PURPOSE:

To outline the activities required to facilitate a monitoring visit and closeout visit (COV). Monitoring visits are usually performed by a sponsor representative for a protocol. The visit is conducted to ensure that the investigator and site are compliant with the clinical protocol and Good Clinical Practice (GCP), that data are of high quality and integrity, and that the facilities and staffing are adequate to continue participation.

This standard operating procedure (SOP) describes the processes followed at this investigative site when the sponsor's monitor conducts a monitoring visit to:

- Assess adherence to the protocol
- Review regulatory files for completeness
- Ensure appropriate study drug storage, dispensing, and accountability
- Verify data in case report forms (CRFs) with source documentation
- Meet with the research nurse/coordinator and investigator to discuss progress of the study and any concerns raised as a result of the visit.
- Close the investigative site.

DEFINITIONS/ABBREVIATIONS:

- **Adverse Event (AE):** Any untoward medical occurrence encountered by an individual during the course of a clinical trial which may or may not be associated with the study 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 drug, it is considered an Adverse Drug Reaction.
- **AE Reports:** Investigator reports of all adverse events (both serious sand non-serious), injuries, and deaths given to the sponsor, the IRB and the FDA or appropriate regulatory body
- **Case Report Form (CRF):** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.
- **Clinical Research Nurse/Coordinator (CRC):** Clinical Trials staff responsible for oversight and coordination of assigned protocols.
- **Clinical Trials Office (CTO):** Centralized clinical trials staff, responsible for the conduct and support of SLUHN clinical trial functions
- **Closeout Visit (COV):** Final monitoring visit performed at the investigative site to complete a final review and reconciliation of all regulatory files, all data and source documentation, reconcile all unused study drug, and discuss requirements for document storage.
- **Research Finance Compliance Analyst (RFCA):** Clinical Trials Office staff member responsible for the overall day to day pre and post-award financial operations of SLUHN industry or grant funded clinical trials.

- **Food and Drug Administration (FDA):** Agency of the United States Department of Health and Human Services (DHHS), responsible for the regulation of clinical trials.
- **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of research that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of subjects are protected.
- **Informed Consent Form (ICF):** IRB approved form outlining all aspects of a clinical trial in lay language, signed by the subject consenting to participate.
- **Institutional Review Board (IRB):** Independent ethics committee formally designated to approve, monitor, and review biomedical and behavioral research involving human subjects.
- **Interim Monitor Visit (IMV):** A visit conducted by the study sponsor or designee to ensure that the investigator and site are compliant with the clinical protocol and Good Clinical Practice (GCP), that data are of high quality and integrity, and that the facilities and staffing are adequate to continue participation.
- **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)**
- **UAP Reports:** Investigator reports of all Unanticipated Problems posing risks to subjects or others given to the sponsor, the IRB and the FDA or appropriate regulatory body
- **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 clinical research site personnel involved in the conduct of clinical research.

This policy describes the process:

- Starting from the time the monitor schedules a monitoring visit
- Ending when all follow-up activities associated with the visit have been completed and the study is closed

This policy is applicable to the following studies:

- Industry-sponsored clinical trials
- Government- sponsored clinical trials requiring monitoring visits
- Non-SLUHN sponsored clinical trials requiring monitoring visits

PERSONNEL RESPONSIBLE:

This SOP applies to those members of the clinical research team involved in arranging, managing, participating in or following up after the monitoring visit. 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 assisting with arranging the monitoring visits as necessary, and reconciling any deficiencies or outstanding items as needed as necessary.

Clinical Trials Manager: The Clinical Trials Manager or designee shall be responsible for ensuring all Monitoring Visits are conducted in accordance with the Monitoring Visit Schedule ***(see Attachment A)***, 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. The Clinical Trials Manager shall also be responsible for identifying studies that may be closed based on patient status and study status, as well as assisting with the scheduling of the final COV as necessary.

Research Financial Compliance Analyst (RFCA) or designee: The RFCA shall be responsible for reviewing all payment history prior to the COV, sending a final invoice to the sponsor/CRO, reconciling all outstanding payments prior to closure with the IRB, and informing the Regulatory Coordinator when final payments are received.

Regulatory Coordinator: The regulatory coordinator shall be responsible for ensuring all regulatory files are maintained appropriately, and are available at the time of the Monitoring Visit 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 CRC shall be responsible for ensuring all patient files are maintained appropriately with notations and source documentation, and are available at the time of the Monitoring Visit for review. The CRC shall also be responsible for ensuring

protocol compliance, reporting and documenting all AEs and UAPs as necessary, accurate and timely data entry, and any action items are resolved in a timely manner. They shall also be responsible for the accurate and timely submission of all data via paper CRFs or electronic CRFs, as well as the timely reconciliation of all data queries. Any action items/follow-up items resulting from the IMV with regard to data shall also be resolved in a timely manner by the CRC or designee.

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 Monitoring Visit. The Investigational Drug Pharmacist shall also be responsible for destroying or returning all unused product at the conclusion of the study as necessary, and informing the appropriate CTO staff once drug is returned/destroyed.

Principal Investigator or designee: The PI or designee shall be responsible for:

- Overall oversight and responsibility for clinical trial conduct at SLUHN
- Being available during the Monitoring Visit and COV (in person when available, or ad hoc via phone or email when necessary)
- Addressing any corrective action that is required

Administrative Assistant: The Administrative Assistant shall be responsible for the coordination and scheduling of the Monitoring Visits and COVs with the clinical trials staff and sponsor representative, and ensuring that all visits are scheduled in a timely manner. The Administrative Assistant shall also be responsible for maintaining a Monitoring Visit Log ***(see Attachment B).***

PROCEDURES:

- The Administrative Assistant or designee shall schedule and arrange the visits as requested by the sponsor representative. Attendees shall include all pertinent clinical trials staff (only if available).
- Scheduling for the PI shall be handled separately directly between the sponsor and the PI or designee as the PI's availability during the monitoring visit may not be feasible and may need to occur separately.
- The visits shall be scheduled with as much notice as possible, but no less than two weeks.
- Visits shall not occur more often than once per month, and no less than every eight weeks, depending on enrollment rates and patient status (e.g. if no patients are enrolled, visits do not need to be scheduled).
- Monitoring visits shall be scheduled at mutually convenient times and every attempt shall be made to accommodate monitoring deadlines.

- Monitoring visits shall be limited to one day. Exceptions may be made at the discretion of the Site if multiple studies are to be monitored based on patient enrollment and status.
- Scheduled Monitoring Visits shall be documented in the Monitoring Visit Log ***(see Attachment B)*** and Outlook calendar, and confirmed with all involved.
- Any visits cancelled by the site shall be communicated to the sponsor of the trial by the Administrative Assistant or designee as soon as possible. Any visits cancelled by the sponsor shall be communicated to the Site as soon as possible. All cancellations shall be documented in the Monitoring Visit Log ***(see Attachment B)***, and may or may not be rescheduled depending on staff availability.
- Prior to each visit, the Clinical Trials Manager or designee shall confirm with the sponsor representative what materials will be reviewed so that appropriate documentation and files will be made readily available. These materials could include:
    - Subject source documents and corresponding case report forms (CRFs)
    - Regulatory binder
    - Safety Reports and/or Adverse Event documentation
    - Access to study drug storage and accountability documentation
- The Administrative Assistant or designee shall ensure that an appropriate work area is available for the monitoring visit. The work area shall include:
    - Quiet location
    - Copy machine access
    - Desk and chair
    - Data ports for computers (if necessary)
- The Clinical Trials staff shall schedule time ***(see Attachment A)*** to work with the monitor during the visit to review and complete any data clarifications as necessary.
- The Clinical Trials Manager or designee shall proactively identify any trials that may be ready for closure (e.g. study is closed to enrollment and all patients are completed or deceased, per institutional decision, etc.) and reach out to the sponsor and Administrative Assistant to schedule a COV.
- The Director of Clinical Trials and Research or designee shall inform the RFCA and Regulatory Coordinator of upcoming pending COV.
- RFCA or designee shall review and reconcile all outstanding payments and inform the Regulatory Coordinator once all final payments have been received.
- The Investigational Drug Pharmacist shall destroy or return all unused investigational product at the conclusion of the study as necessary, and inform the appropriate CTO staff once drug is returned/destroyed.
- Devices are managed by the clinical trials staff and returned/accounted for by the designated coordinator and the sponsor.
- The Regulatory Coordinator shall be responsible for submitting a Final Report to the IRB in accordance with ***SOP 204***.

SCHEDULING A MONITORING VISIT

Role	Step	Activity
Administrative Assistant or designee	1.0	Work with the study monitor to schedule a mutually convenient date and time to conduct the monitoring visit. **NOTE:** Study site prefers at least a two week notice. **NOTE:** Monitoring visits shall be limited to one day. Exceptions may be made at the discretion of the Site if multiple studies are to be monitored based on patient enrollment and status.
Manager, Administrative Assistant or designee	1.1	Determine who needs to be available during the Monitoring Visit. **NOTE:** Study PI may or may not be available in person during the visit depending on availability, but shall be available via phone and/or email to address any specific needs from the sponsor. **NOTE:** If sponsor requires time with the PI, this shall be scheduled separately directly between the Sponsor and the PI or designee, and any PI action items unable to be addressed during the visit shall be documented in the IMV Follow-up Letter.
Administrative Assistant or designee	1.2	Schedule and confirm the Monitoring Visit date, location, and time with all parties to be involved, and place in the Monitoring Visit Log (see Attachment ***B***) and appropriate Outlook calendar.
Administrative Assistant or designee	1.3	Send the study Monitor the SLUHN Monitoring Visit Schedule, and reinforce with them that the schedule be strictly adhered to.

PREPARING FOR A MONITORING VISIT

Role	Step	Activity
Regulatory Coordinator	2.0	Ensure all regulatory documentation is complete, accurate, and available for review at least one day prior to the scheduled visit.
CRC or designee	2.1	Ensure all patient charts and source

		documentation is complete, accurate, and available for review at least one day prior to the scheduled visit.
CRC or designee	2.2	Ensure all CRFs are complete, accurate, and available for review at least one day prior to the scheduled visit.
CRC or designee	2.3	Ensure all data queries received to date have been resolved to the extent possible at least one day 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 one day prior to the scheduled visit.

DURING THE MONITORING VISIT

Role	Step	Activity
Clinical Trials Manager or designee	3.0	Provide the Monitor with the Monitoring Visit Schedule ***(see Attachment A)*** and reinforce strict adherence. **NOTE:** The Monitoring Visit Schedule should also be posted in the Monitor Rooms at all locations
Clinical Trials Manager or designee	3.1	Ensure the Monitor signs the study-specific Monitoring Visit Log.
Clinical Trials Manager or designee	3.2	Ensure the Monitor has all documentation required to complete the Monitoring Visit, and provide them with an update on any study-related issues.
CRC, Regulatory Coordinator, Investigation Drug Pharmacist, Clinical Trials Manager, PI	3.3	Meet with the study Monitor at designated time slot in accordance with Monitoring Visit Schedule ***(see Attachment A)*** to discuss any issues. **NOTE:** Study PI may or may not be available in person during the visit depending on availability, but shall be available via phone and/or email to address any specific needs from the sponsor. **NOTE:** If sponsor requires time with the PI, this shall be scheduled separately directly between the Sponsor and the PI or designee, and

		any PI action items unable to be addressed during the visit shall be documented in the IMV Follow-up Letter.
CRC, Regulatory Coordinator, Investigation Drug Pharmacist, Clinical Trials Manager, PI	3.4	Resolve any issues that can be handled prior to the end of the visit, and provide necessary documentation to Study Monitor. **NOTE:** Ensure that all resolved items will be removed from the Monitoring Visit Follow-up Letter, or indicated as completed/resolved.

FOLLOW-UP AFTER MONITORING VISIT

Role	Step	Activity
Clinical Trials Manager or designee	4.0	Review Monitoring Visit Follow-up Letter for accuracy and action items within 24-48 hours of receipt. **NOTE:** If the Monitoring Visit Follow-up Letter is received by another team member other than the manager, ensure the letter is sent to the Manager within 24 hours of receipt.
Clinical Trials Manager or designee	4.1	Follow-up with monitor if Monitoring Visit Follow-up Letter is not received by month's end.
Clinical Trials Manager or designee	4.2	Review Monitoring Visit Follow-up Letter for accuracy, and ensure any reconciled items during the visit were removed. **NOTE:** If Follow-up Letter is not accurate, notify the sponsor of the necessary changes and request a revised letter or addendum to be sent.
Clinical Trials Manager or designee	4.3	Distribute the Monitoring Visit Follow-up Letter to all pertinent clinical trials staff, and delegate action item resolution to appropriate staff within 24-48 hours of receipt for completion/resolution prior to the next monitoring visit to the best of ability.
Regulatory Coordinator	4.4	File the Monitoring Visit Follow-up Letter in study binder and upload a copy into the common drive. **NOTE:** A copy of the Monitoring Visit Follow-up Letter shall also be submitted to the IRB for

		review in accordance with SOP 204.
Clinical Trials Manager or designee	4.5	Ensure all issues identified for resolution or follow-up during the Monitoring Visit and outlined in the follow-up letter are addressed prior to the next Monitoring Visit.

CLOSE OUT VISIT

Role	Step	Activity
Clinical Trials Manager or designee	5.0	Review trial status and status of patients to identify trials that may be closed. Some examples are as follows: Study is closed to enrollment and no patients were enrolled at site Study is closed to enrollment and all patients enrolled at site are deceased, withdrawn, or complete Study is not meeting accrual policy and must be closed per institutional policy Sponsor is closing the study
Clinical Trials Manager or designee	5.1	Reach out to sponsor with request for a COV and provide Administrative Assistant with the information to schedule the COV. NOTE: The Director of Clinical Trials and Research shall be informed of the pending COV to be scheduled.
Administrative Assistant or designee	---	***NOTE: Repeat Steps 1.0 through 1.3 to schedule the COV***
Director of Clinical Trials and Research	5.2	**Inform the FRA** and Regulatory Coordinator **of the pending COV**
FRA	5.3	Review, invoice, and reconcile all outstanding payments and inform the Regulatory Coordinator once all final payments have been received
Not Applicable	---	NOTE: Repeat Steps 2.0 through 2.3
Investigational Drug Pharmacist or designee	5.4	Destroy or return all unused investigational product at the conclusion of the study as necessary, and inform the appropriate CTO staff once drug is returned/destroyed **NOTE:** Devices are managed by the CRC or designee and shall be returned to/reconciled

		with the sponsor as necessary.
Regulatory Coordinator	5.5	Obtain the COV Follow-up Letter, file a copy in the Regulatory Binder, upload a copy in the Common Drive, and submit along with the Final Report to the IRB as outlined in SOP 204.

RESOURCES:

21 CFR 54.15	Proposed Obligations of Clinical Investigators
21 CFR 312.50	General Responsibilities of Sponsors
21 CFR 312.56	Review of Ongoing Investigations
21 CFR 312.59	Disposition of Unused Supply of Investigational Drug
21 CFR 312.60	General Responsibilities of Investigators
21 CFR 312.62	Investigator Recordkeeping and Record Retention
21 CFR 312.64	Investigator Reports
21 CFR 312.66	Assurance of IRB Review
21 CFR 312.68	Inspection of Investigator's Records and Reports

ICH GCP Consolidated Guidelines (Part 5.18 Monitoring)
FDA Compliance Program Guidance Manual (7348.811 and 7348.810)
FDA Guidelines for the Monitoring of Clinical Investigations

Endorsed by: SOP Committee (9/17/12; 3/21/14; 4/17/15; 4/8/16)
Approved by: Tracy Butryn, Director of Clinical Trials and Research (9/18/12; 5/9/14; 4/17/15; 6/24/16)

ATTACHMENT A

Monitor Visit Schedule

It is St. Luke's University Health Network's policy that the time allocation outlined in this schedule be strictly adhered, although the actual time slots may change based on staff availability, so as to avoid clinical trials staff from unduly being pulled from their daily responsibilities and patient care.

While it may be necessary to deviate from the exact times indicated below due to staff schedules, each staff member is not to meet with the monitor for more than ***one hour*** per visit.

Monitors shall not arrive earlier than 8:00am, and must be completed with their visit by 4:30pm, at which time they will be required to leave the facility.

The location and time of the visit shall be determined at the time of scheduling the visit. If more than one location must be visited, it must be determined which location will be visited during specific timeslots (e.g. morning versus afternoon) as space may only be available as scheduled at each location.

Visit Pharmacy and PI as scheduled
Lunch and breaks to be taken as needed

8:00 - 10:30 am:	Review documents/data independently
10:30 - 11:00 am:	Meet with CRC
11:00 - 1:00 pm:	Review documents/data independently
1:00 – 1:30 pm:	Meet with Regulatory Coordinator
1:30 – 2:30 pm:	Review documents/data independently
2:30 - 3:00 pm:	Meet with CRC
3:00 - 4:00 pm:	Review documents/ data, finish up for the day
4:00 – 4:30pm:	Meet with study team to review any final outstanding items

ATTACHMENT B

Monitoring Visit Log

STUDY	COORDINATOR	DATE OF VISIT	VISIT CANCELLED	MONITOR	VISIT INVOICEABLE?	INVOICE # & DATE SENT