[SITE NAME]

STANDARD OPERATING PROCEDURE

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Purpose:
[SITE] is committed to supporting clinical trials and strives for these to be conducted to a high-quality standard. The purpose of this SOP is to define the process and standards of Clinical Research Quality Management at [SITE] campuses.

A clinical Quality Management System is an integrated framework through which organizations systematically define quality objectives linked to their broader strategic goals. The focus will be areas of potential risk to:

Human subject rights protection and safety/wellness

Data integrity/Study Validity

Scope:
This SOP applies to all personnel involved in the conduct of clinical research involving human subjects at [SITE] institutions and associated clinical departments.

Materials:
Attachment 1- Corrective and Preventive Action (CAPA) Form (Template)

Attachment 2 - Corrective and Preventive Action (CAPA) Letter (Template)

Responsibility:

This SOP applies to all the clinical research departments and Institutions actively engaged in clinical research involving human subjects.

By adhering to this SOP, members of the clinical research team and [SITE] can help ensure that the rights and wellbeing of the subjects participating in clinical trials are protected, the trial data is credible and that the trial is conducted in compliance with the approved protocol and applicable regulatory requirements.

Procedure:

The Quality Management System will comprise of:

1) Quality Policy and Clinical Trials Governance Framework
2) Organizational Structure and Responsibilities
3) Data Management and Document Control
4) Written Policies and Procedures
5) Compliance: Internal Quality Assurance Auditing, Quality Control and Monitoring Processes
6) Continuous Improvement in Clinical Research
7) Clinical Research Personnel Education and Training Program

1) Quality Policy and Clinical Trials Governance Framework:

The clinical research activities of -
[SITE] are designed to meet the expectations of regulatory agencies worldwide as established by the World Health Organization (WHO), US Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) Code of Federal Regulations (CFR), and International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use, with emphasis on ICH Good Clinical Practice (GCP) and are also specifically governed by directives, guidelines, and regulations of the WHO, ICH and CFR as well as applicable specific country and state regulations.

[SITE] leadership, including through the [relevant site-specific oversight bodies] provide support for quality initiatives and ensure the implementation and maintenance of research governance principles for all clinical research. The [relevant site-specific oversight bodies] is the overarching structure bringing resources to the clinical research community to improve study conduct processes and compliance.

2) Organizational Structure and Responsibilities

[Site-Specific] leadership ensure appropriate infrastructure is available to facilitate safe, efficient and compliant clinical research.

The Principal Investigator retains ultimate responsibility for each of their studies. However, responsibilities can be delegated by the Principal Investigator, as needed, for each clinical study using a master delegation of authority process and/or a study-specific delegation of authority log.

Responsibilities for research personnel are described in a separate SOP (Clinical Research Personnel Responsibilities and Training Programs).

3) Data Management and Document Control

Clinical research record management and retention will be performed in accordance with Standard Operating Procedure "Data Management: Security, Confidentiality, Sharing, Transmission and Archiving".

All Quality Assurance completed tools and audit reports will be maintained according to clinical research record retention policies but separately from the clinical data/research files.

Facilities and computer system/equipment security and maintenance are in accordance with [SITE NAME] policies.

4) Written Policies and Procedures

All SOPs within the Quality Management System will be reviewed and approved prior to distribution. There will generally be a 4-week period between approval of SOPs and their effective date to allow time for training of personnel.

Clinical research teams/departments are expected to develop written operating procedures to establish standards with regards to clinical trial conduct.

5) Compliance: Internal Quality Assurance Auditing, Quality Control and Monitoring Processes

Quality Assurance audit personnel will be independent from the personnel involved in the conduct of the clinical trial and perform internal audits that include trial-specific audits to continually assess the compliance of ongoing trials. Institutional internal audits can be routine or for-cause and can be led by [Site- specific governing bodies] and/or research-team members.

As per ICH Guideline for Good Clinical Practice (GCP), an audit is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, SOPs, GCP and the applicable regulatory requirements.

<u>Internal Quality Assurance Auditing:</u>

The internal audit is a valuable tool in a quality management system. An internal audit can help to:

- prepare for an external audit;
- identify the gaps or nonconformities that need to be corrected and the opportunities for improvement;
- understand where preventive or corrective action is needed;
- identify areas where training needs to occur;
- increase staff awareness of quality requirements and PI/site responsibilities

Findings resulting from internal audits will be categorized as either minor or major according to the risk to human subject protection and safety or to data integrity/study validity.

Selection of Trials for Audit:

All clinical research at [SITE NAME] may be subject to internal audit. Priority will be given to protocols that are actively enrolling participants.

For Investigator-initiated trials (whether federally-funded or not), at least 10% of trials opened on an annual basis will be randomly chosen for audit, with priority given to trials that are open to accrual and/or determined to be of high risk.

For Industry-Sponsored and Cooperative Group trials, a random selection of these trials will be chosen, with an aim to audit 10% of open trials annually, with priority given to trials that are open to accrual and/or determined to be of high risk.

Where possible at least 10% of subject charts from each selected trial will be reviewed.

An audit plan, usually in the form of a letter, will be generated prior to any randomly selected trial-specific audit performed and should include the audit scope and auditing methods to be used. The plan will be reviewed by the [Site-specific governing body] and provided to the study PI at least 2 weeks prior to the planned start of audit, where possible. A mutually convenient time will be arranged for the audit.

QA audit may begin following enrollment of first 2 subjects (or within 6 months of first subject enrollment, whichever occurs first), as possible.

The following will be included in the audit:

a. 100% review of informed consent, eligibility, treatment administration, adverse events, endpoints/outcome, and medical/laboratory/test procedures for randomly selected participants to represent 10% (a minimum of 2) of enrolled participants
b. Verify the accuracy and completeness of Case Report Form (CRF) data entries using source documents and records for selected participants.
c. Regulatory File requirements and completeness.

d. Protocol and regulatory compliance.
e. For studies with Investigational Product, accountability and receipt/storage/disposition will be reviewed.

QA reserves the right to change the scope, number and/or frequency of audits conducted based on institutional requirements.

Reporting of Audits:
When possible, an exit meeting with relevant staff will be conducted to ensure issues that should be corrected be discussed as soon as possible. A report, including audit findings, will be prepared and sent to the PI within 10 working days of the audit exit meeting, as possible. The [Site-specific clinical trials management system] audit report or another report format may be used. Findings will be categorized as follows:

A **major finding** is defined as a variance from protocol-specified procedures that makes the resulting data questionable or increases risk to subject safety.

A **minor finding** is one that is judged not to have a significant impact on the outcome or interpretation of the study or subject safety. An unacceptable number of minor findings may be treated as a major finding in determining the final assessment.

Quality Control/Monitoring Activities:
Any QC procedures implemented to ensure that participant safety has been maintained and data are reliable and have been processed correctly according to the protocol and applicable regulations, will be detailed in study protocols, quality/data safety monitoring plans and/or departmental Standard Operating Procedures.

For Investigator-initiated trials, especially those that are linked to an FDA IDE or IND (with no external Sponsor/monitor), there should be a monitoring plan developed to ensure related regulatory requirements are met. There may be an internal monitor assigned to ensure quality and compliance on an on-going basis during study conduct.

6) Continuous Improvement in Clinical Research

Corrective and Preventive Action (CAPA):
The Corrective and Preventive Actions (CAPA) process establishes a method for conducting and documenting internal activities for continual assessment of compliance with clinical trial protocols, established regulations, ICH GCP guidelines, adherence to internal standard operating procedures and initiatives to actively seek quality improvement processes.

CAPA should be maintained by each department and can originate from performing QC, monitoring activities or from external/internal audits. Issues will be identified where possible as

being critical, major or minor risk to the safety of human subjects and to the integrity of the trial according to the following:

Critical: Adversely affect the rights, safety or wellbeing of trial subjects and/or the integrity of the clinical trial or data
Major: Possibility of adversely affecting the rights, safety or wellbeing of trial subjects and/or the integrity of the clinical trial or data
Minor: An issue that is not in accordance with the principles of GCP but where there is no expected impact on the rights, safety or wellbeing of trial subjects and/or the integrity of the clinical trial or data

The notification of CAPA issues will be as follows:

- The PIs will be notified for any issues that are related to their specific trials.
- The IRB will be notified according to reporting requirements for issues involving human subject safety.

The [Site-specific governing body] should be notified of all critical issues.

1. For critical and major issues, a CAPA Form will be completed that should include the following:
   1.1. Identification of issue: Describe the problem or potential problem.
   1.2. Evaluate: Assess the magnitude and risk of the issue and identify/assign an owner.
   1.3. Root cause Investigation: Perform a root cause analysis of the problem, collect pertinent documentation, as applicable, and describe the root cause of the issue.
   1.4. Corrective Action and Preventive Action Plan: Create a list of required actions and due dates to eliminate the problem (corrective action if not already performed) and prevent recurrence (preventive action).
   1.5. Assignment: Identify the team member(s) responsible for tasks.
   1.6. Effectiveness verification: Assess the effectiveness of the plan. Make changes to the plan if needed and repeat until the issue is considered closed/resolved.

Refer to Attachment 1 and 2: Corrective and Preventive Action (CAPA) Form and Letter that can be used as needed (Template)

The [Site-specific governing body] may track CAPA that are deemed critical and will periodically evaluate the process to ensure all issues are resolved in a timely manner and to analyze any pertinent trends. The CAPA oversight will help inform process improvement initiatives across the institution. The [Site-specific governing body] can also assist with the departmental CAPA processes as needed.

Other metrics, such as protocol deviations and internal audit findings, may be tracked and trended in order to determine required quality improvement initiatives and identify potential risks.

7) Clinical Research Personnel Education and Training program

Training records will be the responsibility of each individual to ensure it is accurate and up to date. At minimum, these will include a CV (signed/dated at least every 2 years), licensure (as applicable) as well as evidence of continuing internal and external training.

A comprehensive onboarding and continuing education training program for research team members is outlined in a separate SOP "Clinical Research Personnel Responsibilities and Training Programs."

History of Revisions to SOP

Effective Date	Nature of Revision