PURPOSE:

To outline the process of a Food and Drug Administration (FDA) inspection at the research site and describe activities that should be done to facilitate the inspection. The FDA inspection is typically conducted at sites to determine compliance with federal regulations and adherence to guidelines, to verify the validity and integrity of clinical data submitted in applications for approval, and to assure that the rights and welfare of subjects in the research have been protected.

DEFINITIONS:

- **Adverse Event (AE):** An unfavorable and unintended experience encountered by an individual during the course of a clinical trial that is associated with the drug, procedure, or device. An AE can include previously undetected symptoms, or the exacerbation of a pre-existing condition. When an AE has been determined to be related to the investigational product, it is considered an Adverse Drug Reaction
- **Case Report Form (CRF):** A Case Report Form can be either paper (CRF) or electronic (eCRF). These forms are used to collect data that is then submitted to the sponsor of the clinical trial. The CRF is constructed to collect pertinent information to the clinical trial from the patient's records. Patient records are kept in a shadow chart.
- **Clinical Laboratory Improvement Amendments (CLIA):** A program used to ensure quality laboratory testing regulated by Centers for Medicare and Medicaid Services (CMS)
- **College of American Pathologists (CAP):** Laboratory document used to confirm accreditation of laboratory facilities
- **Establishment Inspection Report (EIR):** Report generated by FDA inspector after the completion of inspection
- **Food and Drug Administration (FDA):** Agency of the United States Department of Health and Human Services (DHHS), responsible for the regulation of clinical trials.
- **Inspection Observation (FDA Form 483):** Official FDA inspection form, completed by FDA investigators which note deviations, if any, and is presented to the most responsible person at the inspected site at the end of the inspection.
- **Institutional Review Board (IRB):** Independent ethics committee formally designated to approve, monitor, and review biomedical and behavioral research involving human subjects.
- **Investigator Brochure (IB):** A compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and study staff with the information necessary to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures.
- **Note to File (NTF):** Regulatory document used to confirm and document aspects of a clinical trial
- **Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE):** A letter to inform the recipient clinical investigator that FDA is initiating an

administrative proceeding to determine whether the clinical investigator should be disqualified from receiving investigational products pursuant to the Food and Drug Administration's regulations.

- **Notice of Inspection (FDA form 482):** Official FDA inspection form completed by FDA investigators and presented to the most responsible person at the site being inspected at the start of any inspection type.
- **Notice of Opportunity for Hearing (NOOH):** Provides an individual with the opportunity for a hearing on a regulatory action, including a proposed action (such as disqualification), before a presiding officer designated by the Commissioner.
- **Principal Investigator (PI):** Lead investigator, responsible for the sound conduct of the project in accordance with the protocol and regulations.
- **St. Luke's University Health Network (SLUHN)**
- **Unanticipated Problems Involving Risk (UAP):** Unanticipated Problems posing risks to subjects or others that are unforeseen and indicate that participants or others are at increased risk of harm

SCOPE:

This SOP applies to all site personnel involved in the implementation and coordination of clinical research.

This policy describes the process:

- Starting from the time the site becomes aware of an FDA inspection
- Ending when all follow-up activities associated with the inspection have been completed

This policy is applicable to the following studies:

- All clinical trials conducted at SLUHN and run through the SLUHN CTO

PERSONNEL RESPONSIBLE:

This SOP applies to those members of the clinical research team involved in clinical trials, facilitating the inspection, or following up after the inspection is complete. This includes the following:

- Principal Investigator (PI)
- Clinical Trials Management
- Research Nurse/Coordinator
- Regulatory Coordinator
- Study Pharmacist
- Support staff

ROLES:
The following information describes which areas and associated roles that shall adhere to this policy:

Director of Clinical Trials and Research: The Director or designee shall be responsible for facilitating the inspection, and reconciling any deficiencies or outstanding items as needed.

Clinical Trials Manager: The Clinical Trials Manager or designee shall be responsible for ensuring that the appropriate staff is available during the visit, and that all action items are resolved in a timely manner. The Manager or designee shall also be responsible for ensuring all clinical trials documentation and files are "audit ready" at all times.

Regulatory Coordinator: The Regulatory Coordinator shall be responsible for ensuring all regulatory files are maintained appropriately, and are available at the time of the inspection for review. The Regulatory Coordinator shall also be responsible for ensuring all regulatory items are up-to-date and accurate, and any regulatory action items are resolved in a timely manner.

Research Nurse/Coordinator: The Research Nurse/Coordinator shall be responsible for ensuring all patient files are maintained appropriately with appropriate notations and source documentation, and are available at the time of the inspection for review. The Research Nurse/Coordinator shall also be responsible for ensuring protocol compliance, reporting and documenting all AEs and UAPs as necessary, accurate and timely data entry and query resolution, and any action items are resolved in a timely manner.

Investigational Drug Pharmacist: The Investigational Drug Pharmacist shall be responsible for ensuring drug handling and dispensing is in compliance with the protocol, and that drug accountability is clearly documented and available at the time of the inspection.

Principal Investigator or designee: The principal investigator or designee shall be responsible for:

- Overall oversight and responsibility for clinical trial conduct at SLUHN
- Being available during the inspection as needed
- Addressing any corrective action that is required

Administrative Assistant: The Administrative Assistant shall be responsible for the administrative support necessary during the inspection, such as securing a suitable location, making copies of any required documentation, etc.

PROCEDURES:

- Sponsor contact shall be made immediately upon notification from FDA of the audit.
- A private conference room shall be reserved, if available, for inspector to conduct their required review.

- Upon receiving a notification from the FDA inspector, the PI and clinical trials management, or his/her designee shall make all requested study-related documents available, and shall inform proper institutional officials of the upcoming inspection.
- The PI, clinical trials management, and other pertinent staff shall be available during the FDA inspection.
- A liaison shall be designated to facilitate the audit and communicate directly with the FDA inspector prior to the designated audit date (if possible).
- The Director of Clinical Trials or his/her designee shall greet the FDA inspector (s) and verify identification/credentials.
- The inspector must provide a FDA Form 482 (Notice of Inspection).
- The designated liaison shall:
    - Provide requested documents
    - Accompany auditor(s) during tours and interviews
    - Maintain a list of questions asked that require consultation with staff not readily available to answer.
    - Maintain a list of documents requested.
    - Maintain a list of documents copied.
    - Assist the inspector(s) as needed.
    - Arrange for a debriefing at the conclusion of the audit.
    - Arrange follow-up if required.
- If the FDA inspector provides the principal investigator with a response to the audit in the form of a FDA Form 483, the PI and clinical trials management shall prepare a written response to any observations noted on this form and send the response to the FDA within the appropriate time. The written response shall include:
    - Adequate responses to each observation and explanation of what steps have been taken or will be taken to remedy the observation and prevent future occurrences.
    - Timelines for completion
    - Responses that are factual and cooperative (in tone)
- A copy of the FDA Form 483 and the response to the observations shall be sent to the sponsor representative of the research (if applicable).

NOTIFICATION OF INSPECTION

Role	Step	Activity
Unknown (person who takes phone call)	1.0	Transfer the call to Administrative Assistant
Administrative Assistant or designee	1.1	Request & record the following information • FDA inspector(s) name and contact information • PI being inspected

		• Study and subjects being inspected • What personnel and documents needed • Date and duration of the inspection **NOTE:** Immediately inform the Director of Clinical Trials with this information
Director of Clinical Trials	1.2	Notify the following institutional officials and other pertinent staff of the upcoming inspection: • Vice President of Quality • Senior Vice President of Medical Affairs • University Senior Counsel and Corporate Compliance Officer • Medical Director of Research and Innovation • Hospital Administration, if applicable • Department Chair • Study team (PI, Sub-Is, and Key Personnel) • IRB • Sponsor (if applicable) • Investigational Drug Pharmacist
Administrative Assistant or designee	1.3	Schedule and secure a conference room location and time with all parties to be involved, and place in the appropriate outlook calendars within 48 hours of initial contact. **NOTE:** Ensure conference room is in close proximity to a bathroom and copier, and is equipped with computer and internet access, as well as a phone

INSPECTION PREPARATION

Role	Step	Activity
Director of Clinical Trials or designee	2.0	Ensure the following are up-to-date and in a presentable format: • SOPs • Clinical Trials Portfolio
Regulatory Coordinator	2.1	Ensure all regulatory documentation is complete, accurate, and available for review at least two days prior to the scheduled visit. This shall include, at a minimum, the following: • All IRB/FDA submissions and approval letters • Current and previous version of FDA Form

		1572 • All protocol, consent, and IB versions • Financial Disclosure Forms • Delegation of Authority Logs • Documentation of Training • CVs and Medical Licenses • Monitor communications • Lab documents (certification, CLIA, CAP, normal and reference ranges)
Research Nurse Coordinator	2.2	Ensure all patient charts and source documentation are complete, accurate, and available for review at least two days prior to the scheduled visit. This shall include, at a minimum, the following: • Source documents • CRFs • AE/SAE documentation • UAP documentation • Signed and dated consents • Documentation of consent process • Comparison of data filed with FDA to onsite • Documentation of eligibility • Medical records including notes • Enrollment logs • Protocol deviations • Recording of con-meds • NTFs for anything requiring additional explanation
Research Nurse Coordinator or designee	2.3	Ensure all data queries received to date have been resolved to the extent possible at least two days prior to the scheduled visit.
Investigational Drug Pharmacist or designee	2.4	Ensure that the study drug storage, including temperature logs and all accountability records, are complete, accurate, and available for review at least two days prior to the scheduled visit. This shall include, at a minimum, the following: • Shipping records • Receipt of drug • Dispensing of drug • Disposition of unused investigational product

Administrative Assistant or designee	2.5	Set up the conference room with plenty of water and coffee, organize the study documents to be reviewed, and ensure the room is clean and sterile
Not Applicable	---	**NOTE:** FDA inspector is ***not*** entitled to review or copy financial records, personnel records (other than training records) and internal audit records

DURING THE INSPECTION

Role	Step	Activity
Director of Clinical Trials or designee	3.0	Greet the inspector, request FDA Form 482, and escort the inspector to reserved conference room.
Designated liaison	3.1	Escort the FDA inspector everywhere, and coordinate requests as necessary throughout the inspection. Such requests shall include copying, obtaining necessary access to required records, and ensuring any questions are answered by the appropriate individual. **NOTE:** FDA inspector is ***not*** authorized to review financial records or personnel records **NOTE:** Any copies made or photographs taken shall be made in duplicate (one copy for inspector and one for the site) and stamped "Confidential" **NOTE:** Provide only those documents that are specifically requested. Do ***not*** provide anything additional.
Research Nurse Coordinator Regulatory Coordinator Investigation Drug Pharmacist Clinical Trials Manager Principal Investigator	3.2	Set time aside each day to meet with the inspector to answer any questions or concerns **NOTE:** Be sure to adhere to the following guidelines: • Answer ***only*** the question that was asked • Defer to others if you do not know the answer (***do not*** attempt to answer something you are not sure of) • Use documentation for support if available • ***Stop*** when the question is answered (***do not*** provide additional information that is not needed

AFTER THE INSPECTION

Role	Step	Activity
Research Nurse Coordinator Regulatory Coordinator Investigation Drug Pharmacist Clinical Trials Manager Principal Investigator	4.0	Attend Exit Interview, and obtain FDA Form 483 (if applicable – only issued if deficiencies are noted) **NOTE:** If FDA Form 483 is issued, please ensure Step 4.2 is completed **NOTE:** The FDA inspector will assign one of the following compliance categories: 1. No Action Indicated (NAI): firm is in compliance 2. Voluntary Action Indicated (VAI): voluntary correction required, marginal compliance 3. Official Action Indicated (OAI): serious non-compliance requiring regulatory or administrative action
Director of Clinical Trials or designee	4.1	Obtain one of the following letters from the FDA: 1. A letter that generally states that FDA observed basic compliance with pertinent regulations. 2. An *Informational or Untitled Letter* that identifies deviations from statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. 3. A *Warning Letter* that identifies serious deviations from applicable statutes and regulations. A Warning Letter is issued for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. 4. A *Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)*. FDA may initiate a process to disqualify the clinical investigator from receiving investigational new drugs and/or biologics if disqualified under part 312, or investigational devices if disqualified under part 812, if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any

		required report. 5. Notice of Opportunity for Hearing (NOOH) – issued if a NIDPOE is given without adequate response from investigator **NOTE:** a letter is not always sent when FDA observes no significant deviations.
PI and Clinical Trials Management	4.2	Provide a written response to FDA Form 483 within 2 weeks (15 calendar days) to include the following: • An evaluation of the extent of the problem • Assessment of the root cause of the problem • Any corrective actions • Preventive actions to prevent recurrence of the problem in future studies • Supporting documentation **NOTE:** This letter shall be directed to the FDA District Office located in the upper left corner of the FDA Form 483
Not Applicable	---	**NOTE:** FDA Form 483 and EIR are publicly disclosable under the Freedom of Information Act

RESOURCES:

- FDA's Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - FDA Inspections of Clinical Investigators
- 21 CFR 312 – Investigational New drugs
- 21 CFR 812 – Investigational Device Exemptions
- FDA's Information Sheet Guidance, "Clinical Investigator Administrative Actions - Disqualification."

Endorsed by: SOP Committee (12/20/13; 2/20/15; 4/8/16)
Approved by: Tracy Butryn, Director of Clinical Trials (12/30/13; 2/20/15; 6/24/16)