Study Management
SM – 305.00

STANDARD OPERATING PROCEDURE FOR
Closeout Visits

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I. INTRODUCTION AND PURPOSE

This standard operating procedure (SOP) describes the processes followed by Georgia CORE when conducting site visits at the conclusion of a study. Georgia CORE is responsible for final review and determination that the Investigator's obligations have been met and all applicable study and regulatory requirements have been fulfilled.

Closeout visits are conducted to:

- Review all regulatory files for completeness
- Complete the verification of all data in case report forms (CRFs) with source documentation
- Meet with the research team to discuss the:
    - results of the final audit of the regulatory files
    - results of the final source data verification
    - reconciliation of the study drug shipment and receipt records with drug accountability records
    - disposition of the investigational product and other ancillary items
    - possibility of a industry, sponsor and/or FDA audit
    - requirements for records retention and study reporting requirements.

2. SCOPE

This SOP applies to the Georgia CORE procedures for conducting closeout 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. It describes the steps followed by Georgia CORE from the time the monitor schedules the closeout visit until all follow-up activities associated with the visit have been completed. For the purposes of this SOP, the term 'Investigator' includes both Investigators and Subinvestigators.

3. Applicable Regulations and Guidelines

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
January 1988	FDA Guidelines for the Monitoring of Clinical Investigations
May 1997	International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline

4. REFERENCES TO OTHER APPLICABLE SOPs

GA-102	Sponsor Responsibility and Delegation of Responsibility
SS-204	Site Initiation Visit
SM-301	Communication
SM-302	Interactions with the IRB
SM-303	Documentation and Records Retention
SM-304	Routine Monitoring Visits
SM-307	Investigational Product Management
SM-308	Specimen Management
DM-401	Data Management
QA-601	Audits by Third Parties

5. ATTACHMENTS

A. Suspension Due to Inadequate Enrollment
B. Study Termination Due to Protocol Violations
C. Site Responsibilities Prior to Closeout Visit
D. Closeout Visit Checklist and Report

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 closeout visits.

7. DEFINITIONS

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

Audit: 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, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

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), good clinical practice (GCP), and the applicable regulatory requirement(s).

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).

8. PROCESS OVERVIEW

A. Scheduling and preparing for the closeout visit
B. Conducting the closeout visit
C. Conducting the closeout visit meeting
D. Following up after the closeout visit

9. PROCEDURES

A. Scheduling and preparing for the closeout visit

• Designee	Schedule a closeout visit for one of the following reasons: • The requirements of the protocol have been satisfied, the number of subjects that were specified for that site was enrolled, and the Investigator has followed the participants for the duration of time specified in the protocol and/or the last subject had concluded his/her participation. • The clinical site determines that they will not participate in the study any longer, and requests termination of the study agreement. The closeout visit will be scheduled when all follow-up on existing subjects has been completed or the subjects have been transferred to another clinical study site. • The study at the site is suspended when subject enrollment was insufficient or the terms of the protocol were not met. The closeout visit will be scheduled when all follow-up on existing subjects has been completed. (Attachment A Suspension Due to Inadequate Enrollment) • The study is terminated at the site before the designated time period if subjects are placed at unreasonable risk, if the terms of the clinical protocol are violated, or by FDA order. (Attachment B Study Termination Due to Protocol Violations) Also See SOP 304 Attachment D Investigator Compliance Meeting Summary and Action Items
	Review the previous monitoring reports, assess the scope of documentation required for review, and identify outstanding action items.
	Contact the investigator or designee regarding scheduling and conducting the closeout visit. Record discussions on the Telephone Contact Log. (Reference SOP 301 Attachment A)

	Confirm date and logistics of the closeout visit via e mail or in writing and provide the Investigator and research manager with the site responsibilities to be completed prior to the visit. (Attachment C Site Responsibilities Prior to Closeout Visit)

B. Conducting the closeout visit

• Designee	Complete routine monitoring visit, review regulatory documents and CRFs that have not been previously monitored.
	Review resolutions to any outstanding data queries.
	Collect all remaining CRFs and update any outstanding data corrections tabulations.
	Obtain an update from site research staff on any study-related issues.
	Review the Investigator's study files to ensure all study documentation is current and complete.
	Review signed Informed Consent forms for all subjects enrolled since the last monitoring visit and compare with the Investigator's subject enrollment records, as well as any screen failures, if required by the protocol.
	Reconcile and collect original Investigational Product Accountability records.
	Ensure that complete documentation is available in situations where the randomization code on any study drug was broken.
	Verify that all specimens for laboratory studies have been forwarded to the appropriate location per the protocol.
	Confirm that documentation exists of all prior visits by monitors and other authorized parties. (See SOP SS-204.00 Site Initiation Visit, Attachment D Site Visit Log)
	Ensure that any equipment loaned to the site for the study is returned appropriately.
	Complete the Closeout Visit Checklist and Report to document the closeout visit (Attachment D Closeout Visit Checklist and Report)

C. Conducting the closeout visit meeting

• Designee	Discuss the requirements for site follow-up of patients for serious adverse events after formal closure from the study.
	Review arrangements to have remaining unused investigational product and other study incidentals and accessories disposed of as specified in the protocol. Ensure that copies of accountability records are made and maintained by the site.
	Remind the site to inform the local IRB, if applicable, of the completion of the study and file the appropriate final report, if the site has not already done so. The IRB report format typically requires the following information:

	• Date study closed • Total subjects who signed the consent form • If there were any unanticipated problems involving risks to subjects or others at the site that were not previously reported to the central IRB • Any other pertinent comments about the study, including outcome results of the study, if known.
	If CRF data was entered into the computer by the site, discuss when hard copies of CRFs will be provided to the site. Review with the site staff the requirements for protecting the integrity of the electronic data. (Reference SOP DM401 Data Management and SOP PP 501 Safeguarding Protected Health Information)
	Discuss the requirements for maintaining clinical study documentation after the completion of the study for the period of time specified in applicable regulations and study agreement.
	Discuss any issues related to: • Final audit of regulatory files • Final source data verification • Study drug reconciliation • Requirements for data retention and storage.

D. Follow-up after the study closeout visit

• Designee	Forward all pertinent data and other information to the Investigator who initiated the study.
	If the study product and other related items were not disposed of according to the protocol by the time of the closeout visit, obtain documentation of the appropriate disposition as soon as possible.
	Inform the central IRB that the study is over and submit the final report. Ensure that sites using a local IRB have submitted their final report to the IRB with a copy to Georgia CORE. Georgia CORE and the sites will use their IRB report format which typically requires the following information: • Date study closed • Total subjects who signed the consent form • If there were any unanticipated problems involving risks to subjects or others at the site that were not previously reported to the central IRB • Any other pertinent comments about the study, including outcome results of the study, if known.
	After all data queries have been resolved, ensure Georgia CORE study files are complete. Arrange for transfer of study documents to secure storage, noting storage location in an appropriate file at Georgia CORE's headquarters.
	Send final letter to the Investigator stating that study has been closed out and all outstanding activities have been completed.

10. History of Changes

Version Number	Section Number	Modification	Approval Date
305.00	All	Original Version	
305.00	All	No change was necessary	09 March 2012
305.00	All	No change was necessary	01 July 2014
305.00	All	No change was necessary	21 March 2017

Attachment A

SUSPENSION DUE TO INADEQUATE ENROLLMENT

A study site may be suspended when subject enrollment has been insufficient and the terms of the protocol and agreement are not met.

Periodic assessments of enrollment by Georgia CORE and the Principal Investigator form the basis for decisions to suspend a protocol for inadequate enrollment. Georgia CORE and the Principal Investigator should determine whether site enrollment is appropriate and timely.

If enrollment is lagging, Georgia CORE and the Principal Investigator should ascertain possible remedies to restore the desired rate of enrollment (e.g. additional recruitment efforts).

If enrollment is not expected to reach optimum levels, Georgia CORE and the Principal Investigator must decide if the site should continue enrolling participants.

If continuing enrollment is determined not to be in the best interest of the study, Georgia CORE and the Principal Investigator may decide to suspend enrollment per terms defined in the agreement, and will confirm the decision in writing.

The monitor will schedule a closeout visit when all follow-up on existing subjects has been completed.

The Designee will report the suspension of the study to the IRB and other appropriate regulatory authorities.

Attachment B

STUDY TERMINATION DUE TO PROTOCOL VIOLATIONS

A clinical study will be terminated if subjects are placed at unreasonable risk, if the terms of the clinical protocol are violated, or by FDA order.

If the FDA orders Georgia CORE to terminate a study, Georgia CORE will immediately contact all participating network investigators and research managers to notify them of the termination.

If Georgia CORE or the Principal Investigator becomes aware of any circumstance that puts study subjects at unreasonable risk, Georgia CORE will proceed to terminate the study by contacting all participating network investigators and research managers and will apprise the central IRB of the action.

During routine monitoring visits, if Georgia CORE observes or otherwise discovers protocol violations, the monitor should document the findings and contact the Principal Investigator and Georgia CORE President and CEO immediately to present the findings.

Protocol violations may result in study subjects being put at risk or study data being rendered untrustworthy. Examples of protocol violations include:

- Enrollment of subjects in a manner not specified by the clinical protocol
- Failure to document appropriate use of the investigational product as specified in the protocol
- Reporting of inaccurate or fraudulent data as revealed during routine monitoring of source documents
- Failure to apply correct randomization procedures
- Failure to conduct and report on required follow-up assessments
- Failure to employ adequate stock control or ensure accountability for investigational products.

Georgia CORE and the Principal Investigator will ascertain whether the violation(s) is (are) isolated or represent an ongoing pattern of non-compliance.

Georgia CORE and the Principal Investigator will also ascertain the severity of the violation(s), to determine whether a warning or immediate termination is the appropriate action.

If the site is otherwise in compliance with the protocol and without a history of prior non-compliance, Georgia CORE should contact the network investigator and discuss the violation(s), issue a warning stating that no further violations will be permitted.

If a pattern of non-compliance is ascertained at the site, or if the violations are so severe that participants are at risk of injury, Georgia CORE will contact the network investigator and advise him/her that the study is being terminated with the date and the reason(s) for the termination.

The network investigator will be advised to cease enrolling subjects and report the study termination to the local IRB, if applicable, and any other appropriate internal and external regulatory authorities.

Georgia CORE and the Principal Investigator will create a plan of action for managing subjects already enrolled to assure appropriate transition off study (e.g., may need to taper off study agent or need other medical treatment, etc.)

Georgia CORE will confirm all verbal discussion with the network site investigator by follow-up letter via certified mail return receipt.

Subject enrollment is discontinued at the site but the closeout visit cannot occur until all enrolled study subjects have completed their specified follow-up visits and have completed their participation in the study.

The Designee will schedule a monitoring visit promptly to retrieve all unused investigational product and current study documentation.

The Designee will schedule a final closeout visit after all subject follow-up visits have been completed.

Attachment C

SITE RESPONSIBILITIES PRIOR TO CLOSEOUT VISIT

The following activities should be completed by the appropriate research site personnel prior to the closeout visit:

_____ All subjects must have completed all study visits.

_____ Review all case report forms (CRFs) and source documents to verify accuracy and completeness, including resolution of all data queries received to date or designation that such queries are unresolvable.

_____ Ensure that all regulatory documentation and CRFs not previously monitored are complete and available for review.

_____ Review the study and regulatory files and recover any missing documents or place an explanation in the file.

_____ Ensure that the appropriate patient medical records will be available for review at the time of the study closeout visit.

_____ Any instances of emergency breaking of the blind are appropriately documented.

_____ Collect all unused investigational products from all subjects.

_____ Inventory all used and unused investigational products.

_____ Dispose used and unused investigational products as specified in the protocol.

_____ File copies of the investigational product accountability forms, final inventory and product return documents in the study file.

_____ Ensure all other required reports are completed and sent to Georgia CORE, with copies in the study file.

_____ Collect information for Institutional Review Board (IRB) study closure, send a final report to the local IRB with a copy to Georgia CORE and the Principal Investigator, if applicable, or to Georgia CORE for submission to the central IRB and to the Principal Investigator and retain a file copy.

_____ Closeout letter received from local IRB, if applicable

_____ Ensure Georgia CORE copied on all local IRB correspondence, if applicable

_____ Return any equipment that was on loan for the study.

_____ Prepare study files for long-term storage.

Attachment D

CLOSEOUT 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:

☐ Closeout Visit

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?				
Was the study staff adequate in number/training for the study?				
Has the PI completed his/her obligations to the sponsor/IRB/FDA?				
Has the PI/study staff completed required study responsibilities?				
Has the Investigator been accessible during visits?				
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 CRF 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?				
Have all CRFs been collected?				
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**
Were product storage facilities adequate, secure during the study?				
Did the location of product storage change since the last visit?				

Product inventory checked and counted?				
Was study product inventory verified to Investigational Product Accountability Forms and CRFs?				
Is the site product accountability form accurate and complete?				
Are the patient product accountability log(s) accurate and complete?				
Was study product dispensed properly during the study?				
Was the study blind broken for any patients during the study?				
If yes, was it reported to the sponsor?				
If yes, was it documented?				
Was the study product returned as directed by the protocol?				
If yes, to whose attention was the study product returned to:				
If yes, what carrier was used for transport?				
Were study supplies stored adequately during the study?				
Were study supplies inventoried?				
Were unused study supplies appropriately disposed of/returned?				
REVIEW OF SITE REGULATORY BINDER	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Is the study binder accurate and complete?				
Were any critical documents retrieved at this visit?				
Final IRB Report?				
Other?				
Were any study documents retrieved at this visit?				
Monitor Log Sheet				
Site Signature Log				
Subject Screening/Enrollment Log				
Drug Accountability Log				
Subject Product Accountability Log				
GENERAL CONDUCT OF THE STUDY	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Was the protocol followed, with no significant deviations?				
Is the site in compliance with sponsor/FDA requirements?				
Are final IRB reporting requirements understood/complete?				
Have all previously unresolved issues been addressed?				
Was the patient enrollment rate acceptable?				
Was the overall progress/performance of the site acceptable?				
Were procedures in the event of contact by FDA discussed?				
Was retention of study records discussed?				
CRFs and study records will be stored:				

Who will be responsible for study related queries? Name, Phone and E-mail address				
WRAP-UP/INVESTIGATOR AND MONITOR MEETING	**YES**	**NO**	**N/A**	**ACTION ITEMS/ISSUES/COMMENTS**
Collected all CRFs and other data worksheets?				
Reconciled product accountability records?				
Review of findings conducted with Investigator and study staff?				
Was study specific review conducted with the Investigator and staff (procedures/forms, e.g. to notify IRB of completion)				
Was a Question and Answer session conducted?				
Was the Monitor Visit Log completed?				

*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:

_____ _____
Monitor's Name (please print) Signature
Date

_____ _____
Investigator's Name (please print) Signature
Date

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