Study Management
SM – 304.00

STANDARD OPERATING PROCEDURE FOR
Routine Monitoring Visits

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I. INTRODUCTION AND PURPOSE

Routine monitoring visits occur one or more times during the period after the Study Initiation Visit but before the Study Closeout Visit. Guidelines for scheduling monitoring visits shall be determined according to the stage of development, complexity of the study, the rate of subject accrual and other factors.

These visits are conducted for routine monitoring only and are intended to ensure that the protocol and applicable regulatory requirements are being followed, that subjects' rights and safety are protected, and to confirm data integrity and quality.

The objectives of routine monitoring visits are to:

- Document and report on study progress
- Document that the protocol and associated forms are current
- Update the site team of any changes in study conduct/documentation
- Ensure that Georgia CORE requirements and Investigator obligations are met
- Ensure continued acceptability of the Investigator, his/her team and facility
- Obtain and review current data, reports and source documents
- Ensure adequate investigational product inventory and accountability

2. SCOPE

This SOP applies to the Georgia CORE procedures for conducting routine monitoring visits for all clinical studies subject to investigational new drug (IND) regulations for drugs and biologics or those eligible for investigational new drug (IND) exemption during all investigational phases of development. For the purposes of this SOP, the term 'Investigator' includes both Investigators and Subinvestigators.

3. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.53	Selecting Investigators and Monitors
21 CFR 312.56	Review of ongoing investigations
ICH E6, 4.1	Investigator's Qualifications and Agreement
ICH E6, 5.5	Trial Management, Data Handling and Record Keeping
January 1988	Guidelines for the Monitoring of Clinical Investigations
01 March 2014	NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network for the (NCTN) Program, Community Clinical Oncology Program (CCOP)/NCI Community Oncology Research Program (NCORP) and Research Bases
September 1993	FDA Internal Compliance Program Guidance Manual 7348.811: Clinical Investigators

October 2009	Guidance for Industry Investigator Responsibilities---Protecting the Rights, Safety, and Welfare of Study Subjects

4. REFERENCES TO OTHER APPLICABLE SOPs

SS-204	Site Initiation Visit
SM-301	Communication
SM-302	Interactions with the IRB
SM-303	Documentation and Records Retention
SM-306	Adverse Event Reporting
SM-307	Investigational Product Management
SM-308	Specimen Management
DM-401	Data Management
PP-501	Safeguarding Protected Health Information

5. ATTACHMENTS

A. Monitoring Site Visit Checklist and Report
B. Screening and Enrollment Log Template
C. Subject Eligibility Criteria Form
D. Investigator Compliance Meeting Summary and Action Items

6. RESPONSIBILITY

Georgia CORE is responsible for designating a trained and qualified staff member or consultant to serve as study monitor. The monitor is responsible for preparing for, conducting and documenting all monitoring visits.

7. DEFINITIONS

The following definitions from the International Conference on Harmonization, Good Clinical Practice: Consolidated Guideline apply to this SOP.

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.

Compliance (in relation to trials): Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable

precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

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 a trial, and the actions taken.

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, analyses, 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.

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Subinvestigator: Any individual member of the clinical trial team designated and supervised by the Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

8. PROCESS OVERVIEW

A. Scheduling/Frequency of monitoring visits
B. Preparing for the monitoring visit
C. Conducting the monitoring visit
D. Following up after the monitoring visit

9. PROCEDURES

A. Scheduling/Frequency of the monitoring visit

• Research Staff/Consultant	Estimate the number of anticipated monitoring visits based on study design, complexity, phase of development, Investigator's experience, previous site compliance, rate of subject enrollment and any other unique attributes of the study and the site. In addition to above NCORP monitoring visit case selection will be a minimum of 10% of accrual for that period of time between interim visits. Finalize the monitoring plan with the Investigator initiating the study and the CMO.
	Conduct a minimum of one routine monitoring visit at each study site. Monitoring high-risk or critical studies warrants scheduling the first visit after the enrollment of the first subject, with multiple monitoring visits occurring thereafter. Monitoring visits for NCORP member who have at least one year of conducting NCTN trials without any previous documented deviations or high staff turnover rate will occur at a minimum of every 6 months.
	Conduct unscheduled monitoring visits as needed. Unscheduled visits may be based on reports or evidence of potential noncompliance with any sponsor/regulatory requirements (noted during a prior scheduled visit or received from any other source, including employees of the Investigator), significant increases in subject enrollment rates, and/or changes in protocol/personnel and training activities.
	Contact the Investigator or designee regarding scheduling and conducting the monitoring visits. Record discussions on the telephone contact log. (See SOP SM 301, Attachment A Telephone contact log)
	Confirm date and logistics of the monitoring visit in writing and provide the Investigator with a list of source documents and records (e.g., hospital charts, laboratory records, etc) to be reviewed.

B. Preparing for the monitoring visit

• Research Staff/Consultant	Review the relevant contents of the project and site files in the Regulatory Master File prior to the monitoring visit.

	Review the current protocol and informed consent form prior to the monitoring visit.
	Review CRFs for any queries to the Investigator needing clarification or correction.
	Review previous monitoring reports and NCI corrective action plan of action (CAPA) for any outstanding items that must be addressed prior to or during the next scheduled visit.
	Prepare a list of questions and issues to be checked against source documents or other documents at the site.
	Determine the site's inventory of investigational products, forms or other relevant materials and arrange to provide additional items as necessary.
	Make copies of the NCI IRB/ICC audit worksheet, Pharmacy Audit worksheet, Patient Case Audit worksheet for the number of cases/protocols that are reviewed.

C. Conducting the monitoring visit

C1. Overall Study Status

• Research Staff/Consultant	Document the monitoring visit by signing a Site Visit Log at the investigative site (See SOP SS-204 Site Initiation Visit Attachment D).
	Document all findings during the monitoring visit on a Monitoring Site Visit Checklist and Report (Attachment A) or if NCORP the NCI worksheets https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm
	Assess whether the key study personnel and facilities continue to be acceptable to the study and that the site's Investigator is appropriately involved in the conduct of the study.
	Verify that the site's study files contain all required documents and records and that they are accurate, complete and current.
	Confirm that the Investigator or designee routinely files and forwards essential and required information to other required parties appropriately (e.g. IRB).
	Assess subject enrollment rates and examine unexpectedly high or low recruitment.
	Obtain information on subjects who failed to meet inclusion criteria, did not give informed consent, or withdrew from the study for any reason. Review Subject Screening and Enrollment Logs and Subject Eligibility Checklists to ensure they have been signed and dated by the Investigator or qualified designee. (See Attachment B for Subject Screening and Enrollment Log template and Attachment

	C for Subject Eligibility Criteria Form template)
	Confirm eligibility of enrolled subjects by review of inclusion and exclusion criteria and completion of study events per protocol.
	Confirm that all subjects have signed the appropriate informed consent form(s) and that informed consent was obtained before any protocol-related procedures were conducted (except those specified in the protocol).
	Evaluate status of follow-up plans and visits for subjects (assess all or a sample of subject records) and identify problems.
	Confirm that safety and efficacy assessments are conducted per protocol; confirm that serious adverse events have been reported and followed up on appropriately.

C2. Case Report Form (CRF) and Source Document Monitoring Review

• Research Staff/Consultant	Verify that CRFs are being completed in a timely manner and per protocol requirements by inspecting CRF pages for completeness, accuracy and internal consistency.
	Review all CRFs (or a sample) to ensure they are complete, legible, and consistent with protocol specifications and signed by the investigator.
	Compare CRFs with the source documents to ensure protocol compliance and data accuracy and completeness.
	Review and address omissions and queries and ensure corrections are properly made by the Investigator or Investigator-designee prior to the end of the monitoring visit. Unresolved discrepancies will be documented on the Data Clarification Form (DCF) (Reference SOP DM-401 Attachment B) and referenced on the Monitoring Site Visit Checklist and Report for follow up. Note: Monitors may not enter data, correct data, or write on the CRFs. If a recorded entry on a CRF appears to be aberrant, but after review of the source documents is found to be correct, the Monitor will indicate on the monitoring visit report that the entry was verified.
	Track CRF changes, corrections and outstanding queries on the Monitoring Site Visit Checklist and Report.
	The following information must be included in the case history (basic medical record or hospital chart) for each participant: notice of participation in the investigational study, medical condition being treated, dosage or amount or type of investigational product being administered or used, the approximate duration of therapy, any concomitant therapy, and study events and other relevant information.
	Evaluate allocation of investigational products and verify that the randomization procedures were carried out per protocol.
	Assess whether all SAEs have been documented and reported as

	specified in the protocol and other relevant regulatory procedures.

C3. Investigational Products, Supplies and Storage Monitoring

• Research Staff/Consultant	Ensure that investigational product accountability and reconciliation obligations are being followed, and verify all investigational products expiration dates.
	Examine storage refrigerator, freezers, and other storage equipment to confirm they are appropriate for the protocol's requirements and that calibration and temperature logs are maintained in the site's study file.
	Check the site's inventory of investigational product, forms, or other relevant materials, and arrange to provide additional items as necessary after concluding the visit.

C4. Specimen and Laboratory Monitoring

• Research Staff/Consultant	Verify that all specimens for protocol-specific laboratory studies are being stored and forwarded properly and that specimen preparation documentation is maintained.
	Inspect specimen storage equipment as noted above in section 3.

C5. Staff and Facilities

• Research Staff/Consultant	Confirm the Investigator's control of the study and assess his/her ongoing participation. Identify any previously unreported delegations of authority.
	Assess the ongoing suitability of facilities and staff for conducting the study.
	Note and record any changes in staff or the facility not previously reported.
	Provide or schedule additional study training for new staff.

C6. Communications Records

• Research Staff/Consultant	Confirm that copies of all study related mail (electronic, paper) and facsimile correspondence and notes of telephone conversations (Reference SOP SM 301 Attachment A Telephone Contact Log) are appropriately filed at the site.

C7. Protocol Violations

• Research Staff/Consultant	Note if the records show any evidence that protocol violations have occurred and record the nature of the violations on the Monitoring Site Visit Checklist and Report.
	Review any study conduct issues or other incidents of noncompliance with the Investigator and other key study personnel

	and document the issues and follow up plan on the Monitoring Site Visit Checklist and Report.

C8. Concluding the Monitoring Visit

• Research Staff/Consultant	Meet with the Investigator and key staff to discuss any scientific or administrative problems (including study conduct issues or incidents of non-compliance) and possible solutions; document on the Monitoring Visit Checklist and Report, include a follow up plan.
	As necessary, remind the Investigator that all records and reports pertaining to the study must be retained at the study site as required by the study agreement and applicable regulatory requirements.
	As necessary, remind the Investigator to provide all updated information pertaining to the study including changes in key personnel to the monitor on a timely basis.
	After concluding the monitoring visit, report any significant unresolved problems or protocol violations immediately to the Principal Investigator and the Georgia CORE President, who may confer with the Chief Medical Officer regarding the findings. Provide Attachment D (Investigator Compliance Meeting Summary and Action Items) for use if the meeting is deemed necessary.

10. History of Changes

Version Number	Section Number	Modification	Approval Date
304.00	All	Original Version	
304.00	All	No change was necessary	09 March 2012
304.00	All	No change was necessary	01 July 2014
304.00	3, 9A, B, C	Inclusion of NCORP and NCI Auditing guidelines	17 March 2017

Attachment A

MONITORING SITE VISIT CHECKLIST AND REPORT

Protocol Title: **Protocol Number:**

Site Sub-PI: **Site Name:**

Site #: **Site Contact:** **Visit Date:**

Study Personnel Present During Visit Name(s) and Title(s):
Name_____ Title_____
Name_____ Title_____
Name_____ Title_____
Name_____ Title_____

Monitor Name:

Type of Visit:

☐ Routine/Scheduled

☐ Unscheduled/For Cause:

_____

Subject Status:
Date of First Subject Enrolled_____ **Date of Most Recent Subject Enrolled**_____
Total # Subjects Enrolled_____ **Total # Subjects Planned**_____
 # Subjects Screened_____ **Total # Subjects Completed**_____
#Subjects Active_____ **# Subjects Prematurely Withdrawn**_____
#Unanticipated AEs_____ **#CRF Collected: To Date**_____
#Protocol Deviations_____ **#CRF Collected: This Visit**_____

FACILITIES/STAFF	YES	NO	N/A	ACTION ITEMS/ISSUES/COMMENTS
Changes in staff?				
If yes, was the study documentation updated?				
If yes, was the staff properly trained for the study?				
Has investigator accepted new studies since last year?				
Is investigator properly supervising other personnel?				
Is investigator devoting enough time for the study?				
Investigator accessible during visit?				
Has facility/work area changed since last visit?				
If yes, was study documentation updated?				
If yes, were the new facilities/equipment inspected?				
Are treatment facilities adequate?				
SERIOUS ADVERSE EVENTS (SAEs)	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Any SAEs since last visit?				
If yes, were required forms completed and submitted?				
Outstanding data or forms for this or previous events?				
Were any unreported SAEs discovered?				
IRB informed, if required?				
SUBJECT VERIFICATION AND CRF REVIEW*	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Protocol requirements being followed:				
Consent form(s) signed before enrollment?				
Subsequent, applicable consent form(s) signed?				
CRFs reviewed?				
Source documents reviewed?				
Was the data collected verifiable?				
Were there any inconsistencies noted in reviews?				
Are CRFs completed properly and on a timely basis?				
Are CRFs legible, accurate and complete?				
Are other worksheets legible, accurate, and complete?				
Are the CRF Binders accurate and complete for each patient?				
CRF problems discussed with staff?				
CRF corrections made?				
Were proper CRF correction procedures followed?				
Subject eligibility confirmed?				
Subject enrollment log up-to-date?				
Recruitment on schedule?				
Did subjects have required lab work, etc?				
Were any significant laboratory abnormalities discovered?				
Is follow-up current and properly recorded?				
Are dropouts/withdrawn subjects documented?				

Have adverse events been adequately documented?				
Have there been protocol deviations since last visit?				
Do site records match up with sponsor records?				
Completed CRFs collected?				
Investigational Product Accountability	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Are product storage facilities adequate, secure?				
Did the location of product storage change since the last visit?				
Product forms complete and up to date?				
Product inventory checked and counted?				
Is the site product accountability log complete and up to date?				
Are the patient product accountability log(s) accurate and complete?				
Study supplies adequate?				
REVIEW OF SITE REGULATORY BINDER	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Protocol – IRB approved				
Signed protocol signature page				
Current investigator brochure or packet inserts				
IRB-approved amendments signed & dated				
IRB-approved consent(s)				
IRB letters of approval				
IRB Annual Report				
IRB Annual Re-approval letter(s)				
Safety Updates/Reports submitted to IRB				
IRB Approved Patient Advertisement/Recruitment Tools				
IRB correspondence – Annual, SAEs				
IRB composition				
Signed and completed FDA 1572				
Signed and completed revised FDA 1572				
CVs for PI and sub-investigators				
CVs for Key site research personnel, e.g. Lab Director				
Medical Licenses for all Investigator(s) and sub-investigator(s)				
Financial disclosure forms for investigators				
Shipping records for investigational products and accountability records				
Agreements/contracts -executed				
Agreements/contracts amendments - executed				
Lab certifications (licenses and accreditation)				
Lab normal ranges				
Screening & Enrollment Log				
Signature Participant Log/Delegation of Responsibility Log				
Study Monitor Visit Log current				
Telephone Logs current				
All pertinent correspondence				

INVESTIGATOR/MONITORING MEETING	YES	NO	N/A	ACTION ITEMS/ISSUES/COMMENTS
Reviewed all significant findings?				
Reviewed any unresolved issues and corrected items from previous visits?				
Discussed results of visits and action items with investigator and staff?				
Findings provided to the site in writing?				
Appointment made for next visit?				
Overall Review of Study Status	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Is maintenance of records complete?				
Is site in compliance with protocol and IRB?				
Are subjects accruing within timelines?				
Is additional clinical/technical training required?				

*Subject Verification and CRF Review
If all subjects cannot be reviewed, select a statistically valid number of subjects for complete review. List selected CRFs by subject's identification code below. List inconsistencies in table and discuss in the appropriate comment section.

_____ _____ _____ _____ _____ _____ _____ _____ _____

SUMMARY OF FINDINGS:

Finding	Action Item	Resolved Yes	Resolved No

SUMMARY:

Recommendations of Monitor

☐ No action needed – study conduct is compliant with regulations, protocol and IRB requirements

☐ No action required, but visit site again in _____ weeks to ensure corrections have been made

☐ Action required: Investigator is noncompliant, schedule review meeting

☐ Action required: Terminate study at site

Monitor Signature and Date:

Recommendations of Principal Investigator and/or President and CEO

☐ I agree with the recommendations of the monitor

☐ I do not agree with the recommendations of the monitor
Reason:

Principal Investigator and/or President and CEO Signature and Date:

Cc: PI (with original CRFs), Site, Georgia CORE regulatory files

Attachment B

SCREENING AND ENROLLMENT LOG TEMPLATE

Protocol:	Investigator: Site Name: Site Number:

Screening Number	Patient Initials	Patient Date of Birth	Date Screened	Date of Informed Consent	Date of HIPAA	Patient Number (if enrolled)	Date of Enrollment	Screening Failure Yes/No

Attachment C

SUBJECT ELIGIBILITY CRITERIA FORM

Protocol Name/Number: _____		
Investigator Name: _____	**Phone:** _____	**Site:** _____
Patient ID: _____	**Patient Initials:** _____	**Gender:** _____
Eligible: Yes ☐ **No** ☐ **(See Instructions Below)** **If not eligible, provide reason:** _____		
Screened by: _____ **Signature:** _____ **Date:** _____		

INCLUSION CRITERIA **(To be eligible, all must be answered Yes)**	**Yes**	**No**
1.	☐	☐
2.	☐	☐
3.	☐	☐
Etc.	☐	☐

EXCLUSION CRITERIA ***(To be eligible, all must be answered No)***	**Yes**	**No**
1.	☐	☐
2.	☐	☐
3.	☐	☐
Etc.	☐	☐

Review by Investigator:_____

Signature: _____ Date: _____

INSTRUCTIONS

Include the dates of any test results addressed in the criteria.

If the Investigator or designee determines the participant meets the protocol eligibility criteria, he/she must mark 'Yes" in the section marked "Eligible" at the top of the form, and complete the "Screened by" section.

If the Investigator or designee determines the participant does not meet the protocol eligibility criteria, he/she must mark 'No" in the section marked "Eligible" at the top of the form, document the reason for ineligibility, and complete the "Screened by" section.

If a designee completed the Participant Eligibility Checklist and made the eligibility determination, the Checklist and final determination must be reviewed and approved by the Investigator.

Attachment D

INVESTIGATOR COMPLIANCE MEETING SUMMARY AND ACTION ITEMS

Investigator
Date(s) of noncompliance

Protocol #
Date of meeting

Reviewers
Name

Title

_____ _____
_____ _____
_____ _____

Information Reviewed

_____ Monitoring Visit Checklist and Report(s) dated _____
_____ Case Report Forms
_____ Other _____

Specific Noncompliance

Comment/Discussion

_____ Failure to report serious or life-threatening AEs

_____ Serious protocol violations

_____ Repeated or deliberate failure to obtain adequate informed consent

_____ Falsification of study safety data

_____ Failure to obtain IRB approval before
- _____ Initiating study procedures
- _____ Initiating significant protocol changes

_____ Failure to adequately supervise the trial such that subjects are or may be exposed to unreasonable and significant risk of illness or injury

_____ Repeated or deliberate failure to:
- _____ Limit use of the study article to subjects who are under the investigator's supervision
- _____ Comply with conditions placed on the study by the IRB, Sponsor or FDA
- _____ Follow the investigator statement or protocol
- _____ Maintain accurate study records
- _____ Falsification or concealment of study records

_____ Repeated or deliberate failure to adequately supervise the trial to a degree that subjects may be exposed to an unreasonable significant risk

Findings

_____ Is noncompliant ____No ____Yes
Investigator Name

The compliance is _____Not Serious _____Serious

Action(s) (Check all that apply)

_____ Secure compliance by: _____ Retraining _____ Increased Monitoring

_____ Conduct audit within _____ days/weeks

_____ Suspend study at site as of _____

_____ Discontinue shipment of product as of _____

_____ Terminate study at site as of _____ and notify FDA by _____

Completed by

_____ _____
Signature Date

Reviewed by Georgia CORE President and CEO

_____ I agree with the recommendations of this determination

_____ I do not agree with the recommendations of this determination.

Reason:
_____
_____
_____

_____ _____
Signature Date