *Ureter* – the tube that carries urine from the kidneys to the bladder
- *Urethra* – the tube that carries urine from the bladder outside the body
- *Urinalysis* – urine examination
- *Vaginitis* – infection in the vagina or birth canal
- *Vein* – blood vessel
- *Venipuncture* – to put a needle into a blood vessel
- *Verbal* – in spoken or written words
- *Vertigo* – a feeling of losing one's balance; dizziness
- *Void* – to make or to pass urine
- *Waive* – give up
- *Withdraw* – leave the study; quit

1. REFERENCE

Informed Consent Glossary, *Applied Clinical Trials*. May 1997; 71-73

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Guidance G 704: 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.

2. RESPONSIBILITY FOR UNDERSTANDING THE GUIDANCE:

IRB Chair; IRB Vice-Chair; IRB Members, IRB Manager; IRB Human Research Protections Coordinator, and Appointed/elected IRB members

GUIDANCE:

Investigators generally do not disclose identifying information about research subjects 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 a subject's participation in a clinical research study that could include name, address, and medical history.

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 subjects 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 subject enrolls in a study, information identifying the subject will never be disclosed unless the subject or in certain specific circumstances, investigator volunteers it.

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 IRB has determined that the research is of a sensitive nature if it involves collecting information:

- Relating to sexual attitudes, practices or preferences
- Relating to use of alcohol, drugs, or other addictive products
- Pertaining to illegal conduct
- That if released could be potentially damaging to an individual's financial standing, employability, or reputation in the community
- That would normally be recorded in the subject's medical record and the disclosure of which could reasonably lead to social stigmatization or discrimination
- Pertaining to an individual's psychological well-being or mental health
- Relating to genetics

3.1: 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. Certificates of Confidentiality are not limited to federally funded studies. FDA accepts applications for certificates of confidentiality for research that is of a sensitive nature and involves an investigational drug exemption.

3.2: Limitations on Certificates of Confidentiality

It is important to note that the certificate of confidentiality does not apply to voluntary disclosure of identifying information by either the subject or the investigator; even if the study is covered by a certificate, the subject may voluntarily disclose information about himself or herself. The investigator may also voluntarily disclose specific urgent issues such as child abuse involving a subject or a subject's threats about violence to self or others. Subjects should be advised about the exceptions to the protections the certificate offers.

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3.3: 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.

Once a subject enrolls in a study in which a certificate of confidentiality is in place, the protection afforded by the certificate is permanent and information identifying that subject will never be disclosed unless it is volunteered by the subject or the investigator for certain urgent issue, or it expires.

3.4: Contacts for Information about obtaining a Certificate of Confidentiality

The IRB website contains a list of contacts at different federal agencies for information about obtaining an application for a Certificate of Confidentiality.

Once a subject enrolls in a study in which a certificate of confidentiality is in place, the protection afforded by the certificate is permanent and information identifying that subject will never be disclosed unless it is volunteered by the subject or the investigator for certain urgent issue, or it expires.

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Guidance G 705: Guidance on Behavioral Research

1. PURPOSE

To provide information regarding issues critical in the performance of behavioral research

2. RESPONSIBILITY for UNDERSTANDING THE GUIDANCE:

IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members.

3. GUIDANCE

3.1: Federal Regulations

Federal regulations apply to research involving human subjects that is conducted not only in medical therapeutics, but in areas such as human behavior, social science, anthropology, epidemiology, and education. Studies of these types often present only slight to minimal risk and in these cases may be exempt from IRB review or given an expedited review, as per Policies RR 403 and RR 404, respectively.

3.2: Psychological/Social Risk

Behavioral research generally does not involve any physical risk to the subject because there is no physical intervention. However, they do carry concerns for other types of potential harms, including psychological, economic, social and legal risks to the subjects that may be as harmful as any risk faced by a subject in a medical study.

The risks of psychological harm range from temporary anxiety and distress to a relapse in a behavioral disorder or the precipitation of a disorder. Social harms include personal embarrassment, ostracism, stigmatization or possible loss of social status. Economic risks include decreased employability and possible job loss. Among the possible legal risks are arrest, prosecution and civil or criminal liability. Many of these potential harms would be the result of another risk: breach of confidentiality.

In assessing the potential risks presented by a behavioral study, investigators and IRBs should ensure that the design of the study provides an adequate level of protection against these potential risks. In behavioral studies, the traditional risk/benefit balance is changed such that benefits rarely accrue to the subject, but rather to science or society.

3.3: Deception in Behavioral Research

Deception in a clinical research study involves intentionally misleading subjects or withholding full information about the study in order to achieve study aims. Misleading or omitted information might 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 subject to give informed consent and presents a limitation on the protection afforded by informed consent. However, it is important to note that humans act differently depending on the circumstances, and that in some cases the subjects' full knowledge of the study would bias the results. In such instances, deception may be necessary. Under federal regulations, deception is permitted with the limitations that it must be ethically and scientifically justified by the investigator and approved by an IRB.

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 subjects must be fully debriefed at the end of the study. Furthermore, the subject 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.

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3.4: Vulnerable Subjects

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.

3.5: Privacy and Confidentiality

Privacy and confidentiality are central considerations in all types of research. A violation of an individual's privacy is not only a harm, 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.

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Guidance G 706: Quality of Life Issues

1. PURPOSE:

To provide an awareness of quality-of-life issues as they pertain to a research protocol involving human subjects, and a list of some specific quality of life issues that should be addressed in the design of a protocol, with the intent to minimize the effect on the research subject to the greatest possible degree.

2. RESPONSIBILITY FOR UNDERSTANDING THE GUIDANCE

IRB Chair; IRB Vice-Chair; IRB Members, HRPO; Appointed/Elected IRB Members.

3. 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 leading to a decline in aspects of lifestyle.

But beyond the design or requirements of the protocol, the quality-of-life issues 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 subject's protocol, and be clearly communicated to the subject as possible experiences during their participation in the study.

Some examples of quality-of-life 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 that are hard to complete given the subjects pre-existing condition
- Excessive or redundant questionnaires or study procedures
- Travel time/cost of travel
- Imposition on family members, care givers, or parents particularly in pediatric studies
- Unnecessary visits, tests or measures
- Restricted diets
- Washout periods/withholding of certain medications during study participation

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Guidance G 707: Respecting the Privacy of Research Subjects and Potential Research Subjects

1. PURPOSE

To elucidate the issue of privacy of research subjects and potential research subjects and how it can best be respected.

2. RESPONSIBILITY FOR THE GUIDANCE

Investigators and Key Personnel, as well as the IRB leaders and members

3. GUIDANCE

Privacy is supported by “Respect for Persons” and “Beneficence”, two of the principles of research ethics identified in the *Belmont Report*. Both 45 CFR §46.111 and 21 CFR §56.111 require the IRB to determine, as part of its review of research, that privacy is protected when appropriate.

Privacy is an individual’s desire to be left alone, not approached, or not contacted. This is embodied in the research setting most notably during the recruitment process, before an individual has given his/her consent to participate in the various procedures, visits, tests, and contacts that comprises a research study. In many cases, the individual will not know the recruiter, and it is at this point that the recruiter must be sensitive to the privacy wishes of the individual. But ultimately, if the individual says no, this means no. Any further pressure from the recruiter could be construed as coercion, and any individual enrolled under coercion has not given his or her true informed consent.

By consenting to participate in a research study, an individual has accepted the commitments of time and effort that will be involved in the participation. The individual has a certain level of comfort with adhering to the various procedures that s/he has committed to. However, this commitment on the part of the individual should not dampen the researcher’s sensitivity to individual privacy. The researcher needs to maintain a level of flexibility when dealing with the individual, as the individual may have specific privacy needs, such as being contacted only at certain times of day or at a particular phone number. Also, if the individual withdraws from the research study, the expressed privacy wishes of the individual should continue to be observed.

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Guidance G 708: Independent Monitoring of Investigator-Initiated Clinical Trials

1. PURPOSE

To provide guidance to investigators for establishing acceptable monitoring procedures for investigator-initiated clinical trials.

2. RESPONSIBILITY FOR UNDERSTANDING THE GUIDANCE

Investigators; IRB Chair; IRB Vice-Chair; IRB Members; HRPO; Appointed/Elected IRB Members

3. OVERVIEW

Investigator-initiated trials are those in which the investigator is considered to be the sponsor, whether or not s/he receives any 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 often not provide monitoring. Therefore, independent monitoring of investigator-initiated trials (IITs) that employ new drugs, biologicals, or medical devices becomes an issue of great importance in order to ensure 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. Risk 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. These ways exist in a continuum that includes monitoring by the PI, monitoring of an independent and unaffiliated individual with the appropriate expertise (e.g. Medical Monitor), a SLUHN-based Data Safety Monitoring Board (DSMB) or IRB Sub-Committee, or the establishment of an independent DSMB.

Minimal risk trials in general do not require monitoring beyond that provided by the PI and annual review by the IRB.

Greater than minimal risk studies do require monitoring procedures that should include establishing a Data Safety Monitoring Plan (DSMP) outlined in the protocol, appointing an individual as an Independent Medical Monitor, or appointing a DSMB or IRB Sub-Committee responsible for monitoring oversight.

3.1: Independent Medical Monitor

An Independent Medical Monitor should be an appropriately trained and qualified individual who is not involved in the study in any other way. The study monitor may be a SLUHN employee or someone who is not employed by SLUHN. If the study is partially or wholly funded by a non-SLUHN entity, the Medical Monitor should not be an employee of that entity. The ISM should be familiar with the protocol and risks of the study and should provide periodic written reports that are 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 explained in the SLUHN Data and Safety Monitoring Review Form.

3.2: Elements of a DSMP should include the following as appropriate:

- Reviews of adverse events and unanticipated problems posing risks to subjects or others.
- Depending on the complexity of the research, the plan may include assessments of data quality, participant recruitment, accrual and retention.

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- Plan to assure data accuracy and protocol compliance.
- Parameters that would define the need for suspension of enrollment or closure of the study.

3.3: The following research situations require the oversight of a DSMB:

- The study is FDA-regulated, and the PI is the Sponsor-Investigator (e.g. SLUHN/PI holds the IND or IDE)
- The study is intended to provide definitive information about the effectiveness and/or safety of a medical intervention.
- Prior data suggest 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 subjects regarding both safety and effectiveness.
- The primary question has been definitively answered, even if secondary questions or complete safety information have not yet been fully addressed.

3.4: 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 conflicts of interest (i.e., financial, intellectual, professional, or regulatory).

4. IRB REVIEW OF THE DATA AND SAFETY MONITORING PLAN

The IRB will review the DSMP as described in the protocol and Initial IRB Application at the time of initial review of the protocol and at each Continuing Review.