University of Nebraska Medical Center

Center for Clinical and Translational Research Standard Operating Procedure

Nebraska Medicine

Section: **Clinical Research Center**

Date Created**: November 1, 2010**

Title: **Audits and Inspections**

Version Date: **January 1, 2023**

SOP Number: **SM38**

PURPOSE: This standard operating procedure (SOP) describes the operations followed at this site when an audit occurs including FDA inspections/audits conducted under FDA's Bioresearch Monitoring (BIMO) program.

SCOPE: This SOP applies to the procedures to prepare for an audit conducted at this site. It describes the steps the site follows from the time the site is notified of the audit until all follow-up activities associated with the audit are completed.

PERSONNEL RESPONSIBLE: This SOP applies to members of the clinical research team involved in arranging, managing, or participating in the audit at this research site. This includes the following: Sponsor, Sponsor-Investigator, Principal Investigator, Sub-Investigators, Assistant Vice Chancellor of Clinical Research, Research Nurse Manager, or CRC representative, Research Nurse Coordinators, Regulatory Designee, Investigational Pharmacists, and/or other pertinent staff.

DEFINITIONS:

- **Audit:** A systematic and independent examination of trial-related activities and documents by the Food and Drug Administration (FDA), sponsor or other regulatory agency. An audit is to determine whether the trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, site's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirements(s).
- **Audit Trail:** Documentation that allows reconstruction of the course of events.
- **Bioresearch Monitoring (BIMO) Program:** The objectives of the bioresearch monitoring program are twofold: (1) to ensure the quality and integrity of data and information submitted in support of investigational and marketing clearance applications or submissions [IDEs, PMAs, and 510(k)s]; and (2) to ensure that human subjects taking part in investigations are protected from undue hazard or risk. The Division is also charged with the implementation of the FDA's Application Integrity Policy (AIP) for medical devices and radiological health products.
- **Compliance:** Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
- **Direct Access:** Permission granted to any party (e.g., domestic, and foreign regulatory authorities, sponsors, monitors, and auditors) to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial.
- **Documentation:** All records, in any form (including, but not limited to written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that

describe or record the methods, conduct, and/or results of a trial, the factors affecting research, and the actions taken.

- **Food and Drug Administration (FDA or USFDA):** –A federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription, and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed and veterinary products.
- **Essential Documents:** Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
- **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
- **Source Documents:** Original documents, data, and records (e.g., hospital records, laboratory results, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records) that contain the first recording of pertinent information.
- **Standard Operating Procedures (SOPs):** Detailed, written instructions which describe department specific activities, clarify expectations for staff performances, provide supporting documentation for auditors and facilitate critical evaluation of department practices.

PROCEDURES:

Notification of Audit:

1. Write down all information that is shared and verify the information is correct. Obtain the following information:
    a. Contact information if we need to call back
    b. Date and time we can expect the auditor
    c. Name of the auditor(s)
    d. Name of the study they are auditing
    e. Type of audit

Preparing for the audit

Responsible Team Members	***Tasks to Implement:***
• PI • Research Nurse Manager • Research nurse/coordinator • Support staff • Regulatory designee	If notified of an FDA audit, the PI is responsible to ensure the following are immediately notified: • Research Staff involved with the trial • Sponsor / Clinical Research Organization (CRO) • Section Chief • IRB (and Scientific Review Committee Chair if applicable) • Investigational Pharmacy (if applicable) • UNMC, NM, IRB compliance officers • Associate Vice-Chancellor for Clinical Research at UNMC, Vice President for Research at Nebraska Medicine, Research Nurse Manager, and others, as applicable Ensure that all documentation, including informed consent forms, source documents, CRFs, and the regulatory binder for the study that are identified as the focus of the audit are accurate, complete, and available for review by the auditor. (Attachment A, Audit Preparation Checklist).
• Research nurse/coordinator • Study pharmacist	Ensure that the study drug/device dispensing records are accurate, complete, and available for review. If there were any instances in which emergency breaking of the blind was required, have that documentation available. (Attachment A Audit Preparation Checklist)
• Study pharmacist	Ensure that drug accountability records are accurate, complete, and available for review.

During the audit

• PI • Research Nurse Manager • Research nurse/coordinator	Meet with the auditor or inspector. Request to see identification, and if this is an FDA audit, request Form FDA 482.

• Regulatory designee • Support staff • Legal Council	Provide orientation and access to the study records and files. Provide copies of requested study-related documents. Ensure that questions posed by the auditor or inspector are answered by appropriate study personnel. If you do not know the answer to the question, do not guess. Answer only what is asked. Put the auditor in a room without other records/study documents. (See Attachment A) Maintain an accurate record of questions asked, answers provided, concerns raised, positive observations, and records provided. Be honest, always and without exception.
FOR FDA AUDIT ONLY	An individual listed on the IRB for the study will be identified to log into Electronic Medical Record production version and navigate patient charts on behalf of the FDA auditor.

Following up after the audit

• PI • Research Nurse Manager • Research nurse/coordinator • Legal counsel	Participate in the exit interview with the auditor or inspector. **NOTE**: if an FDA 483 is issued it must be responded to within 15 days of receipt. The sponsor should be provided with an opportunity to assist in the response. The reply should be routed through VCR Office, Legal Counsel, IRB, & SRC if applicable prior to submitting to FDA.

• PI • Research Nurse Manager • Research nurse/coordinator • Legal Council	PI will respond to the audit report as soon as possible after its receipt. Reply to each item in the report, providing clarification or steps that will be taken to institute corrective action. When responding to a FDA audit, PI will prepare a written response(s) after collaboration with the VCR office and IRB. All FDA audit response(s) will be communicated with UNMC and NM leadership by the PI in collaboration with VCR office.

ASSOCIATED FORMS:

Attachment A – Audit Preparation Checklist

RESOURCES:

- Compliance Program 7348.810 Bioresearch Monitoring: Sponsors, Contract Research Organizations and Monitors https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
- Compliance Program 7348.811 Bioresearch Monitoring: Clinical Investigators
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs*Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors – FDA Inspections of Clinical Investigators (*Rep*.). (*June 2010). US Department of Health and Human Services FDA.
- International Conference on Harmonization (ICH) https://www.ich.org/home.html
- Perelman. (2014, March 27) *How to Survive an FDA Inspection.* Presented at School of Medicine Office of Research.
- *What You Need to Know to Prepare for a FDA Audit.* Presented at Forte Research Systems Webinar.
- UNMC: #6109 Investigations by Government Officials, Regulatory Agencies, and Other Third Parties.
- Nebraska Medicine:
    - LD03 Government Investigations Response Guide

- MS40 Vendor Interaction Policy

Department Approval

Signed Serena Gaines Signed: 2/21/2023
Research Nurse Manager

Signed Signed: 4/3/2023
Assistant Vice Chancellor for Clinical Research

AUDIT PREPARATION CHECKLIST

I. ORGANIZATIONAL ACTIVITIES		COMPLETED	N/A	COMMENTS
Notify all parties	Sponsor (If an FDA audit)/CRO	❒	❒	
	IRB	❒	❒	402-559-6463
	PI & Sub-investigators	❒	❒	
	Assoicate Vice Chancellor for Research and Research Nurse Manager	❒	❒	402-955-4496 and 402-559-5417
	Investigational Pharmacy	❒	❒	402-559-5255 or 402-559-1665
	Section Chair	❒	❒	
	Research Staff	❒	❒	
	Administration	❒	❒	
	Legal Counsel/Compliance	❒	❒	402-559-9576 and 402-559-6767 or 402-559-3479
	SRC Chair (if oncology)			
	Reserve workspace for the auditor	❒	❒	
General Overview	Prepare a general overview of the study	❒	❒	
	Gather or locate SOPs, institutional policies in case needed for the auditor.	❒	❒	Recommended ones: IDS SOPs, SOP SM37; NM - EC33, EC01, EC03, IC13, IM01, IM17, LD03, LD04, UNMC #6109
	List all personnel and responsibilities delegated	❒	❒	
List of subjects	List all subjects enrolled including name, address, and/or phone number, date enrolled, and completed, medical record number (to be kept as a reference for site research staff)	❒	❒	
II. FILE MANAGEMENT		**COMPLETED**	**N/A**	**COMMENTS**
Organize all regulatory files by general heading in chronological order	Protocol (all versions)	❒	❒	
	Investigator's Brochure (all versions)	❒	❒	
	Protocol Amendments	❒	❒	
	Form FDA 1572 (all versions)	❒	❒	
	CVs for PI and sub-investigators listed on all versions of the Form FDA 1572	❒	❒	
IRB Files	Approved Letter (initial) for initial protocol with original consent form	❒	❒	

AUDIT PREPARATION CHECKLIST

	Amendment approval(s) with approved informed consent forms (if applicable)	❒	❒	
	Informed consent forms (originals) for all subjects screened and enrolled;.	❒	❒	
	Status reports for:			
	❑ Yearly renewal(s)	❒	❒	
	❑ Adverse events	❒	❒	
	❑ Deaths	❒	❒	
	❑ Study termination	❒	❒	
	❑ Final summary	❒	❒	
Communication	Sponsor correspondence	❒	❒	
	CRO correspondence	❒	❒	
	IRB correspondence	❒	❒	
	Monitoring Log	❒	❒	
Laboratory	_____Lab certification and normal ranges	❒	❒	
Drug Accountability	Drug log including:	❒	❒	
	❑ Receipt of drug			
	❑ Dispensing			
	❑ Return			
Device Accountability	Device log including:	❒	❒	
	❑ Receipt of device			
	❑ Dispensing			
	❑ Return			
Equipment Accountability	Equipment log including:	❒	❒	
	❑ Receipt of equipment			
	❑ Dispensing			
	❑ Return			
Subject Selection	Completed CRFs for each subject enrolled	❒	❒	
	Source documents for each subject enrolled	❒	❒	
III. REVIEW		**COMPLETED**	**N/A**	**COMMENTS**

AUDIT PREPARATION CHECKLIST

Collect and review for each subject enrolled	CRFs completed for each subject enrolled	❒	❒	
	Source documents for each subject enrolled that documents the following:	❒	❒	
Every visit should have forms in the same order. Source documents should list location of each piece of information (i.e. CBC,MEMR, 1/1/19, 2:40pm)	❑ Condition of subject at time of entry into the study (Inclusion/Exclusion met)			
	❑ Case history documents Informed consent process was charted and obtained prior to start of study procedures			
	❑ Exposure to test article			
	❑ Concomitant medication			
	❑ Clinical assessments of the subject during the course of the study			
	❑ Laboratory reports			
	❑ Diagnostic tests			
	❑ Dose modifications			
	❑ Adverse events/death			
	❑ Protocol exemptions			
	❑ Early termination			
IV. Site Specific		**COMPLETED**	**N/A**	**COMMENTS**

AUDIT PREPARATION CHECKLIST

FDA AUDIT ONLY	An individual listed on the IRB application for the study will need to be identified to log into Electronic Medical Record production version and navigate patient charts on behalf of the FDA auditor.	❒	❒	
Temperature logs	❑ Medication Storage Location	❒	❒	
	❑ Specimen Refrigerator	❒	❒	
	❑ Specimen Freezer *(-20)*	❒	❒	
	❑ Specimen Freezer *(-70)*	❒	❒	
	❑ Medication Shipment			
Equipment	❑ Centrifuge			
	❑ Calibration logs	❒	❒	
	❑ Inspection reports	❒	❒	
	❑ Permits	❒	❒	