1 PURPOSE

This procedure describes the activities performed during the monitoring of clinical study at investigative sites. In an investigator initiated study, the Principal Investigator is the sponsor, and is responsible for the oversight of the designated monitor. Externally sponsored studies are often overseen by contracted monitors who visit the site periodically throughout the study to ensure that the protocol is being adhered to, that the site is abiding by the appropriate regulations and that the data integrity and quality are preserved.

2 GENERAL INSTRUCTIONS AND RESPONSIBILITIES

a) The Investigator-Sponsor is responsible for ensuring that all investigator initiated clinical studies are monitored at appropriate intervals.

b) The Investigator-Sponsor is responsible for designating a trained and qualified individual to serve as the study Monitor.

c) The Monitor is responsible for preparing for, conducting and documenting periodic clinical site monitoring visits. The objectives of site monitoring are:

- Document and report on clinical study progress
- Document that the protocol and associated forms are correct and are being adhered to
- Update investigative site personnel of changes in study conduct/documentation
- Ensure that qualified subjects are enrolled into the study
- Ensure that Institutional/Sponsor requirements and obligations are being met
- Ensure continued acceptability of the Investigator and his/her key personnel and facility
- Ensure that informed consent has been appropriately obtained for all enrolled subjects
• Obtain and review current clinical data, reports, and source documents
• Ensure adequate investigational product inventory, management, and accountability
• Ensure that all regulatory requirements are being met
d) The Investigator and their study personnel are responsible for cooperating with the Monitor in all aspects of the monitoring visit including:
   • Providing access to medical records, patient study binders, regulatory files, investigational product accountability records
   • Allocating time during the visit to meet and discuss findings
   • Respond to any questions, queries or discrepancies found by the monitor

3. SPECIFIC PROCEDURES
3.1 Scheduling/Frequency of Visits
   a) The Sponsor will determine the number of anticipated monitoring visits for a particular clinical study, based on the complexity of the study design, phase of development, previous site experience, compliance with study requirements, rate of subject enrollment, and any other unique attributes of the study and the site.
   b) Monitoring visits will be conducted at each site throughout the clinical study, with the first occurring after enrollment commences or as specified in the study Data and Safety Monitoring Plan (when provided).
   c) The clinical protocol and/or associated study Data and Safety Monitoring Plan will outline the anticipated monitoring schedule; however, the number of visits may change as monitoring visit results dictate, to include additional scheduled and unscheduled monitoring visits.
   d) The Monitor will conduct monitoring visits, as needed, based on reports or evidence of potential non-compliance with the protocol, other concerns about the proper conduct of the study and subject safety, and any other Sponsor/regulatory requirements, which may have been noted during the prior scheduled visit or received from any other source, including employees at the site.
   e) Monitoring visits may also be added due to significant increases in subject enrollment rates, and changes in the protocol or key study personnel.
   f) The Sponsor or designated Monitor will contact the Investigator at each study site regarding scheduling and conducting upcoming monitoring study visits.
   g) The Monitor will confirm the 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.) that will be reviewed during the monitoring visit.

3.2 Preparing for a Monitoring Visit
   The Monitor should:
   a) Review the relevant contents of the study and site files in the Regulatory Master File (RMF) prior to the monitoring visit (where possible).
b) Review previous Monitor's Reports for any outstanding items that must be addressed during the next scheduled visit.

c) Note any questions and issues to be checked against source documents or other documents at the site.

d) Confirm with the site 1-2 days prior to the scheduled visit that they will be available and adequately prepared for the visit.

3.3 Conducting a Monitoring Visit

3.3.1 General Monitoring Instructions

a) The Monitor will document the monitoring visit by signing a Site Visit Log at the investigative site (See SOP 401 Attachment B). The original document should be kept in the Trial Master File/Regulatory Binder.

b) The Monitor will assess whether the key study personnel and facilities continue to be acceptable for the study and that the site's Investigator is appropriately involved in the conduct of the study.

c) The Monitor will review the contents of the site's study files to ensure that all required documents are on file and current, and that the Investigator routinely completes files and forwards essential and required information to other required parties appropriately (i.e. Institutional Review Board (IRB), Contract Research Organization (CRO)).

d) The Monitor will review any study conduct issues or incidents of non-compliance with the site's Investigator and other key study personnel and document the issues on the Monitoring Visit Report.

e) If necessary, the Monitor will remind the site's Investigator of the obligation to immediately record and report serious adverse events, other unanticipated problems involving risks to subjects or others, and protocol deviations, to the IRB, other appropriate regulatory authorities, and the Sponsor, and provide follow-up reports of the final outcome.

f) The Monitor must confirm that all informed consent forms and HIPAA authorizations have been appropriately obtained and documented for all subjects, and that informed consent was obtained before any protocol-related procedures were conducted (except those specified in the clinical protocol).

g) The Monitor will document all findings during the monitoring visit on a Monitoring Visit Report (may use Attachment A as a reference/guide when none has been provided by the sponsor) and provide a post-visit letter to the Investigator and appropriate members of the research within 2-3 weeks of the visit.

3.3.2 Case Report Form and Source Document Monitoring

a) The Monitor will compare subject case report forms (CRFs) with the source documents to ensure protocol compliance and that data are accurate. Elements of the CRF and source document verification by the Monitor will include:
- Verification that the CRFs are being completed in a timely manner and according to protocol requirements by inspecting CRF pages for completeness, accuracy, and internal consistency
- Review of key efficacy and safety parameters routinely for all subjects including primary and secondary endpoints
- Review of inclusion and exclusion criteria and study events routinely for all subjects
- Track IP accountability, dispensation, storage and destruction for accuracy
- Review of subject Screening and Enrollment Logs and Subject Eligibility Checklists to ensure they have been signed and dated by the Investigator, Study Coordinator, Nurse Manager or qualified designee (See SOP 603 Attachments A & B)

b) 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 apparently aberrant entry was verified.

c) The Monitor will immediately notify the Investigator or designee of discrepancies and improper completion of CRFs. Unresolved discrepancies will be documented and followed up.

d) The following information must be included in the case history (basic medical record or hospital chart) for each subject: 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.

e) The Monitor will remind the Investigator that all records and reports pertaining to the study must be retained at the study site as required by the Investigator and applicable regulatory requirements.

f) The Monitor will remind the Investigator to provide all updated information pertaining to the study including changes in key personnel to the Sponsor and IRB on a timely basis.

3.3.3 Inventory and Storage Monitoring

a) The Monitor will ensure that the Investigational product accountability and reconciliation obligations are being followed, and verify all investigational products’ expiration dates.

b) The Monitor will examine storage, refrigeration, freezers, and other equipment to confirm they are appropriate for the clinical protocol’s requirements and that calibration and temperature logs are maintained in the site’s study file. Any excursions should be promptly reported to the sponsor and IRB.

c) The Monitor will 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.
3.3.4 Specimen and Laboratory Monitoring

a) The Monitor will verify that all specimens for protocol-specific laboratory studies are being stored and/or shipped properly and that specimen preparation documentation is maintained.

b) The Monitor will inspect specimen storage equipment as noted above in Section 3.3.3 (b).

c) If laboratories are being used for any part of the study that are not licensed or certified by an established licensing or certificating body, those laboratories must be audited to ensure consistency and reproducibility of the testing being conducted at the laboratory (Reference SOP 106 Vendor Selection).

3.3.5 Concluding the Monitoring Visit

a) Upon concluding the monitoring visit, the Monitor will report any significant unresolved problems or protocol violations immediately to the Investigator, who may confer with the OHR regarding those findings.

b) At the end of the monitoring visit, the Monitor should meet with the site Principal Investigator, and appropriate research staff to review any monitoring findings and discuss management of such findings as applicable. If an in-person visit cannot be arranged due to scheduling conflicts, then a teleconference should be scheduled to discuss the findings. This should be followed up with a post-visit letter to the PI and research team documenting what was reviewed, and the discrepancies noted, and what action items are pending.

c) The designated site personnel should respond to the monitoring visit letter (whether externally monitored by a contract CCRA or internally reviewed by the Compliance and Monitoring Officer) within 1 month of receipt, or prior to the next monitoring visit, if possible.

4 REFERENCES TO OTHER APPLICABLE SOPS

- 106 Vendor Selection
- 301 Clinical Protocol Development, Implementation, and Compliance
- 502 Investigational Product Inventory Management
- 601 Informed Consent
- 603 Subject Screening and Enrollment
- 604 Specimen Management
- 605 Adverse Event Recognition and Reporting
- 702 Clinical Research Data Management

5 ATTACHMENTS

A. Monitoring Visit Report
6 APPLICABLE REGULATIONS AND GUIDELINES

- Review of Ongoing Investigations (21 CFR 312.56)
- Monitoring Investigations (21 CFR 812.46)
- Investigator’s Qualifications and Agreement (ICH E6, Section 4.1)
- Trial Management, Data Handling, and Record Keeping (ICH E6, Section 5.5)
- Monitoring (ICH E6, Section 5.18)