MUTI-SITE PROCEDURE MANUAL

St. Luke's University Health Network (SLUHN)
Clinical Trials Office

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Principle Investigator
*will be determined per trial

Research Coordinator
*will be determined per trial

Data manager
*will be determined per trial

Participating Site(s):
*will be determined per trial

GENERAL ROLES AND RESPONSIBILITIES

In accordance with GCP Multi-Center Guidelines, the Protocol Chair, Coordinating Site (St. Luke's University Health Network), and the Participating Institution(s) will all agree to the general responsibilities as follows:

Protocol Chair (SLUHN Principal Investigator)

Principal Investigator will accept responsibility for:

- Overseeing the coordination, development, submission and approval of the protocol as well as subsequent amendments
- Assure all participating institutions are using the correct version of the protocol
- Ensure that all participating sites demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA Requirements.
- Monitor progress and overall conduct of the study at all participating institutions
- Ensure all SLUHN and other applicable reporting requirements are met
- Review data and maintain timely submission of data for study analysis
- Submit IRB approval of all participating sites to the SLUHN IRB

Coordinating Site (SLUHN)

The Coordinating Center is the SLUHN study team from the Clinical Trials Office (Director, Manager, Study Start-up Project Coordinator, Research Nurse Coordinator, Regulatory Coordinator, data manager) and designees (i.e. Medical Monitor). They will assume the following general responsibilities:

- Maintain Regulatory Binders (with applicable approvals) on all participating institutions.
- Verify eligibility/register subjects
- Maintain updated subject screening/enrollment logs
- Maintain documentation of Adverse Event (AE) and Serious Adverse Event (SAE) reports submitted by Participating Sites and submit to SLUHN Regulatory Bodies appropriately
- If IND study, report AE/SAEs to FDA and participating site via MedWatch 3500A Form and provide a copy to participating site within 15 days of PI notification of event
- Provide on-site reportable AEs and SAEs to participating site within 15 days of PI notification of event for all trials (IND or not)
- Monitor and oversee study conduct at Participating Sites (e.g. data and safety monitoring, audits, conference calls, source verification, etc.)
- Maintain a tracking log of all on-site AEs to be sent to participating site quarterly prior to quarterly conference call for discussion

Participating Site (TBD based on protocol)

Each participating site must provide SLUHN with a list of key personnel involved in the study, their role and contact information.

The general responsibilities for each participating site are as follows:

- Submit protocol and/or amendments to the study to their local IRB, and provide copies of all approvals to the SLUHN Regulatory team for central filing

- Update SLUHN with research staff changes in a timely manner (within 15 business days) via an updated FDA Form 1572 (if change in investigator), updated Delegation of Authority Log, and Updated Site Contact List, along with corresponding CVs and Medical Licenses
- Register patients through SLUHN
- Collect data on protocol specific CRFs
- Submit source documents, research records, and CRF's to SLUHN
- Submit Adverse Event and Serious Adverse Event report to local IRB (per local IRBs reporting policy) and SLUHN (per SLUHN Reporting Policy – described below) and protocol
    - If IND study, also submit MedWatch 3500A Form to FDA using appropriate channels and within appropriate timeline per regulations, and send a copy to SLUHN Study Coordinator and Regulatory team
- Maintain a tracking log of all AEs to be sent to SLUHN monthly prior to monthly monitoring conference call for discussion

INITIAL REGULATORY REQUIREMENTS

Coordinating Site (SLUHN

Once this study has received final IRB approval at SLUHN, the following study documentation will be forwarded to the participating site for processing/regulatory submission:

- Study Start-up Checklist
- Finalized study protocol
- Multi-site Manual of Procedures
- SLUHN IRB approval letter
- SLUHN Template ICF
- IND Exemption Letter (if applicable)
- Blank FDA Form 1572
- Blank Financial Disclosure Form
- Blank Site Contact Information Sheet
- Blank Delegation of Authority Log
- Training Logs
- Clinical Trial Agreement/Subcontract/Collaborating Agreement
- Budget (if applicable)
- Other study templates (e.g. CRFs, AE log, SAE Report Form, UAP Report Form, etc.)

Participating Site

Prior to submitting this study to the local IRB for review/approval, the template informed consent form should be forwarded to the Regulatory Team at SLUHN for review/approval at: Angela.Gunkle@sluhn.org and Jayne.Silva@sluhn.org. Upon submission to the IRB, please provide SLUHN the anticipated IRB review date.

Once all regulatory approvals have been received, the following documentation will need to be forwarded to SLUHN:

1. IRB approval of the study and stamped informed consent form
2. Signed and dated 1572
3. Current signed and dated CVs (within 2 years) for PI and Sub-Is on 1572
4. Current Medical Licenses for PI and Sub-Is on 1572
5. Local Lab Certificates: CLIA, CAP, Lab Permit
6. Current Local Lab Normals
7. Complete Site Contact Information Sheet
8. Signed Delegation of Authority Log
9. Signed Clinical Trial Agreement/Subcontract/Collaborating Agreement
10. IRB FWA
11. Documentation of Training for all investigators and key personnel

SLUHN will maintain a separate Regulatory Binder for each "participating site"

Please note that all regulatory requirements must be in place and approved by SLUHN prior to site activation and enrollment.

SITE INITIATION VISIT AND TRAINING

Once all necessary approvals have been obtained and the site has been determined "Regulatory Ready," the SLUHN Study Team will contact participating site to schedule a Site Initiation Visit (SIV).

This SIV will take place onsite at participating site when feasible. We will have a video or teleconference for sites that are geographically out of the area. All key study team members must be in attendance; this includes the Principal Investigator, the Research Coordinator(s), Regulatory Coordinator, Data Managers, and Pharmacy Contact. Please allow at least 2 hours for this meeting. A detailed agenda will be forwarded to the site prior to the visit.

The following topics will be reviewed in detail:

1. Study Protocol
    - Objectives
    - Inclusion/exclusion criteria
    - Study schedule/assessments
    - Dose reductions/treatment delays
    - Concomitant medications and ancillary treatments/procedures
    - AE/SAE reporting
2. Manual of Procedures
    - Ongoing study management
    - Screening/Enrollment
    - Patient Registration
    - Study logistics
3. Case Report Forms
    - Completion and timeline for submission
4. Role of Coordinating Site (SLUHN)

- Monitoring and oversight of the participating site by SLUHN(e.g. data and safety monitoring, audits, conference calls, etc.)

5. Pharmacy
    - Drug ordering/shipment
    - Drug accountability/storage

All applicable template forms (both electronic and hard copies) will be provided to the participating site for study use and reviewed in detail at this time.

All attendees will be asked to sign an attendance sheet to document their participation in this SIV. A copy of this attendance sheet and the SIV agenda will be provided to the site for their Regulatory Records. Originals will be maintained by SLUHN.

Once this Site Initiation Visit is completed, and all outstanding issues have been resolved, a formal "Activation Notice" will be sent to participating site at which time the participating site may begin screening and enrollment.

SUBJECT ELIGIBILITY AND ENROLLMENT

When a potential patient is identified, the SLUHN Research Nurse/Coordinator should be contacted via email/phone to:

1. Notify them of the pending patient registration
2. Confirm the method of sending registration documents (i.e. fax, email, etc)
3. Communicate the desired timeline of the registration.

The following documentation should be forwarded to the SLUHN Study Team to confirm eligibility:

1. Signed informed consent form
2. Signed/dated eligibility checklist
3. All Eligibility source documents (e.g. Lab Reports/other eligibility scans, tests, etc.)

*****Note: These source documents should be de-identified*****

Once eligibility has been established, SLUHN will email the Research Coordinator at the "participating site" to confirm eligibility. The subject will then be assigned a registration number. This number is unique to the participant on this trial and must be used moving forward (i.e. for CRF completion, SAE reporting, etc).

A master study enrollment log will be maintained by the study team at SLUHN. The participating site will also be asked to maintain an enrollment/screening log on-site, and fax this information to SLUHN twice a month to the SLUHN clinical coordinator.

Patients cannot be registered to this study on the weekends. If a patient is to be registered on a Friday, they will need to contact the SLUHN Research coordinator by Friday at noon at the latest.

If a patient is enrolled at the participating site, without approval from the coordinating site, SLUHN will:

1. temporarily suspend the participating site to enrollment
2. Complete mandatory re-training of staff at the participating site on the enrollment process.

*****This training will be fully documented*****

If enrollment without approval occurs a second time, the participating site will not be able to continue to participate in this study.

ONGOING REGULATORY OVERSIGHT

The CTO at SLUHN will maintain a separate Regulatory Binder for each participating site. All relevant correspondence, study logs, IRB approvals, submissions, monitoring reports, AE/SAEs/unanticipated problems, etc. will be maintained appropriately and will be available for review/audit upon request.

Amendments to the Protocol, ICF or other study documents will be communicated to the participating site via email once SLUHN IRB approval has been received. Changes to the ICF must be approved by SLUHN prior to IRB submission at the "participating site." The amendment must be submitted by the participating site to their local IRB and approved within 90 days of receipt of the amendment. Once IRB approvals have been received at the participating site, copies of this documentation should be forwarded electronically to the SLUHN Regulatory Office (Jayne.Silva@sluhn.org). This includes: copies of each submission, IRB approval/acknowledgement, and stamped informed consent form.

A log will be maintained by the SLUHN CTO to track regulatory submissions/approvals at participating site .

DATA SUBMISSION AND CASE REPORT FORM REVIEW

Paper case report forms will be utilized to capture data for these studies, unless otherwise advised.

The participating site will be required to submit all Case Report Forms to the Coordinating Site (SLUHN) Research Nurse/Research Coordinator via fax at 484-XXX-XXXX (TBD based on coordinator assignment) within 3 days of the corresponding visits.

A separate research chart will be maintained for each subject enrolled at the "participating site." Case Report Forms will be reviewed and data queries will be issued via email as applicable. All applicable data/forms will be filed in the subject's research chart accordingly.

The SLUHN Study Team or delegate will conduct a monitoring visit (either on site or via phone) within 2 weeks of the first subject enrollment at the "participating site." Additional monitoring by the Coordinating Site (SLUHN) Study Team or delegate will take place on a monthly basis via telephone or as needed based on enrollment.

The Participating Site will be asked to track all study AEs in a spreadsheet over the course of this study. This information should be kept up-to-date and available upon request by the Coordinating Site, Medical Monitor, or PI. It will be forwarded to the Coordinating Site monthly for the formal monthly conference call monitoring visit.

The SLUHN Clinical Trial Management System (DDOTS) will be used to track patient enrollment and screening information for all patients enrolled on this study at both the coordinating site (SLUHN) and "participating site."

PROCESSING AND SHIPMENT OF SPECIMENS

To be determined per protocol.

AE/SAE AND UNANTICIPATED PROBLEMS (UAP) REPORTING

Adverse Events (AEs)and Serious Adverse Events (SAEs)

Participating Site:
All AE/SAEs occurring at participating site must be reported to their local IRB per local IRB guidelines, and also to the SLUHN clinical study coordinator within 24 hours of notification as outlined in the study protocol. This initial notification can take place via email, followed by the submission of a formal report. AE/SAEs should be reported using a MedWatch 3500A Form, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

If an IND study, the participating site will also be responsible for sending the FDA MedWatch 3500A Form to the FDA.

These formal AE/SAE Reports via the MedWatch 3500A Form should then be faxed to the SLUHN coordinator within 48 hours at 484-XXX-XXX (TBD) attention SLUHN coordinator, as well as to the funding sponsor (TBD per protocol) via fax to: Global Safety; FAX 215 993-1220 by the participating site. The SLUHN coordinator will notify the SLUHN PI, and report these events to the SLUHN IRB appropriately (in a spreadsheet every month).

Additional follow-up AE/SAE reports should be submitted when available.

Any non-reportable AE must be kept by the "participating site" on an ongoing tracking log to be reviewed by SLUHN monthly.

Coordinating Site:
All reportable AE/SAEs occurring at the coordinating site must be reported to the SLUHN IRB as outlined in the protocol and per local IRB guidelines using the SAE Report Form, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should also be included.

Reportable AE/SAEs from SLUHN will then also be faxed to the "Participating Site" coordinator, as well as the funding sponsor (Global Safety; FAX 215 993-1220), per same guidelines as outlined above.

Additional follow-up SAE reports should be submitted when available.

Unanticipated Problems Involving Risk (UAPs)
Unanticipated Problems posing risks to subjects or others are unforeseen and indicate that participants or others are at increased risk of harm. 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.

Participating Site:
UAPs that pose risk to subjects or others, and that are not AE/SAEs should be reported to SLUHN using the UAP Reporting Form, and should be faxed to the SLUHN coordinator within 5 days at 484-XXX-XXX (TBD) attention SLUHN coordinator.

Coordinating Site:
UAPs that pose risk to subjects or others, and that are not AEs/SAEs should be reported to SLUHN IRB within 10 working days using the UAP Report Form, and should be faxed to the Participating Site coordinator within 5 days.

Note: Deviations from eligibility are not acceptable under any condition unless approved by SLUHN PI*

DATA AND SAFETY MONITORING

The SLUHN Protocol Chair (PI), along with an unaffiliated Physician (e.g. Medical Monitor) will review all AE/SAEs and UAPs on a quarterly basis. All AE/SAEs and UAPS from the coordinating site, as well as all participating sites, will be provided to the Protocol Chair and Medical Monitor by the SLUHN Research Coordinator.

Medical Monitor:
A Medical Monitor has been assigned to this study by SLUHN. This is a physician/pharmacist who is not directly involved in the trial. The role of the Medical Monitor is to review all AE/SAEs, including grading, toxicity assignments, non-reportable AEs, protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at both the participating sites and at SLUHN. The Medical Monitor may recommend suspension or termination of the study. This review will be done on a quarterly basis, along with the Protocol Chair (SLUHN PI), and will be documented in a formal data and safety monitoring report. This report will then be submitted to the SLUHN IRB for review and acknowledgement. A copy of the report will be provided to all participating sites for submission to their local IRB as necessary.

Copies of each report and documentation of IRB notification will be kept in the regulatory binder.

Follow-up Reports
Significant new information on ongoing serious adverse events should be provided promptly to the Coordinating Site for applicable submission to the SLUHN IRB and Medical Monitor.

INTERIM MONITORING

Coordinating Site Study Team
Representatives from the SLUHN Study Team or delegate will monitor on site (or virtually if geographically impossible) within 2 weeks of the first subject enrolling and monthly via teleconference. All source documentation (de-identified) shall be sent to the SLUHN Study Coordinator along with completed CRFs as outlined on Page 9.

Study Team Conference Calls
Teleconferences with the PIs, research nurses/coordinators, and regulatory staff will occur monthly. This will be a forum to discuss study related issues including accrual, SAE/AEs

experienced, study response, deviations/violations and study management issues. Minutes of these discussions will be taken by the Manager to document the date of these meetings, the participants and the issues that were discussed. Copies of these minutes will be sent to all participating sites, and maintained in the Regulatory Binders at both sites.

SPONSOR REQUIRED STATUS REPORTS

Participating Site

Each participating site will be responsible for sending the Coordinating Site a monthly progress report prior to the Monthly Monitoring Conference calls. These reports shall contain all study progress information as follows:

- How many subject enrolled since last monthly report
- How many subjects enrolled total at site
- AE/SAEs since last monthly report
- Follow-up information of any previous AE/SAEs
- UAPs and Deviations/Violations
- Amendments or other IRB submissions since last monthly report
- Any other issues/concerns

Coordinating Site

The Coordinating Site will compile these monthly reports from all sites, including SLUHN, on a quarterly basis and will submit a quarterly status report to the funding sponsor (TBD based on protocol) using whatever method required by the funding sponsor (e.g. online, paper, etc.)