

# Clinical Monitoring Plan Template

## Instructions: Not applicable sections will be removed at the time of the creation of this monitoring plan

## Tool Revision History:

| **Version Number** | **Version Date** | **Summary of Revisions Made:** |
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| 1.0 | 14Aug2023 | Initial |
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|  |  |  |

**OVPRI**

**Clinical Monitoring Plan**

**Protocol No.:** <protocol number>

“<protocol title>”

By signing below, I acknowledge my agreement to this plan.

Principal Investigator

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_

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# LIST OF ABBREVIATIONS

AE Adverse Event

CFR Code of Federal Regulations

CMP Clinical monitoring Plan

COV Close-Out Visit

CRF Case Report Form

OVPRI Clinical Research Operations Management and Support

CSOC Clinical Study Oversight Committee

DCF Data Correction Form

DSMB Data Safety monitoring Board

eCRF Electronic Case Report Form

EDC Electronic Data Capture

ED Essential Documents

FDA Food and Drug Administration

GCP Good Clinical Practice

ICH International Conference on Harmonization

IDS Investigational Drug Service

IMV Interim monitoring Visit

IRB Institutional Review Board

ISF Investigator Site File

MOP Manual of Procedures

OVPRI Office of the Vice President for Research & Innovation

PI Principal Investigator

SAE Serious Adverse Event

SC Study Coordinator

SIV Site Initiation Visit

SOP Standard Operating Procedures

TMF Trial Master File

UP Unanticipated Problem

# INTRODUCTION

The Clinical Monitoring Plan (CMP) establishes the guidelines for conducting monitoring visits and related tasks for monitoring Virginia Commonwealth (VCU) Protocol <protocol number, protocol title>. The CMP was developed by the Regulatory Affairs & Clinical Operations Management (OVPRI) group, in collaboration with the Principal Investigator (PI). OVPRI Administrators and Clinical Research Associate(s) (monitor(s)) will perform monitoring tasks in accordance with the protocol specific requirements, Title 45, Part 46 of the Code of Federal Regulations (CFR), the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines (GCP), the Code of Federal Regulations Part 312, 812, and other applicable requirements.

# MONITORING COMMUNICATION PLAN

### Email Distribution

The OVPRI designee will send monitoring communications to include: site visit confirmation letters, agendas, follow-up letters, and action item trackers to the following:

**Program Contacts**

| **Representative** | **Role** |
| --- | --- |
| **Study Program** | |
|  | Principal Investigator |
|  | Study Contact |
| **Study Sites** | |
|  | Site PI |
|  | Primary Site Contact |
| **VCU-PROGRAM** | |
|  | Program Official |
|  | Medical monitor |
|  | Health Specialist |
| **VCU-OVPRI** | |
|  | FDA program administrator |
|  |  |
| **OVPRI** | |
|  |  |
|  |  |

**Site Contacts:**

| **Representative** | **Role** |
| --- | --- |
| ***<Insert Site Name>*** | |
|  | Site PI |
|  | Primary Site Contact |
| ***<Insert Site Name>*** | |
|  | Site PI |
|  | Primary Site Contact |
| ***<Insert Site Name>*** | |
|  | Site PI |
|  | Primary Site Contact |
| ***<Insert Site Name>*** | |
|  | Site PI |
|  | Primary Site Contact |
| ***<Insert Site Name>*** | |
|  | Site PI |
|  | Primary Site Contact |

#### Monitoring Communications

Final versions of agendas, confirmation and follow-up letters, action item trackers, and <insert other study specific items associated with monitoring visits> will be emailed to the study team

# VISIT SCHEDULING

The OVPRI designee will work with the Site Principal Investigator (PI) and Site Primary Contact to schedule monitoring visits. The Study (Grant) PI and OVPRI will be apprised of visit scheduling. The study monitor will work with the PI to assure the reported trial data are accurate, complete, and verifiable.[[1]](#footnote-1)

Visit scheduling will be determined by OVPRI using a Risk-Based monitoring Score. Modern trial monitoring frequency is focused on protecting patient safety and data integrity through Risk-Based monitoring. Factors which affect the risk score include but are not limited to: protocol complexity, enrollment, protocol, population (e.g., gravid patients), lab history of FDA warning letter, and etc.

### Low Intensity Monitoring

Examples of studies requiring low intensity monitoring include: 1) healthy volunteers using well-described research procedures and / or single dose administration; 2) post-marketing studies, phase IV drug or device studies with minor safety concerns; 3) studies where the interventions or invasive procedures present a low risk that are reasonably commensurate with standard of care medical or dental practice.

### Moderate Intensity Monitoring

Examples of studies requiring medium intensity monitoring include: 1) healthy volunteers using multiple dose administration; 2) phase I-III drug or device studies with modest safety concerns; 3) studies where the interventions or invasive procedures present a moderate risk that exceeds the risk commensurate with standard of care medical or dental practice.

### High Intensity Monitoring

Examples of studies requiring high intensity monitoring include: 1) acute care patients receiving treatments that present risks greater than that of the standard of care (SOC) treatment; 2) first-in-human (FIH) studies with a new drug from a new drug class; 3) phase I or II drug or device studies with major safety concerns; 4) studies where the interventions or invasive procedures present risks that are not commensurate with standard of care medical or dental practice; 5) studies where the intervention is a new small molecule, and 6) studies where the interventions or invasive procedures triggered a prior hold letter for serious unexpected adverse events.

Prior to the visit, the PI will receive a visit confirmation letter, agenda and a list of participants to be monitored. Please see Section 7.2 for details on the selection of participant files for review. The monitor will ensure that this information is communicated to the site personnel within a mutually agreed upon timeframe to allow sufficient time for record requests. The PI and research staff will be expected to secure workspace for the monitor(s) and to be available during the visits to facilitate monitoring activities. The monitor will be available at the end of each monitoring visit day to discuss findings and answer questions from the study staff. The Site PI and Primary Site Contact are also expected to be available for a wrap-up meeting at the conclusion of the visit, as schedules allow. These expectations will be explained in the visit confirmation letter.

# ESSENTIAL DOCUMENTS/TRIAL MASTER FILE

### Required Essential Documents

A binder(s), which for purposes of this clinical monitoring plan will be defined as the investigator site file (ISF), will be maintained at the trial site and serves as the central source for essential document (ED) maintenance at the site.

#### A combination of paper and/or electronic files?

EDs for this trial will be maintained by each study site as a combination of paper and electronic documents. The contents of the ISF will include:

* Essential documents maintained in paper form
* Essential documents maintained electronically at the site will have a page referencing the electronically maintained location of the ED. Note: The site may elect to file a paper copy of the electronically maintained document in the ISF

E6(R2)[[2]](#footnote-2) sets forth documents that represent a complete site essential document packet and are to be maintained in the ISF.

### Trial Master File (TMF)

TMF will be held by the site.

The PI maintains the TMF during the study, and if the study is single site, originals of above referenced documents and any other necessary study documentation will be maintained at the site, i.e., the TMF will be held by the site.

### Monitor’s Role in Essential Document Maintenance

During the course of routine monitoring visits, the OVPRI monitor will review for accuracy and completeness, the ISF and all associated documents as noted in section 5.1.

As noted in section 5.2, the PI’s team is tasked with maintenance of the TMF. The OVPRI designee will support this endeavor by:

The monitor will alert the study staff to discrepancies and upcoming expiration dates.

# Monitoring REPORTS / ACTION ITEMS

Monitoring visit findings and resulting action items will be documented in reports. OVPRI will send drafts of the reports to OVPRI within 14 calendar days of the last day of the monitoring visit. A brief teleconference may be scheduled to allow the team to resolve identified findings/comments prior to the final, signed report issuing.

Once the visit documents are finalized, documents will be made available to identified study team members. These documents should be printed and stored (or electronically stored) in the ISF. Ideally, documents will be provided to the site in approximately 21 calendar days of visit conclusion.

An OVPRI designee will work with designated site staff to resolve any outstanding action items as communicated in the Action Item Tracker presented as an attachment. At a mutually agreed upon time, or at the next visit, the OVPRI designee and site research staff designee will meet via telephone conference to discuss resolved, in process, and pending Action Items. At this time the need for, and frequency of subsequent meetings will be discussed.

# TYPES OF VISITS AND Monitoring ACTIVITIES

OVPRI will conduct several types of monitoring visits and reports. For the ease and convenience of investigators, the results of monitoring reports will also be summarized in the trial monitoring dashboard.

* A Site Initiation Visit (SIV) will be conducted prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training prior to the assigned Program Official activating the site for enrollment.
* Interim monitoring Visits (IMVs) will be conducted to confirm participants’ rights, safety, and welfare are being protected, the study is being conducted according to the protocol and applicable regulations, including GCP, confirm accurate reporting of participant safety data and study endpoints.
* For-cause visits (FCVs) are conducted to address any unanticipated issues that arise which require training, remediation or other situations in which the site requires assistance. For-cause visits can be mandated by OVPRI, its designees, or can be requested by the site.
* A Close-Out Visit (COV) will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. The types of activities that may be conducted at each onsite visit are described in detail below.

### Site Initiation Visit Activities

The site initiation visit (SIV) will be conducted prior to participant enrollment. The following activities may be conducted during the SIV.

#### Site Investigator and Site Responsibilities

* Verify that the PI understands and accepts the responsibility to obtain and maintain IRB approval of any amended protocols, consent documents, or advertisements. Verify that the PI is willing to shoulder the responsibility of ensuring continuing review of this study by the IRB.
* Verify that the PI understands and accepts responsibility for overseeing the conduct of the study in accordance with the protocol, applicable regulations and GCP, as well as ensuring the conduct of all staff performing study procedures.

#### Review of Facilities

* The OVPRI monitor will hold responsibility for the agenda, leadership and facilitation of the SIV.
* Tour of site facilities where study activities will be conducted, including but not limited to: consent discussions, participant visits, laboratory specimen collection, processing, and storage, records and ISF management, and monitoring workspace.
* Verify presence of study-required equipment, including but not limited to:

1. <list protocol specific study-required equipment>
2. EKG;
3. Blood pressure;
4. Centrifuge;
5. Fridge;
6. Freezer; and
7. Temp logger.

##### Protocol Review

* Review study objectives, study design, and study population.
* Review study inclusion/exclusion criteria.
* Review participant randomization.
* Review the study schedule of events and sample collection.
* Review protocol required clinical and laboratory assessments.
* Review responsibility to review, sign, and follow-up on laboratory reports.
* Review guidelines for premature discontinuation of study participants.

##### Informed Consent Process

* Discuss the site’s informed consent procedures.
* Verify that the PI understands and accepts the responsibility to obtain informed consent in accordance with all applicable regulations and to document the informed consent process for each participant.[[3]](#footnote-3)
* Run the ICF checklist and ensure the 8 required statutory elements are present.

##### Manual of Procedures (MOP) / Standard Operating Procedures (SOP)

* Review to ensure understanding of the necessity of standardization of protocol execution across all relevant study team members.
* In the absence of a MOP, review the applicable site SOPs.

##### Study Documentation

* Review the document retention requirement for all study-related records. Inform the PI that all study records must be retained at least 2 years (per FDA) and possibly as long as 10 years for IVD, and 15 years for implantable devices (per EU regulatory requirements).[[4]](#footnote-4)
* Verify that the PI understands that he/she is responsible for retaining all study records and making them available for monitoring and audits during the conduct of the study and throughout the retention period.

##### Investigator Site File

* Sign and date the site visit log each day of the visit.
* Verify that all study documents are present in the ISF and make the PI and site personnel aware of their responsibility to keep the file complete and current.
* Verify that the Delegation of Responsibilities Log is current and signed by the PI.
* Verify training log dates are internally consistent with start dates and DOAL delegation dates.

##### IP records in Vestigo IDS

* Obtain study-specific Vestigo access ahead of the visit date by requesting at: [support@vestigo.biz](mailto:support@vestigo.biz).
* Review investigational product accountability records in Vestigo and date the site visit log each day of the visit.

##### Electronic Case Report Form (eCRF) Review and Laboratory Tracking Training

* Review and provide training on the use of the electronic data capture system and the specimen management and tracking system for the study.

##### Safety Reporting

* Review adverse event (AE), serious adverse event (SAE), and unanticipated problems (UP) definitions, grading, attribution, reporting, and review.
* Review requirements for IRB and Office for Human Research Protections (OHRP) notification of UPs, AEs, and SAEs.

##### Review Source Documentation Requirements and eCRF Completion.

* Review requirements for maintaining adequate source documentation that supports the data recorded in the eCRFs.
* Review and provide instruction for eCRF completion.
* Ensure that the PI and site personnel are aware of eCRF correction and data clarification requirements.

##### Review Laboratory Supplies and Procedures

* Verify that the site has adequate supplies available.
* Verify that the site has on the fly ordering.
* Review collection, handling, storage, and transport procedures for laboratory samples. Samples collected for this study include: <insert list of samples to be collected, i.e., clinical samples, DNA, future use, etc.,<

##### Discussion of General Items

* Obtain documentation of all site personnel present for the SIV on the SIV Training Log.
* Ensure that all required supplies/clinical trial materials (e.g., CRFs, MOP, ISF) have been received by the clinical study site prior to screening or enrolling the first study participant.
* Discuss the expected schedule of monitoring visits with site personnel, including the timing of the first monitoring visit, personnel availability, and monitoring space availability.
* Initiate discussion of site close-out procedures. Study close-out procedures will be discussed in further detail during IMVs.
* Review the findings and action items of the visit with the PI and appropriate site personnel.

### Interim Monitoring Visit Activities

The following activities may take place at the first site visit:

During the first visit at each study site, in addition to performing IMV associated tasks, the monitor will confirm operational and facility related items as discussed in site assessment calls and previous communication with the study staff.

Items for confirmation may include:

1. Roles and Responsibilities for site personnel

* Communication between team members
* Appropriate delegation of study tasks to qualified team members

1. Site record keeping

* ISF
* Participant source documentation

1. Protocol submissions, deviations and associated regulatory reporting
2. Safety Reporting

* Process
* Safety Reports to date

1. Data collection methods

* Case Report Forms
* Entry
* Query resolution
* Interaction with the DCC

1. Facilities appropriate to study execution

* Office set up appropriate to GCP and patient privacy
* Adequate facilities for study supply storage, sample processing, availability to necessary technology for data entry

1. Enrollment: target, current, recruitment strategies

At the conclusion of the visit, or after review of the above, (to include site files) the OVPRI monitor will meet with the Site PI and Site Study Coordinator (SC) to determine a monitoring strategy for future visits. This strategy will include the type of data to be monitored, an anticipated standard percentage of data to be monitored, as well as any other administrative or study support items for which the site may be delinquent. The first IMV report will include in the overall comment section a bullet point outline of the strategy to be implemented. This strategy may be modified or updated as needed or requested by OVPRI, or the site.

Frequency of future IMVs will be based on the developed monitoring strategy taking into consideration: enrollment status, data quality, protocol compliance, GCP compliance, and the prescribed amount of data to be monitored according to the monitoring plan. Irrespective of other factors, the site will be monitored at least twice per year.

At a minimum the following participant data will be included in the monitoring strategy to be monitored at each visit:

The first IMV will be conducted at each site approximately 4 weeks after the first dosing or implantation, subsequent visits will be conducted after approximately every >>6-8, 8-12, 26, weeks<<. The frequency of future IMVs will be based on enrollment status, data quality, protocol compliance, the prescribed amount of data to be monitored according to the monitoring plan, and rolling recalculation of the risk score.

At a minimum the following participant data will be monitored at each visit:

* 100% review of consent documents for all participants consented or re-consented since the last onsite visit
* 100% of SAEs
* 100% of study files for <10%, 30%> of participants enrolled at the site overall. The OVPRI will randomly select participant files for review at each interim visit. Once selected, these participants will be monitored through the entirety of their participation in the study.
* 100% of participants dosed since last onsite visit
* 100% of key variable CRF pages noted below for unmonitored participants:
  + For medium to high-risk studies, CRF pages for the primary and secondary endpoints will be monitored for all patients.

All data for all monitored participants will be monitored over the course of the trial, but not necessarily at each visit. The participants selected for monitoring and the extent of record review at each visit will be based on the progress of enrollment, as well as any concerns that may emerge about the safety of human participants or the integrity of study data.

While follow-up data will be monitored for all participants, the amount and frequency of follow-up data monitored at each visit will vary based on time and resources.

Findings of the monitor that might indicate lack of understanding of protocol requirements, deviation from GCP (for example: inadequate attention to protection of human participants), unreported or underreported safety information or other non-compliance may result in an increase in the percentage of participant data monitored or monitoring visit frequency. Targeted learning modules may be implemented through the learning management system (LMS).

The following activities may be conducted at each IMV:

1. Consent Document Review for All Participants

* Verify consent was obtained prior to initiating study procedures.
* Verify appropriate signatures and dates were obtained.
* Verify that the correct version of the consent document was signed and dated.
* Verify that ongoing participants were re-consented with updated consent documents as directed by the IRB.
* Verify that source documentation includes a description of the consent process.

1. Source Documentation and CRF Review

* Verify that accurate, complete, and current source documentation is maintained.
* Verify participant eligibility.
* Verify that all procedures outlined in the protocol were completed.
* Verify that missed visits, clinical procedures, and tests are recorded appropriately and reported to the IRB as protocol deviations, as defined by IRB policy.
* Verify that the PI assessed all abnormal lab values for clinical significance.
* Verify that all withdrawals and dropouts of enrolled participants are recorded in the source documentation and on the CRF.
* Verify that AEs, SAEs, UPs, and concomitant medications are documented and reported according to the protocol.
* Ensure that the PI has reviewed, signed, and dated all required CRF pages <specify for paper-based studies, wet ink signature, or electronically signed all necessary electronic Case Report Forms (eCRF) pages (for Electronic Data Capture (EDC) systems)>.
* Verify data entries in the CRF pages with the source documentation, and note any errors, omissions, or discrepancies by issuing manual queries <insert form or system as appropriate (e.g., on Data Correction Forms (DCF); within the EDC system), and revise other bullets/text accordingly.>
* Work with site staff to resolve queries while on-site and request the resolution of any remaining queries that cannot be resolved during the visit.
* Provide the site staff with copies of DCFs
* Verify that previously outstanding data queries have been resolved, signed, <wet ink signature for paper studies, remove if EDC> and dated by the PI or designee.

1. Unanticipated Problems, Adverse Events, and Serious Adverse Events

* Follow-up on previously reported UPs, AEs, and SAEs.
* Verify all newly reported UPs, AEs, and SAEs against source documentation.
* Confirm that all UPs, AEs, and SAEs have been reported to the IRB, Office of Biological Agents (OBA), and Food Drug Administration (FDA) as required.
* Identify any unreported UPs, AEs, and SAEs in source documentation.
* Review UP, AE, and SAE reporting procedures, as necessary.

1. Investigational Product

* Confirm that investigational product is stored at the correct temperature in a secure storage area.
* Review temperature logs to confirm stability of storage conditions.
* Confirm that investigational product is being dispensed according to protocol.
* Confirm that product accountability records are accurate, current, and reconciled.

1. Laboratory and Specimen Management

* Assess maintenance of research specimen logs and associated documentation.
* Review handling of laboratory specimens.
* Review specimen storage conditions and maintenance of temperature logs.
* Ensure organization and storage of specimens in a secure location.
* Ensure appropriate specimen labeling.

1. Protocol Deviations

* Verify that all protocol deviations are documented appropriately in each participant’s research record and on the appropriate protocol deviation form.
* Ensure that the site has reported all protocol deviations to the IRB, as defined by IRB policy.
* Address any protocol deviations with site personnel during the IMV and identify ways to prevent the recurrence of similar issues.
* Protocol deviations will also be reviewed throughout the study with the PI during routine conference calls, which include OVPRI staff and the clinical site. Any trends or serious errors will be discussed, and the group will develop a plan of action to prevent further problems.

1. Quality Management (QM) Documentation

* Review site-generated quality management efforts and documentation.
* Review site-generated quality management reports, if utilized, to confirm the items identified by the study team have been addressed. The monitor may offer suggestions for additional quality control efforts or additional follow-up for the site to consider.

1. Investigator Site File

* Ensure that essential document files are complete and current.
* <Insert appropriate task for review and/or collection of ED based on section 5.0>

1. Investigator and Site Personnel Responsibilities

* Ensure that the Delegation of Responsibilities Log is complete and signed.
* Ensure that the Authorized Signature Log is complete and signed.
* Verify that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements and good clinical practice guidelines.
* Verify that study activities are being performed by the PI or have been delegated to personnel qualified by appropriate education or training.

Provide and document any necessary training for the PI and site personnel, such as training on good clinical practice guidelines and use of the data management and lab tracking system software.

1. Visit Conclusion

At the conclusion of the visit, the monitor will meet with the PI and site research staff to review visit findings and answer questions. The monitor will discuss the following topics at a minimum:

* Enrollment progress.
* Consent process and documentation.
* Study conduct and documentation of study activities.
* UPs, AEs, and SAEs experienced by study participants.
* Scheduling of the next IMV.

1. Action Plan for Identified Issues

The monitor will meet with the site SC and PI periodically during the visit to explain findings, ask questions, and work with the SC and PI to address issues at the time of the IMV. Issues identified and resolved at the IMV will be documented in the IMV report and associated follow-up letter. Additional actions that need to be taken by the site staff following the visit will be documented in the Action Item Tracker presented as an attachment to visit documentation. If the monitor encounters a serious issue related to patient safety, the monitor will evaluate an appropriate course of action.

### For-cause Visit Activities

During for-cause visits, the monitor may complete any of the activities listed for the IMV, discuss clinical operations and study management methods with the research staff, and/or provide training to the research staff.

### Close-out Visit Activities

Study closure activities may require more than one visit to ensure the proper closure of the study. These activities may be conducted during a series of on-site visits or by telephone. Close-out visits may be conducted at study completion or earlier in the case of study termination by the IRB, Data Safety monitoring Board (DSMB), OHRP, FDA, or Clinical Study Oversight Committee. The outcome of the visit and other close-out activities will be documented in a report and follow-up letter.

Monitors will perform the activities below during the study close-out process:

1. Consent Documents

* Confirm that consent was obtained for each participant prior to initiating study activities.
* Confirm that consents contain appropriate signatures and dates.
* Confirm that the correct version of the consent document was signed and dated.
* Confirm that additional consent was obtained for protocol amendments as required by the site’s IRB.

1. Investigator Site File

* Ensure that essential document files are complete and current.
* Identify any missing study documents.
* Ensure that the Authorized Signature and Delegation Logs are complete and signed by the PI.

1. Source Documentation and CRF Review

* Reconcile the final status of all participants listed on the screening log.
* Confirm that all required data fields have been verified against source.
* Confirm that all data queries have been resolved.
* Confirm that the PI has reviewed, signed, and dated all required CRF pages.
* Verify that the site has legible copies of all CRFs
* Confirm that protocol deviations are noted in the source documents.

1. Unanticipated Problems, Adverse Events, and Serious Adverse Events

* Confirm that all UPs, AEs, and SAEs have been reported to the appropriate regulatory agencies as required.
* Confirm that the site has and will continue to meet safety reporting requirements.
* Ensure that copies of SAE reports are filed with the corresponding site files.

1. Investigational Product

* Confirm that all investigational product accountability records have been maintained appropriately and are consistent with the amount of remaining product.
* Ensure that remaining IP will be destroyed per institutional requirements. Document proper destruction of any remaining product.

1. Laboratory Samples

* Confirm that all lab samples have either been analyzed or stored for future analyses.
* Confirm future use specimen disposition and labeling/de-identification, as appropriate.
* Confirm site process for identification and disposition of future use samples connected to participants who withdraw consent.

1. Regulatory Obligations

* Confirm that the PI has met and will continue to meet regulatory obligations.
* Confirm that the PI has provided written notification of study closure to the IRB and verify acknowledgement by the IRB of study closure.
* If the study was terminated prematurely, the monitor will confirm that enrolled participants were informed and that appropriate therapy and follow-up was initiated by the PI.
* Inform the PI of the possibility of future audits by regulatory authorities.

1. Records Retention

* For IND/IDE studies, review the document retention requirement for all study-related records: [21 CFR 312.57 (c)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.57), 45 CFR 46.115 (b), 45 CFR Part 74, as well as institutional and local IRB requirements; emphasizing that the more stringent retention policy should be followed.
* For IND/IDE studies, inform the PI that all study records and reports must be retained for 2 years after a market application approval for the drug, or until 2 years after shipment and delivery of drug for investigational use is discontinued and Food and Drug Administration (FDA) has been notified (21 CFR 312.57).
* HHS protection of human subjects’ regulations ([45 CFR 46.115](https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-A/section-46.115)) require institutions to retain records of IRB activities and certain other records for at least 3 years after completion of the research.
* 45 CFR Part 74 states that financial records, supporting documents, statistical records, and all other records pertinent to an award shall be retained for a period of 3 years from the date of submission of the final Federal Financial Report (FFR) to the HHS awarding agency (National Institutes of Health (NIH)). *{Extramural studies only}*
* In addition, all study records must be retained in accordance with National Institutes of Health (NIH) policies on document retention and local IRB requirements.
* Discuss PI’s responsibility for retaining all study records and making them available for monitoring and audits during the conduct of the study and throughout the retention period.
* Instruct the PI to notify the Sponsor if the study files are to be relocated or responsibility for site files is transferred to another individual.

1. Visit Conclusion

At the conclusion of the COV, the monitor will meet with the PI and site SC to discuss:

* Any findings noted during the visit.
* Retention timeframes for study-related documents.
* Safety reporting requirements.
* Notification of the IRB that the study has concluded.
* Outstanding issues at study closure and a plan for their resolution.

# PROTOCOL DEVIATIONS

### Documenting Protocol Deviations

Protocol deviations identified during the Interim Monitoring Visit, and not having been previously reported, will be documented in the Monitoring Report. This trial utilizes <*an EDC system*> which will be used to report all protocol deviations to the Sponsor and <*other responsible parties*>. The Site PI will not deviate from the protocol for any reason without prior written approval from the Sponsor and/or site IRB, except in cases of medical emergencies. The Site PI may deviate from the protocol without prior approval only when the change is necessary to eliminate an apparent immediate hazard to the subject.

The Site Monitor will document any protocol deviation finding(s) in the appropriate visit report. The Site Monitor will also address them with site personnel and document the findings and discussion in the follow-up letter.

If the site reports a protocol deviation, the Site Monitor is to address the issue with the appropriate site personnel and document the information in the Monitoring Visit Report as appropriate. In the event that the Site Monitor cannot resolve the issue, the Site Monitor should contact <*who to contact*> to discuss how to address the deviations. The Site Monitor will ensure that the site has reported all protocol deviations to their IRB, according to the IRB's reporting requirements.

### Corrective and Preventative Actions (CAPA)

A CAPA plan may be required in the event of:

* + - A major protocol deviation or trend in deviations discovered by the site, sponsor, monitor, or auditor.
    - Subject complaints related to the research or site staff.
    - Monitor/auditor findings.
    - Operational problems identified on-site.

The need for corrective actions related to non-compliance will be evaluated at the time of discovery of the non-compliance and is based upon the impact to the protection of clinical trial participants and regulatory requirements.

Preventive actions are not dependent on the occurrence of non-compliance and are initiated to eliminate potential causes of nonconformities, regulatory non-compliance, or potential participant quality of research care issues. Not all non-compliance/deviations require CAPAs.

Monitor's Role:

If a monitor discovers an issue on-site that warrants a CAPA, the monitor will note the specific concern in the visit follow-up report. *The Sponsor and or site PI* > will write a formal CAPA Plan and specify the timeline for implementing the CAPA. At the next on-site visit, the monitor will check to make sure:

* + - The actions specified in the CAPA are being followed.
    - The CAPA document is filed in the Regulatory Binder.
    - IRB-acknowledgement of the deviation and CAPA is filed in the Regulatory Binder *if applicable*.
    - Staff re-training resulting from the CAPA is documented in the Regulatory Binder *if applicable*.
    - Sponsor Correspondence pertaining to the CAPA is filed in the Regulatory Binder.

These same documents will be reviewed for all non-monitor-initiated CAPAs. Any non-compliance of CAPAs discovered by a monitor will be reported to the Sponsor within 24 hours of awareness.

# SERIOUS ADVERSE EVENT (SAE) REPORTING

Serious adverse event reporting (SAE) reporting will be conducted as outlined in the study protocol. SAEs must be reported (within 24 hours of discovery) to the Sponsor. SAE source document templates should be completed and the event entered into the EDC system. The Site Monitor will ensure that site personnel have entered information regarding SAEs into the EDC. The Site Monitor will review all SAE source documentation to ensure that SAE information entered onto the SAE reporting form and eCRF is complete, accurate and consistent.

Investigators will be instructed to report all SAEs to their respective IRBs in accordance with their IRB policies and institutional requirements, FDA regulations and ICH GCP Guidelines. Investigators will report SAEs to FDA in accordance with FDA regulations and GCP Guidelines.

1. E6(R2) 5.18.1(b) found at: <https://www.fda.gov/media/93884/download> and <https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf>. [↑](#footnote-ref-1)
2. E6(R2) found on the web at: [*https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1*](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1) [↑](#footnote-ref-2)
3. 21 CFR § 50.25 Elements of informed consent found on the web at: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/subpart-B>. [↑](#footnote-ref-3)
4. MDR requires a 10-year for medical devices and a 15-year after the last device has been placed on the market retention period for implantable medical devices for the following records: [In Vitro Diagnostic Regulations (EU) 2017/746](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746); [Medical Device Regulations (EU) 2017/745](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745). [↑](#footnote-ref-4)