**NIMH Clinical Monitoring Plan (CMP) Template**

**Tool Summary** (*Remove Tool Summary before finalizing and distributing the document)*

***Purpose:*** *This template provides a recommended structure for a Clinical Monitoring Plan (CMP), as well as draft language and other guidance. It is to be used as a starting point for preparing a Clinical Monitoring Plan.*

***Audience/User:*** *Clinical Research Associates (CRAs) or Principal Investigators (PI) responsible for preparing a Clinical Monitoring Plan.*

***How to Use This Template***

*This template contains two types of text: instruction/explanatory and example text.* ***Instruction/ explanatory text*** *are indicated by italics and should deleted. Footnotes to instructional text should also be deleted. This text provides information on the content that should be included.* ***Example text*** *is included to further aid in document development and should either be modified to suit the drug, biologic or device (study intervention), design, and conduct of the planned clinical trial or deleted. Example text is indicated in [brackets with regular font]. Within example text, a need for insertion of specific information is notated by <angle brackets>. Example text can be incorporated as written or tailored to a particular document. If it is not appropriate to the document, however, it too should be deleted.*

***Version control*** *is important to track document development, revisions, and amendments. It is also necessary to ensure that the correct version of this document is used by all staff conducting the study. With each revision, the version number and date located in the header of each page should be updated.*

**CLINICAL MONITORING PLAN ACKNOWLEDGEMENT AND SIGNATURE SHEET**

Principal Investigator: <*Investigator name*>

Funding: National Institutes of Health/ National Institute of Mental Health (NIH/NIMH)

Investigational Intervention: <*Intervention name*>

Protocol Number: <*Protocol number*>

Protocol Title: <*Protocol Title*>

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

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

Principal Investigator <*Name, MD/PhD*>

**CLINICAL MONITORING PLAN**

Principal Investigator: <*Investigator name*>

Funding: National Institutes of Health/ National Institute of Mental Health (NIH/NIMH)

Investigational Intervention: <*Intervention name*>

Protocol Number: <*Protocol number*>

Protocol Title: <*Protocol title*>

Prepared by: <*Nam*e>

 <*Title*>

 <*Company/Affiliation*>

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

Clinical Monitoring Plan Revision History:

|  |  |  |
| --- | --- | --- |
| Version Number | Version Date | Summary of Revisions Made: |
| ***[1.0]*** | *[28Nov2016]* | *[Approved version]* |
|  |  |  |

Table of Contents

[1.0 LIST OF ABBREVIATIONS 5](#_Toc468458014)

[2.0 INTRODUCTION 6](#_Toc468458015)

[3.0 STUDY CONTACT INFORMATION 6](#_Toc468458016)

[4.0 VISIT SCHEDULING 7](#_Toc468458017)

[4.1 Type of Visit 7](#_Toc468458018)

[4.2 Study Monitoring Schedule 8](#_Toc468458019)

[5.0 MONITORING ACTIVITIES 9](#_Toc468458020)

[5.1 Site Initiation Visit 10](#_Toc468458021)

[5.1.1 SIV Preparation 10](#_Toc468458022)

[5.1.2 SIV On-Site Activities 10](#_Toc468458023)

[5.2 Interim Monitoring Visit Activities 14](#_Toc468458024)

[5.2.1 IMV Preparation Activities 14](#_Toc468458025)

[5.2.2 IMV On-site Activities 15](#_Toc468458026)

[5.3 For-cause Visit Activities 18](#_Toc468458027)

[5.4 Close-out Visit Activities 18](#_Toc468458028)

[5.4.1 COV Preparation Activities 18](#_Toc468458029)

[5.4.2 COV On-Site Activities 19](#_Toc468458030)

[6.0 MONITORING REPORTS / ACTION ITEMS 21](#_Toc468458031)

[7.0 ESSENTIAL DOCUMENTS / TRIAL MASTER FILE 22](#_Toc468458032)

[7.1 Required Essential Documents 22](#_Toc468458033)

[7.2 Trial Master File (TMF) 23](#_Toc468458034)

[7.3 Clinical Protocol Logs 23](#_Toc468458035)

[8.0 SOURCE DOCUMENT VERIFICATION 23](#_Toc468458036)

[9.0 PROTOCOL DEVIATIONS 24](#_Toc468458037)

[9.1 Documenting Protocol Deviations 24](#_Toc468458038)

[9.2 Corrective and Preventative Actions (CAPA) 25](#_Toc468458039)

[10.0 SERIOUS ADVERSE EVENT (SAE) REPORTING 26](#_Toc468458040)

[11.0 REPORT WRITING 26](#_Toc468458041)

[12.0 SITE MANAGEMENT AND CORRESPONDENCE 27](#_Toc468458042)

# LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| Acronym | Term |
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| CMP | Clinical Monitoring Plan |
| COI | Conflict of Interest |
| COV | Close-Out Visit |
| COVR | Close-Out Visit Report |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTOBB | Clinical Trials Operations and Biostatistics Branch |
| 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 |
| FDF | Financial Disclosure Form |
| GCP | Good Clinical Practice |
| IB | Investigator’s Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IMV | Interim Monitoring Visit |
| IMVR | Interim Monitoring Visit Report |
| IP | Investigational Product |
| IRBISM | Institutional Review BoardIndependent Safety Monitor  |
| LAR | Legally Authorized Representative  |
| MOP | Manual of Procedures |
| NIH | National Institutes of Health |
| NIMH | National Institute of Mental Health |
| OCR | Office of Clinical Research |
| OHRP | Office for Human Research Protections |
| PI  | Principal Investigator |
| SAE | Serious Adverse Event |
| SC | Study Coordinator |
| SD | Source Documents |
| SDV | Study Document Verification |
| SIV | Site Initiation Visit |
| SIVR | Site Initiation Visit Report |
| SOP | Standard Operating Procedures |
| TMF | Trial Master File |
| UP | Unanticipated Problem |

#  INTRODUCTION

The sentence listing “monitoring tasks performed in accordance with” should be modified to reflect an FDA-regulated or non-FDA-regulated study. The current language reflects a study that is FDA-regulated.

The Clinical Monitoring Plan (CMP) establishes the guidelines for conducting clinical site monitoring activities for National Institute of Mental Health (NIMH) Protocol <*protocol number, protocol title>.* The CMP was developed by *<development group>,* in collaboration with the NIMH Office of Clinical Research, Clinical Trials Operations Branch (OCR, CTOB) and the Principal Investigator (PI). *<Group performing monitoring (i.e., Site Monitor)>* 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 Harmonisation (ICH) Good Clinical Practice Guidelines (GCP), Title 21 Code of Federal Regulations (CFR) Part 312, and other applicable requirements.

# STUDY CONTACT INFORMATION

Program Contacts

|  |  |  |
| --- | --- | --- |
| **Representative** | **Role** | **Contact Information** |
| Study Program |  |  |
| *<Investigator Name>*  | Principal Investigator |  |
|  | Study Coordinator |  |
| **NIMH** |  |  |
|  | Program Official or Contract Officer  |  |
|  | DSMB Liaison |  |
| **<*Monitoring Group*>** |  |  |
|  | Monitoring group operations manager  |  |
|  | Study Site Monitor/CRA |  |
| **<*Other*>** |  |  |
|  | Medical Monitor |  |

Site Contacts:

|  |  |  |
| --- | --- | --- |
| **Representative** | **Role** | **Contact Information** |
| <Insert Site Name> |  |  |
|  | Site PI |  |
|  | Site Study Coordinator |  |
| <Insert Site Name> |  |  |
|  | Site PI |  |
|  | Site Study Coordinator |  |
| <Insert Site Name> |  |  |
|  | Site PI |  |
|  | Site Study Coordinator |  |

# VISIT SCHEDULING

The Site Monitor will work with the Site Principal Investigator (PI) and Site Study Coordinator (SC) to schedule monitoring visits. The Overall Study (Grant) PI, NIMH Program or Contract Official, and <*other representatives*> will be apprised of the visit scheduling.

Prior to the visit, the Site PI will receive:

* Visit confirmation letter
* Agenda
* List of subjects to be monitored

The Site Monitor will ensure that this information is communicated to the site personnel within <*list time frame*> to allow sufficient time for record requests. The Site PI and research staff will be expected to secure workspace for the Site Monitor(s) and to be available during the visits to facilitate monitoring activities. The Site 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 Site SC are also expected to be available for a wrap-up meeting at the conclusion of the visit. These expectations will be explained in the visit confirmation letter.

## Type of Visit

The Site Monitor is responsible for conducting the following types of monitoring visits for this study.

* 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 or Contract Officer activating the site for enrollment.
* Interim Monitoring Visits (IMVs) will be conducted to confirm subjects’ rights are being protected, the study is being conducted according to the protocol and applicable regulations, subject safety data are being accurately reported, and study dataset reflects the original source data.
* 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.

## Study Monitoring Schedule

The Site Initiation Visit usually occurs after the site has completed all regulatory requirements and has obtained IRB approval for the research study at their site. The SIV is the last step before the study site is sufficiently prepared to begin participant recruitment (i.e., after IRB/DSMB approval, once study staff have been hired and trained, once drug has arrived on site, and after all study documents have been created).

The sponsor and/or monitoring group will develop a monitoring plan that includes the frequency and duration of Interim Monitoring Visits (IMV). The focus of these visits is to evaluate the way the study is being conducted and to perform source document verification. These visits can occur every few weeks to once a year and can take less than one day up to several days at a time. The goal of the first IMV is to be scheduled early on during the clinical trial in order to discover any issues before they affect the trial/data.

Once the research study has been completed at a site, a Close-Out Visit (COV) occurs. This type of visit normally follows after the last subject visit and after all data queries have been resolved.

There will be <*list # of visits*> on-site visits to each participating study site, unless there is cause for additional visits.

* Site Initiation Visit: <*approximately x weeks after IRB approval*>
* Interim Monitoring Visit 1: <*approximately x weeks after the xst patient is completed*>
* Interim Monitoring Visit 2: <*approximately x weeks after the xth patient is completed*>
* Interim Monitoring Visit 3: <*approximately x weeks after the xth patient is completed*>
* Site Close-out Visit: <*approximately x weeks after the last patient is completed*>

# MONITORING ACTIVITIES

The subjects 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 subjects or the integrity of study data.

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

* 100% review of consent documents for all subjects consented or re-consented since the last onsite visit.
* 100% of Adverse Events (AEs) and Serious Adverse Events (SAEs).
* <*xx*>% of subjects enrolled since last onsite visit.

Findings of the Site Monitor that might indicate lack of understanding of protocol requirements, deviation from GCP (e.g., inadequate attention to protection of human subjects), unreported or underreported safety information or other non-compliance may result in an increase in the percentage of subject data monitored or monitoring visit frequency.

## Site Initiation Visit

### SIV Preparation

The Study Initiation Visit Report (SIVR) will be used to document the outcome of these visits. The Site Monitor will send SIV confirmation and SIV follow-up letters to each site in conjunction with these visits. The SIV will be conducted prior to subject enrollment. The Site Monitor performs the following SIV preparation activities:

* Contacts the Site PI or Site SC to schedule a date and time for the on-site SIV.
* Discusses with site personnel the purpose of the visit, the site personnel who are required to attend, and the approximate amount of time required to conduct the visit.
* Sends written confirmation and the SIV agenda to the Site PI or Site SC documenting the contact. This communication confirms the date, time, and location of the visit, the purpose of the visit, the site personnel who are required to attend, and the topics to be discussed. The original letter and agenda are filed in the Regulatory Binder and copies are submitted to the <*Sponsor PI and the Project Officer at NIMH*>.

The Site Monitor reviews the following documents prior to the Site Initiation Visit:

* The study protocol and any amendments
* Case report forms
* The Electronic Data Capture (EDC) system
* Essential Documents (ED) file, noting any missing or incomplete items.
* Investigator Brochure (IB) or Package Inserts
* Clinical Monitoring Plan (CMP)

### SIV On-Site Activities

The following activities may be conducted during the SIV:

1. Investigator and Staff Responsibilities
	* 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.
	* Verify that the PI understands and accepts the responsibility to obtain IRB approval of any amended protocols, consent documents, or advertisements, and to ensure continuing review of this study by the IRB.
	* Identify the roles and responsibilities of each staff member.
	* Review with the Investigator, the Investigator's obligations as listed on the Investigator Record of Agreement document (FDA Form 1572), as applicable.
	* Note any changes to study site staff or facilities since the last contact.
	* Ensure that relevant study documents have been updated, and additional required regulatory documents such as CVs, professional licensures, financial disclosures, etc., are requested as needed. Review proper placement in the Regulatory Binder.
2. Review of Facilities
	* Tour of site facilities where study activities will be conducted, including but not limited to: informed consent discussions, phone screening area, subject visits, laboratory specimen collection, processing, and storage, investigational product (IP) storage, subject records and Regulatory Binder location, and monitoring workspace.
	* Verify presence of study-required equipment, including but not limited to: <*insert protocol specific study-required equipment*>.
3. Protocol Review
	* Review study objectives, study design, and study population.
	* Review study inclusion/exclusion criteria.
	* Review subject randomization. *remove if not applicable*
	* 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 subjects.
4. 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 subject.
5. 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.
6. Study Documentation
	* Review the document retention requirement for all study-related records. Inform the PI that all study records must be retained <*insert timeframe (e.g., until disposal is authorized by the Sponsor; For an Investigational New Drug (IND) study it is 2 years after market application approval, or 2 years after shipment and delivery of drug for investigational use is completed and Food and Drug Administration (FDA) has been notified (312.57) and in accordance with National Institutes of Health (NIH) Clinical Center policies on document retention. Or insert institutional policies as directed. Follow the most conservative policy.)*>.
	* 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.
7. Regulatory Binder
	* Sign and date the site visit log for each day of the visit.
	* Verify that all study documents are present in the Regulatory Binder and ensure the PI and site personnel are aware of their responsibility to keep the file complete and current.
	* <*Insert appropriate task for review and/or collection of ED based on section 7.0*>
	* Verify that the Delegation of Authority Log is current and signed by the PI.
	* Verify that the site has a Protocol Deviation/Violation Log template on file.
8. Safety Reporting
	* Review adverse event AEs, SAEs, 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 Data and Safety Monitoring Board (DSMB) procedures and reports.
	* Review independent safety monitor (ISM) reporting procedures (if applicable).
9. Review Source Documentation (SD) Requirements and Case Report Form (CRF) Completion
	* Verify that the data points collected on the CRFs (including electronic Case Report Forms, eCRFs) match the data points proposed in the grant/contract language, the IRB-approved protocol, and the DSMB approved protocol (if applicable).
	* Review requirements for maintaining adequate source documentation that supports the data recorded in the CRFs and eCRFs.
	* Review and provide instruction for CRFs and eCRF completion, as well as completion instructions listed in the MOP.
	* Ensure that the PI and site personnel are aware of CRFs and eCRF correction and data clarification requirements.
	* Review and provide training on the use of the electronic data capture system and the specimen management and tracking system for the study.
10. Review Laboratory Supplies and Procedures
	* Verify that the site has adequate supplies available as detailed in <*insert where the complete list of study supplies can be found*>.
	* 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.*>.
11. Review Investigational Product (IP) Requirements
	* Review of procedures for the inventory of IP and proper documentation.
	* Confirm that the Site IP Receipt and Accountability Forms/ Logs located in the Regulatory Binder are updated with information regarding the receipt of IP from the site institutional vendor.
	* Review the IP shipping receipts against the physical IP inventory received by the site to ensure the proper IP amount was shipped and received.
	* Document all deviations from inventory and storage requirements in the Study Initiation Visit Report.
12. Discussion of General Items
	* If any training was provided to study staff during the SIV, document the training on a training log.
	* Ensure that all required supplies/clinical trial materials (e.g., CRFs, MOP, etc.) have been received by the clinical study site prior to screening or enrolling the first study subject.
	* 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 objectives of the IMVs are to:

* Document and report on clinical study progress.
* Document that the protocol and associated forms are current.
* Update the site team of any changes in study conduct/documentation.
* Ensure the NIMH requirements and investigator obligations are met.
* Ensure continued acceptability of the Investigator, his/her team and facility.
* Obtain and review current clinical data, reports and source documents.
* Ensure adequate IP inventory and storage, including ensuring that only trained personnel dispense and administer study drug.

The Interim Monitoring Visit Report (IMVR) will be used to document the outcome of these visits. The Site Monitor will send Interim Monitoring Visit confirmation and IMV follow-up letters to each site in conjunction with these visits.

### IMV Preparation Activities

The Site Monitor performs the following IMV preparation activities:

* + - Contact the Site PI to schedule a date and time for the visit. Discuss the purpose of the visit, the anticipated duration of the visit, subjects' study records required for review, outstanding issues requiring resolution, and the study personnel required at the visit.
		- Send an IMV Confirmation Letter to the PI documenting the contact, copying additional site personnel as applicable, at least <*10*> days prior to the date of the visit. The letter confirms the date, time, and location of the visit, the purpose of the visit, the site personnel who are required to attend, and contact information for the Site Monitor. The letter also requests that any outstanding regulatory documents be completed and available for the Site Monitor at the time of the visit. The original letter is filed in the Regulatory Binder and copies are submitted to the NIMH Program or Contract Officer.
		- Review the Regulatory Tracking document maintained by the site and the list of outstanding essential documents to determine if any documents must be collected during the IMV.
		- Determine the status of all eCRFs.
		- Review previous visit reports, correspondence, serious adverse event forms, and any other relevant material, and prepare a list of outstanding issues that require resolution.

### IMV On-site Activities

The following activities may be conducted at each IMV:

1. Consent Document Review for All Subjects
* 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 subjects were re-consented with updated consent documents as directed by the IRB.
1. Source Documentation and CRF Review
* Verify that accurate, complete, and current source documentation is maintained.
* Verify subject 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 subjects are recorded in the source documentation and on the CRFs.
* 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, ink signature, or electronically signed all necessary eCRF pages for 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 if paper based study.
* Verify that previously outstanding data queries have been resolved, signed, <*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 NIMH, IRB, DSMB, OHRP, and 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 (IP)
* 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.
* Physically review the number of IP pills returned against each subject’s CRFs, eCFRs, and Drug Accountability Log.
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 subject’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 Monitoring 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. Regulatory Binder
* Ensure that essential document files are complete and current.
* <*Insert appropriate task for review and/or collection of ED based on section 7.0>*
1. Investigator and Site Personnel Responsibilities
* Ensure that the Delegation of Authority 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 Site Monitor will meet with the PI and site research staff to review visit findings and answer questions. The Site Monitor will discuss the following topics at a minimum:
		+ Enrollment progress.
		+ Consent process and documentation.
		+ UPs, AEs, and SAEs experienced by study subjects.
		+ Scheduling of the next IMV or the COV.
2. Resolution of Routine Action Items (see section 9.2 for resolution of major issues discovered on site)
* The Site Monitor will meet with the Site SC and PI periodically during the visit to explain findings, ask questions, and work with the Site 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 Site Monitor encounters a serious issue, negative performance trend, or general non-compliance, the Site Monitor will contact <*list who to contact*> to determine the appropriate course of action.

## For-cause Visit Activities

During for-cause visits, the Site 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

Close-out visits may be conducted at study completion or earlier in the case of study termination by the IRB, <*insert appropriate Safety Oversight Group or other Regulatory Body: Data Safety Monitoring Board (DSMB), FDA*>. The outcome of the visit and other close-out activities will be documented in a report and follow-up letter.

### COV Preparation Activities

The Site Monitor performs the following COV preparation activities:

* Contacts the Site PI or SC to schedule a date and time for the visit. The Site Monitor discusses the purpose of the visit, the anticipated duration of the visit, subjects' medical records required for review, outstanding issues requiring resolution, and the study personnel required at the visit.
* Sends the COV Confirmation Letter to the Site PI documenting the contact, copying additional site personnel as applicable. The letter confirms the date, time, and location of the visit, the purpose of the visit, the site personnel who are required to attend, and contact information for the Site Monitor. The letter also requests that any outstanding regulatory documents be completed and available for the Site Monitor at the time of the visit. The Site Monitor files the original letter in the Regulatory Binder and submits copies to the NIMH Program or Contract Officer.
* Includes a Final Study Report in the COV Confirmation Letter. The Site Monitor may pre-populate the Final Study Report with the subject enrollment and discontinuation information. The Investigator will review and sign the Final Study Report and add any relevant comments.
* Reviews the list of outstanding essential documents to determine if any documents must be collected during the COV.
* Determines the status of all eCRFs and on-site queries.
* Reviews previous visit reports, correspondence, SAE forms, and any other relevant material, and prepares a list of outstanding issues that require resolution.

### COV On-Site Activities

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

1. Consent Documents
* Confirm that consent was obtained for each subject 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. Regulatory Binder
* Ensure that essential document files are complete and current.
* Identify any missing study documents.
* Ensure that the Delegation of Authority Log is complete and signed by the PI.
1. Source Documentation and CRF Review
* Reconcile the final status of all subjects listed on the screening logs.
* 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 revise bullet to reflect use of an EDC system as applicable.
* 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
* Perform IP accountability for any subjects not reviewed at previous IMVs.
* 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 subjects 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. *IRBs have different policies on the timing of the study closeout report. Most require the study closeout report to be sent to the IRB only when data analysis or manuscript preparation that involves the use of or access to PII has completed*.
* If the study was terminated prematurely, the Site Monitor will confirm that enrolled subjects were informed and 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
* Verify that the record retention and storage plan is consistent with National Institutes of Health (NIH) [policy](https://oma.od.nih.gov/DMS/Pages/Records-Management-Schedule.aspx) as well as institutional or IRB requirements.
* Verify that the record retention and storage plan follows CFR Title 45 Part 46.115(b); research documents will be retained for at least 3 years following the completion of the study. If institutional policy or FDA requirements are more conservative, the site should follow the most conservative policy.
* Instruct the PI to notify NIMH leadership 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 Site Monitor will meet with the Site PI and 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.

# MONITORING REPORTS / ACTION ITEMS

Monitoring visit findings and resulting action items will be documented in trip reports. The Site Monitor will send drafts of the reports to the NIMH Program or Contract Officer within <*14*> calendar days of the last day of the monitoring visit, and the NIMH Program or Contract Officer will send final comments back to <*study PI*> within <*7*> calendar days. Once the visit documents are finalized, documents will be made available to identified study team members as noted in section 3.0. These documents should be printed and stored in the Regulatory Binder. <*Insert where originals will be maintained based on information contained in TMF section*>.

A Site Monitor will work with designated site staff to resolve any outstanding action items as communicated in the Action Item Tracker presented as an attachment to the <*insert appropriate document, for example the detailed follow-up letter or visit report*>.

 *Examples of other information to include: At a mutually agreed upon time, or 4 to 6 weeks post visit, whichever is earlier, the Site Monitor 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.*

# ESSENTIAL DOCUMENTS / TRIAL MASTER FILE

## Required Essential Documents

A Regulatory Binder will be maintained at each study site and serves as the central source for essential document (ED) maintenance at the site. EDs for this trial will be maintained by each study site as a combination of paper and electronic documents. The contents of the Regulatory Binder 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 Regulatory Binder. Any documents to be filed electronically should have a corresponding note-to-file placed in the Regulatory Binder to describe the exact electronic location.

The following documents represent a complete site essential document packet and are to be maintained in the Regulatory Binder: customize as appropriate

* FDA Form 1572
* Curriculum Vitae (CV) for those listed on Delegation of Authority Log (and Form 1572 if applicable)
* Copy of current licensure for PI and all sub-investigators listed on the 1572
* Human Subject Protection Training documentation for relevant personnel
* GCP Training documentation for relevant personnel
* Study-specific Training documentation for relevant personnel
* Financial Disclosure Form (FDF)/ Conflict of Interest (COI) form for relevant personnel *remove if not applicable*
* Protocol/Protocol Amendment(s) Signature Pages
* Site-specific Consent Document; Assent Form *remove if not applicable*
* Institutional Review Board (IRB)-Approved Protocol, Consent Document, Protocol Amendments
* IRB approved Advertisements, Subject Handouts, <*insert specific items pertinent to the protocol; dosing diaries, dosing instructions, etc*>
* IRB Compliance Documentations
	+ Federalwide Assurance number (FWA#)
	+ IRB of record roster
* Letter from site to justify use of a central IRB in lieu of a local IRB *if applicable*
* Laboratory Certifications (CAP and CLIA)
* Laboratory Reference Ranges

## Trial Master File (TMF)

Identify the owner of the TMF and where it will be located.

## Clinical Protocol Logs

Clinical Protocol Logs (study logs) are lists or tables that provide a concise and up-to-date summary of information to assist the capturing of data and help resolve subsequent inconsistencies. The Site Monitor will review the following logs for accuracy during applicable monitoring visits.

Logs that will be utilized for this study are as follows:

* Pre-Screening Log (i.e. subjects who have been pre-screened via phone or email, but have not yet completed an ICF/in-office screening, or subjects who have been pre-screened but failed pre-screening. Tracking this information helps identify trends in exclusion criteria that may lead the study team to submit a protocol amendment to loosen exclusion criteria)
* Subject Screening Log (all in-office screenings)
* Subject Enrollment Log (passed in-office screening)
* Delegation of Authority Log
* Informed Consent Log
* Protocol Deviation/Violation Tracking log
* AE/SAE log
* Monitoring Visit Log
* Drug Accountability Log
* Specimen Tracking Log

# SOURCE DOCUMENT VERIFICATION

*Source document verification (SDV) is the process of confirming accuracy and validity by comparing reported information to the original records to make sure data is reliable and that the study can be reconstructed. However, in the FDA’s draft Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, Risk-Based Monitoring (RBM) is defined as an alternative approach to frequent on-site monitoring and 100% source document verification for all trials. Risk-based monitoring aims to allocate resources based on risk and need instead of equally distributing resources. The goal of RBM is to increase monitoring efficiency without compromising patient safety or data quality. Whichever type of monitoring is chosen, SDV should be customized according to the needs of the protocol.*

Source documentation verification of eCRFs will be conducted for each subject screened and/or enrolled. The Site Monitor will confirm that the following information for all subjects is present in the source documents and that the data in the eCRFs are consistent with the following, but not limited to:

* + - Medical notes/source documents exist for each subject.
		- Subject initials, sex, and date of birth are verified from the Contact Information sheet.
		- Verify that the subject and/or Legally Authorized Representative (LAR) and site staff properly signed and dated the correct version of the Informed Consent Form (ICF) prior to any study procedures being performed.
		- Confirm that the subject meets the inclusion/exclusion criteria.
		- Information concerning all AEs and SAEs.
		- Investigational Product accountability.

Source documentation verification of eCRFs will be conducted for each subject *<customize for screened subjects vs. enrolled subjects>*. The Site Monitor will SDV the following for each consented subject:

* 100% review of consent documents for all subjects
* 100% of Adverse Events (AEs) and Serious Adverse Events (SAEs)
* 100% of Protocol Deviations/Violations/Unanticipated Problems (UPs)
* 100% of Eligibility Criteria
* 100% Primary outcome data points
* The following list of CRFs and eCRFs for each subject: <*insert the names of forms/labs/logs that will be reviewed for each subject (i.e. HAMD-17, MADRS, CSSRS, PHQ9*)>
	+ - Subject Final Disposition

# 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 might warrant a CAPA, the monitor will note the specific concern in the visit follow-up report. If *<the Sponsor*> agrees that a CAPA is required, <*the Sponsor*> will work with Site PI to 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

SAE reporting will be conducted as outlined in the study protocol. SAEs must be reported <*immediately (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.

Upon notification or identification of SAEs during IMVs, the Site Monitor will document in the final report and ensure the site reports the SAE to the Sponsor as required per protocol.

# REPORT WRITING

For each site visit, the Site Monitor will document all findings, including protocol deviation issues and action taken to correct deficiencies in a written report using the appropriate standard report template.

• The Site Monitor documents the visit activities in the SIVR, IMVR or COVR.

• The Site Monitor submits a draft report by email to the <*NIMH Program or Contract Official*> within <*X*>business days of the last day of the visit. All pending action items will be included in the monitoring letter and report, and will be reviewed on the due date specified in the report (electronically) and at the next monitoring visit (on-site).

• The Site Monitor makes any revisions/edits, suggested during the <*NIMH Program or Contract Official*> review, signs and dates the final report. The original document is forwarded to the <*Site PI and Study Sponsor*>. The <*Site PI*> then signs and dates the final report within <*X*>days of receipt of the report.

• The <*Study Sponsor>* will distribute the final report and follow up letter, containing signatures, to all applicable Sponsor designees, as appropriate.

• Once the report is approved and finalized, the Site Monitor sends the following to the Site PI/site within *<X*> days of final approval, to document the visit:

Appropriate follow-up letter requesting a response to any questions/issues not addressed at the time of the pre-study visit.

• SIV follow-up letter

• IMV follow-up letter

• COV follow-up letter

# SITE MANAGEMENT AND CORRESPONDENCE

Correspondence with Site PIs/sites and the information obtained should be documented and filed on an ongoing basis.

Follow-up Letters and other written correspondence

• Follow-up letters and other written correspondence will be electronic, with originals provided upon request.

• Confirmation letters and follow-up letters will be filed in the Regulatory Binder.

• A copy of the Monitoring Report will be maintained <*in the Monitoring Site File within the shared files*>.

E-mail Correspondence

• Any major interim site issues may be reported in e-mail correspondence.

• All e-mail correspondence, which addresses significant site related issues, is to be forwarded to the <*NIMH Program or Contract Official, the Sponsor*>.

• Any protocol specific issues addressed via the telephone should be documented in email correspondence.