**Clinical Manual of Procedures (MOP) Template**

**Purpose:** This template provides a recommended structure by NIMH for developing consistent study procedure implementation and data collection instructions across participant and clinical site activities. It details the study’s organization, operations, procedures, data management, and quality control.

**Responsibility:** To be used by Principal Investigator and study team members who are responsible for developing a manual of procedures.

**Procedure:**

* 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.

**<Full Name of Study>**

**<Acronym>**

**<Name of PI(s) and Site(s)>**

**Manual of Procedures (MOP)**

**Version 1**

**<mm/dd/yyyy>**

**INTRODUCTION**

[The Manual of Procedures (MOP) has been compiled to assist study personnel in conducting <Full Name of Study>. This MOP serves as a supplement to the protocol and contains administrative and technical information about study conduct. The MOP will facilitate consistency in protocol implementation and data collection across participants and study sites. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

The MOP serves as a handbook that details a study’s conduct and operations and describes a study’s organization, operational data definitions, recruitment, screening, enrollment, randomization, follow-up procedures, data collection methods, data flow, case report forms (CRFs), and quality control procedures. The MOP must be reviewed carefully in conjunction with the protocol by all study personnel in advance of study start up, and then throughout the study as the manual is updated. The MOP should be developed and in place prior to study start-up.

The MOP must be modified whenever a change in the protocol is necessitated, or a study step needs to be refined or re-defined for clarity and safety.]

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|  |  |
| --- | --- |
| 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 Harmonization |
| IMV | Interim Monitoring Visit |
| IMVR | Interim Monitoring Visit Report |
| IP | Investigational Product |
| IRB  ISM | Institutional Review Board  Independent 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 |

**ABBREVIATIONS**

# 

# 1.0 STUDY SYNOPSIS *(one page)*

**Name of Study:**

**Objectives:**

**Primary Objectives:**

**Secondary Objectives:**

**Design and Outcomes:**

**Interventions and Duration:**

**Sample Size and Population:**

# 2.0 STUDY STAFF RESPONSIBILITIES

*The roster includes the names, roles/responsibilities, phone numbers, fax numbers, and e-mail addresses of study staff members. A notation of whom to contact regarding special situations and study-related questions/concerns should also be included. Examples of study-related concerns include:*

* *Reporting an adverse event (AE)*
* *Randomizing a participant*
* *Unblinding a participant*

**SITE #1** *Create Roster for all Sites and/or Coordinating Center Involved*

|  |  |  |
| --- | --- | --- |
| Study Staff | Title/Role | Contact Information |
|  | [PI] |  |
|  | [Medical Monitor/Safety Officer] |  |
|  | [Co-Investigator] |  |
|  | [Co-Investigator] |  |
|  | [Study Statistician] |  |
|  | [Lead CRC] |  |
|  | [Backup CRC] |  |
|  | [Unblinded CRC *(Unblinded staff member to prepare DSMB reports)*] |  |
|  | [Study Pharmacist *(Pharmacy and Randomization Procedures)*] |  |
|  | [Backup Study Pharmacist *(Pharmacy and Randomization Procedures)*] |  |
|  | [Data Manager] |  |
|  | [Institutional Review Board] |  |

## 2.1 Who is qualified to conduct assessments and study procedures?

*This table should outline who can complete each of the assessments and procedures for the study.*

|  |  |
| --- | --- |
| Assessment/Study Procedure | Person Qualified |
| [SCID] | [Physician] |
| [Blood Draw] | [Nurse] |
| [CSSRS] | [Physician] |
|  |  |
|  |  |

# 3.0 STUDY ORGANIZATION AND RESPONSIBILITIES

## 3.1 Coordinating Center *Please include the name of the coordinating center*

*This section should detail how the Coordinating Center plans to carry out its delegated responsibilities and day-to-day operations as related to the study.*

[The responsibilities of the Coordinating Center may include (but are not limited to):

* Development and maintenance of the MOP
* Maintaining the study binder including regulatory documents
* Development of the randomization scheme and procedures
* Development of the data flow and data management procedures, including data entry, error identification, and correction
* AE monitoring and reporting
* Communications with study sites, scheduling of meetings and training sessions, and responding to and documenting ad hoc communications
* Site visits to ensure adherence to the protocol and procedures
* Preparing and sending reports to the data safety monitoring board (DSMB) and other oversight or regulatory bodies
* Preparing and sending annual reports to the funding agency
* Quality control procedures
* Distribution of all changes and updates of reports, procedures, and documents to all participating study sites as necessary.]

## 3.2 Site Responsibilities

*This section should outline the responsibilities for each site.*

[The roles and responsibilities of the investigators and study sites may include (but are not limited to):

* Maintaining the study binder including regulatory documents
* Participating in protocol finalization and preparing study materials
* Ensuring compliance with protocol, MOP, IRB, federal and state regulations
* Identifying, recruiting, screening, and enrolling participants
* Protecting participants' rights
* Obtaining informed consent from each participant
* Collecting study data and following participants through study completion
* Ensuring compliance with and accountability of administration of study intervention (in conjunction with the Research Pharmacy), as required
* Retaining specific records (e.g., laboratory drug accountability records)
* Preparing recruitment and enrollment, gender and minority breakdowns, adverse event reports
* Assuring IRB review and approval
* Communicating questions, concerns, and/or observations to the Principal Investigator and/or Coordinating Center
* Organization and participation in Steering Committee meetings
* Transfer of data to Coordinating Center and resolution of all queries]

## 3.3 Pharmacy Activities

*This section of the MOP should describe in detail how the investigational agent is to be prepared/compounded, dispensed, stored, and returned to the Coordinating Center, the Sponsor, or other designated organization. It provides a description of IP destruction procedures (i.e. will the drug be destroyed by the site pharmacies after every round of on-site monitoring by a CRA or sent back to the Coordinating Center). This section also details the process for completing/filing IP shipping records, subject-specific and master (balance/forward) IP accountability logs, IP destruction logs, IP temperature logs, and IP transport logs to show chain of possession once the drug is removed from the pharmacy. Be sure to specify who will compound/prepare drug and in which facilities this will occur.*

*“Pharmacy” refers to the unit responsible for the storage and dispensation of an investigational drug agent. An actual pharmacy may be directly involved in a study, or the investigational agent may be delivered directly to the study site in prelabeled, sealed packages.*

## 3.4 Steering Committee

*The section should describe the responsibilities of the Steering Committee.*

[The following areas typically fall under the purview of the Steering Committee:

* Design and conduct of the study
* Review of data collection practices and procedures
* Monitoring recruitment and retention of study participants
* Changes in study procedures, as appropriate
* Creation and disbanding of study subcommittees
* Allocation of resources based on priorities of competing study demands
* Review of study progress in achieving goals and taking necessary steps to ensuring the likelihood of achieving those goals
* Review and implementation of recommendations from the DSMB]

# 4.0 TRAINING PLAN

*This section should describe the training and certification plan, including timelines and meeting schedules, to train and certify all research staff involved in the study. A log of all study-specific trainings should be maintained in the site regulatory binder.*

# 5.0 COMMUNICATIONS PLAN

*This section should describe the study communications plan, i.e., all PI meetings, site meetings, study coordinator meetings, etc. Include plan for frequency of meetings, timeline for distribution of minutes, and who is to receive the minutes.*

# 6.0 RECRUITMENT and Retention

## 6.1 Recruitment Plan

*This section of the MOP should describe the target population and specify planned recruitment settings and strategies, such as direct mailing, advertising in mass media, identification of primary care referral practices, presentations at community meetings, regional and national societies, and a study Web site.*

*This section should also include detailed plans for improving recruitment and enrollment, if actual enrollment falls behind target enrollment by more than a specified percentage.*

## 6.2 Participant Retention

*For longitudinal studies, a retention plan should be developed. Plans and suggestions for participant retention should be described and may include strategies such as:*

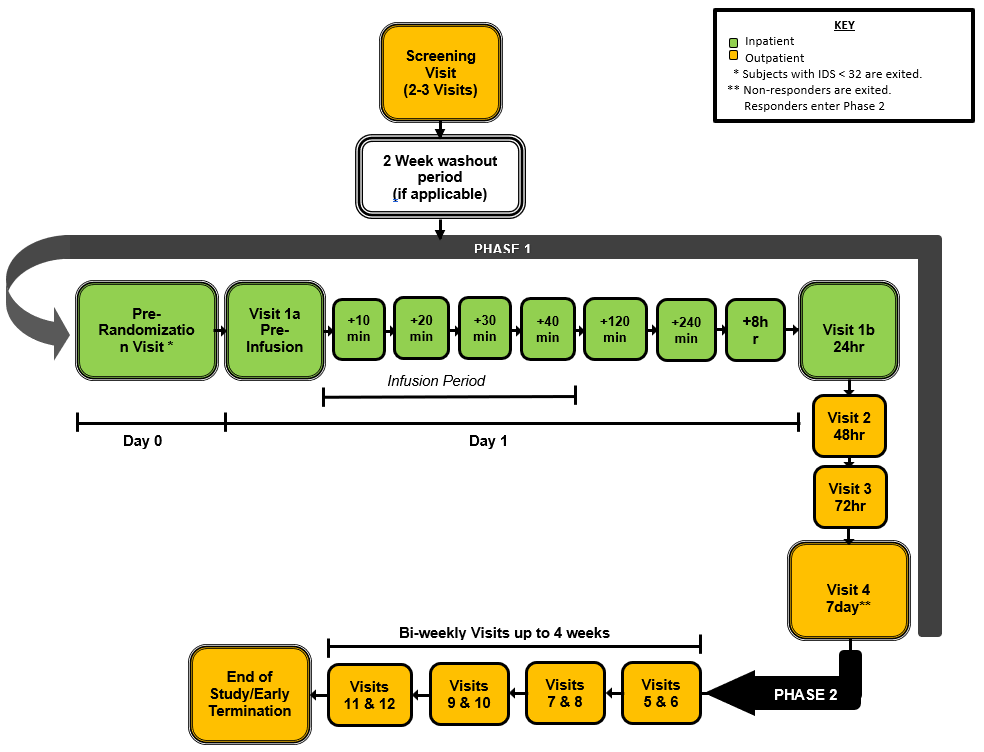
* [Obtaining a specified number of contact options for the participants, including contact information for significant others
* Reminder phone calls and appointment cards prior to all appointments
* Assistance with transportation and parking
* Keeping the duration of follow-up visits brief and not unduly burdensome
* Flexibility with clinic hours to include weekends and evenings
* Possible home visits if necessary]

*An action plan for correcting retention problems should also be provided in this section. This section should also describe whether subjects who do not complete the protocol will be replaced with new subjects for the study to be adequately powered.*

# 7.0 STUDY FLOW

*Provide an overview of the study’s major steps in a flow diagram, as shown in the example below.*

Study Flow:



# 8.0 SCREENING AND eLIGIBILITY criteria

*This section should provide a detailed discussion of the screening procedures utilized to determine participant eligibility. If individuals must be enrolled in the study within a specific window of time following completion of screening procedures, then such requirements should be included in the MOP.*

## 8.1 Subject Screening Log and Subject Enrollment Log

*Provide instructions for completing the Screening Log and the Enrollment Log which provide documentation of all individuals evaluated for study eligibility.*

[The purpose of the Screening Log is to document identification of subjects who

entered pre-trial screening. The Screening Log should contain:

* A pre-enrollment subject identifier (identifier format can vary depending on institutional policy)
* The date of subject pre-screening and method of pre-screening (phone, internet, etc.), consent and the version of the informed consent form used to consent the subject
* The date of subject screening
* Eligibility status: eligible for study participation and date enrolled
* Eligibility status: ineligible for study participation and reason
* Source of subject recruitment (i.e., advertising, referral, etc.)]

*It may also contain the randomization number if different from the screening number, if the subject completed the protocol, and the study completion date. A template Screening and Enrollment Log is available at* ***provide link to Screening and Enrollment Log template in the Web Toolbox****.*

*Note: This information is usually part of the reporting requirements for data and safety monitoring.*

## 8.2 Eligibility Criteria

*This section of the MOP should define the study eligibility criteria, methods for determination if criteria are met (e.g., blood pressure measured in a sitting position after 5-minute rest), and the specific forms needed to document eligibility (e.g., medical history form, physical examination form).*

# 9.0 INFORMED CONSENT AND HIPPA

## 9.1 Informed Consent Process

*This section of the MOP should describe specific instructions for the informed consent process. If there are multiple consent documents (e.g., collecting data from additional sources, participation in ancillary studies), the process for each informed consent document should be outlined in the MOP and accompanied by detailed instructions, which should include the following:*

* *When consent will be obtained*
* *Which study staff member (e.g., research assistant) will discuss the nature of the study with the subject, answer any questions the subject may have, and sign the consent form*
* *When a copy of the signed consent will be given to the participant and where the original signed copy of the consent be stored*
* *Re-consent process, if subjects need to be re-consented at any part of the study*
* *The necessary signatures based on the site's IRB requirements (e.g., the participant/legal representative)*
* *The investigator or person actually obtaining the consent and a witness should be delineated*
* *The source documents (e.g., case note or checklist) should indicate that the ICF was signed, along with the date of signature.*

**9.2** **HIPAA Authorization**

*The Health Insurance Portability and Accountability Act authorization form may be a separate document from the informed consent. Include information about the process for reviewing this form and obtaining the signature of the study participant, in addition to reviewing and signing the consent form. The format of the HIPAA authorization is usually established by the local IRB.*

## 9.3 Release of Information

*If a release of information is needed for the study to be able to obtain a participant’s medical records or any other records (e.g., vital statistics or insurance records), the procedure for completing the release should be outlined in this section.*

# 10.0 RANDOMIZATION

*This section of the MOP describes the randomization approach and procedures, including:*

* *Randomization Plan: The method used for generating randomization codes for assigning participants into treatment groups are described in detail.*
* *Process Responsibilities: The individual who maintains the master randomization list must be identified. This person is responsible for assigning randomization codes, notifying appropriate study staff that the participant has been randomized, and securely storing all randomization files.*
* *Procedure for Randomizing a Participant: At each site, the individual who is responsible for initiating the randomization procedure must be identified. This individual must know who to contact once a participant is determined eligible for a study and which forms must be completed prior to randomization (e.g., informed consent form and participant eligibility form).*

*Randomization assignments must be documented so that they can be reviewed during a data review or audit. Some studies maintain the assigned and blinded randomization code in an automated, computerized log that is separate from the study data, while other studies maintain the assignment in a* *paper-based randomization log. In either case, the method for documenting randomization must be described.*

*This section should also describe the process for ensuring that the randomization scheme will not be compromised if discontinued subjects are replaced (e.g., if subject 005 is discontinued at visit 2 and replaced by subject 009, does subject 009 receive the same randomization as subject 005?). Special attention is needed to randomization schemes involving cohorts (e.g., what happens if the first person in cohort 2 is randomized 1 day prior to the last person in cohort 1?). The section should also include a description of whether the randomization scheme has extra randomization numbers built in for replacement subjects.*

# 11.0 Blinding and Unblinding (Masking and Unmasking)

*This section of the MOP should describe the study blind, the protections for maintaining the blind, and the procedures for breaking the blind. The investigators’ procedures for unblinding should be clearly specified in the MOP.*

*Unblinding is a serious action and should be limited to reduce potential bias.* [If unblinding occurs, the following should be recorded:

* ID of the unblinded participant
* Reason for unblinding
* Study staff person responsible for unblinding
* List of person(s) who have been unblinded
* Related procedures (filing of an SAE report)]

*Include the following table to delineate staff who are blinded in relation to access to study data:*

|  |  |  |  |
| --- | --- | --- | --- |
| Study Staff and Title | Blind/Unblind | Access to safety data (aggregate) | Access to outcome data (aggregate) |
|  |  |  |  |
|  |  |  |  |

# 12.0 Study Intervention

*This section should include a detailed description of the study intervention (for studies that do not include an intervention, see procedures section below), and how the intervention will be implemented.*

*Intervention must be thoroughly described so that the same study guidelines are utilized for all participants in the same condition.*

*For* ***Pharmaceutical studies****, including nutritional and hormonal interventions, the distribution, preparation and handling, labeling, and administration are detailed along with the duration of treatment and criteria for treatment discontinuation. A detailed description of the information that must be provided is documented in the ICH E6 Good Clinical Practice Guidelines. This document is available on the Internet:* [*http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/Guidelines/Efficacy/E6\_R1/Step4/E6\_R1\_\_Guideline.pdf*](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf)

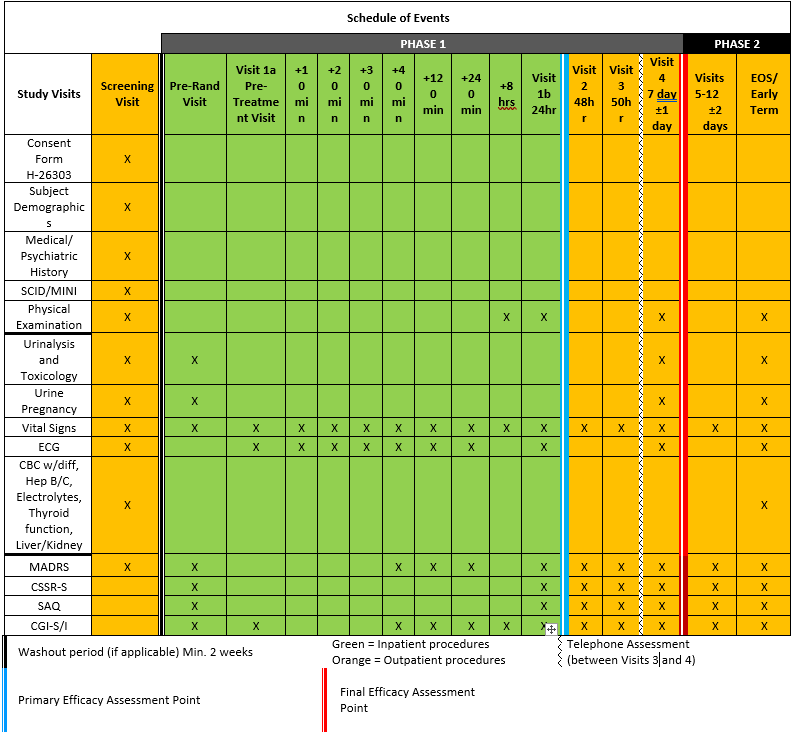
* ***Device studies*** *require a detailed description of the device and its intended use. Information on device studies is provided in the Code of Federal Regulations (CFR) Title 21, Parts 800 - 1299, revised as of April 1, 2000 (see* [*http://www.access.gpo.gov/nara/cfr/waisidx\_00/  
  21cfrv8\_00.html*](http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfrv8_00.html)*).*
* ***Bio-behavioral*** *and* ***life style******studies*** *describe how the intervention is to be carried out as well as documentation of the process.*
* ***Surgical studies*** *require a detailed description of the procedure.*

# 13.0 STUDY PROCEDURES

*To ensure that assessments and measures are conducted consistently across study participants and sites, this section should describe procedures for performing assessments and outcome measures. All outcome and safety evaluations (e.g., blood chemistries) should be delineated in this section.*

## 13.1 Timeline and Visit Schedule

*Include a schedule of visits and evaluations that specifies what is to be done at each study phase and at each contact with the study participant. See example below.*

Schedule of Events:

## 13.2 Study Visits

*In this section of the MOP, each visit should be explained in enough detail for a new or substitute team member to be able to perform the visit. Step-by-step instructions should be provided for all study procedures. This may include defining the purpose of the assessment, the time of data collection, or the processes for handling unscheduled visits.* [This section should outline the following visits:

* Prescreening
* Screening
* Study Visit(s)
* Follow-up]

*If the protocol does not necessitate that subjects come in at exact time points (e.g., at 7, 14, 21, and 28 days post intervention), the PI should consider adding allowable visit windows (i.e., Day 7 ±1 day) to the protocol and MOP to avoid protocol deviations.*

### 13.3 Discontinuation or Withdrawal of Consent

*Procedures for discontinuation or withdrawal of consent should be described in this section. Address whether study participants who discontinue from treatment will still be followed to the end of the study. Also describe what types of efforts will be made to reach subjects before classifying them as lost-to-follow-up (e.g., phone calls, emails, text messages, mailings, etc.).*

## 13.4 Obtaining and Processing Labs

*This section should describe in detail the procedures for obtaining and processing lab samples. If labs are being processed by study staff and not a lab include all specific details, e.g., collect 25 mL of blood in purple tube/site at room temperature for 4 min/centrifuge for 5 min/store immediately in -80 freezer.*

## 13.5 Tapering and Washout

*This section in the MOP should clearly describe the tapering and washout procedures for participants. It should include the following:*

* *Who will complete the tapering and/or washout*
* *When it will be completed during the study*
* *How the taper or washout will be completed*
* *Who will be monitoring the participant during the tapering and washout*
* *Provisions if participant is not tolerant to taper or washout, e.g., extension of taper*

# 14.0 reasons for study discontinuation

*This section should outline all possible reasons for study discontinuation, e.g., score on an assessment, medical reason for a participant’s discontinuation from the study. It should also detail procedures that should be completed following study discontinuation.*

# 15.0 concomitant medicationS

*Please list all required and/or excluded concomitant medications in this section. The MOP should provide a rationale for the concomitant medications that are required and restricted in the protocol. A Subject-specific Concomitant Medication Log can be found at* ***provide link to this log in Web Toolkit****.*

# 16.0 SAFETY REPORTING

*This section of the MOP details the definitions of and procedures for reporting AEs. It should include the following:*

* *Definitions of AEs, serious AEs, and unanticipated problems. The protocol should specify whether the standard OHRP definitions will be used, or specify if the study team definition of AEs and SAEs will be tailored to the study (i.e., only certain types of hospitalizations will be reported as SAEs). All references to adverse events and unanticipated problems in the MOP should be synchronous with the language in the protocol.*
* *Delineate whether determinations of Expectedness and Relatedness will be made regarding the intervention specifically and/or study participation more broadly.*
* *Describe responsibilities of specified study staff in reviewing and reporting events and problems*
* *Reporting processes: timeline for all relevant staff involved in reporting, reviewing and signing off on reports, and delineate recipients of reports*
* *Include reporting timelines and expectations for all review and oversight bodies e.g. IRB and DSMB.*

*This section should delineate the AEs as related to the study, serious AEs, and safety reporting procedures. Describe if participants will be asked about the presence/absence of AEs at every study visit, including those conducted via telephone or electronically. The protocol and MOP should specify the timeframe for collecting AEs (i.e., starting at consent or baseline visit; ending at last study visit; ending 30 days after the last study visit). The protocol and MOP should also include the AE severity grading scale (*[*evs.nci.nih.gov/ftp1/CTCAE/CTCAE\_4.03\_2010-06-14\_QuickReference\_8.5x11.pdf*](file:///\\NIMHHOME01.nimh.nih.gov\CTOB\PI%20Orientation\PI%20Orientation%20Letter%20Packet\evs.nci.nih.gov\ftp1\CTCAE\CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) *), as well as rules for classifying AEs that are characteristic of the study population (i.e., does nausea in pregnant women constitute an AE) to help ensure study staff are classifying AEs consistently. This section uses NIMH as an example of sponsor-specific reporting requirements.*

Reporting Requirements:

| Reportable Event | When is Event Reported to the NIMH | Reported By |
| --- | --- | --- |
| IRB/ISM/DSMB/OHRP/FDA Suspensions or Terminations | Any suspension or termination of approval must include a statement of the reason(s) for the action and must be reported promptly to the NIMH PO within 3 business days of receipt. | Regulatory or Monitoring Entity and Investigator |
| Deaths related to study participation | Deaths must be reported immediately (no later than within 5 business days) of the principal investigator first learning of the death. | Investigator |
| Unexpected Serious Adverse Events related to study participation | Reported to the NIMH PO within 10 business days of the study team becoming aware of the SAE. | Investigator |
| Unanticipated Problems Involving Risks to Subjects or Others | Reported to the NIMH PO within 10 business days of the investigator learning of the event. | Investigator |
| Serious or Continuing Noncompliance | Reported to the NIMH PO within 10 business daysof IRB determination | Institution |
| Adverse Event | For all AEs and SAEs that are deemed expected and/or unrelated to the study, a summary should be submitted to the NIMH PO with the annual progress report. | Investigator |
| Protocol Violations | With the annual progress report. | Investigator |

# 17.0 DATA AND SAFETY MONITORING RESPONSIBILITIES

*The roles and responsibilities of the entities monitoring participant safety and study quality are described in this section. This section should include responsibilities of study staff, such as the PI, medical monitors, and CRAs, as well as independent entities, such as independent safety officer, external DSMB, IRBs, and the FDA.*

# 18.0 STUDY MONITORING

*This section should describe site and coordinating center QI/QC and GCP monitoring that will take place, what will be reviewed at visits, who will be conducting the monitoring, the timeframe for visits, the timeframe for distributing monitoring reports, and who will receive the reports.* *Describe the purpose of monitoring visits, such as:*

* [Ensure the rights and safety of participants
* Confirm that the study is conducted in accordance with GCP guidelines
* Ensure maintenance of required documents and regulatory compliance
* Verify adherence to the protocol
* Monitor the quality of data collected
* Ensure accurate reporting and documentation of all AEs and unanticipated problems.]

*See* ***provide link to Clinical Monitoring Plan template in the Web Toolbox*** *for a template monitoring plan. If there will be a separate monitoring plan document in place, the MOP can refer to the plan and not duplicate information that it is in the monitoring plan.*

*This section should also include any training and certification procedures related to QI/QC and GCP.*

# 19.0 Protocol Compliance

*This section should describe what constitutes protocol deviations and violations and the process for reporting such deviations/violations to appropriate parties, including the investigator, the Coordinating Center, and the DSMB. The Coordinating Center (for the study) and the study coordinator (for the site) should maintain a log of all protocol deviations/violations and should report them routinely to the DSMB. A sample log can be found at* ***provide link to Subject and Study-Wide Protocol Violations/Deviations Log template in the Web Toolbox****.*

*Protocol deviations/violations include noncompliance with the research protocol that may or may not increase risk or decrease benefit to the subject and/or affect the integrity of the data.* *Examples include, but are not limited to the following:*

* [Randomization of an ineligible participant
* Subject’s refusal to complete scheduled research activities
* Failure to obtain Informed Consent
* Enrollment of a participant into another study
* Failure to keep IRB approval up to date
* Wrong treatment administered to participant
* Loss of laptop computer that contained PII
* Outcome measurement not performed]

# 20.0 Data Collection and Study Forms

*This section of the MOP describes the study’s data collection and data management procedures and should include copies of all forms in the attachment section.*

## 20.1 Participant Binder

*This section describes how participant data are maintained in the study. All essential study documents must be retained by the investigator in a Participant Binder (can be electronic if study utilizes direct data entry) and generally include the following:*

* [Source documents (e.g., lab reports, x-rays, etc.)
* Questionnaires completed by the participant
* Case Report Forms (CRFs)
* Data correction forms
* Workbooks]

*Describe storage plans for these binders that follow data security guidelines consistent with the site institution.*

**20.2 Source Documentation**

*Include a complete listing or description of the study’s source documentation in this section.*

## 20.3 Study Forms

*Study CRFs provide the vehicle for consistent data collection. In this section of the MOP, provide:*

* *Study forms and their collection schedule*
* *Description of each study form and questionnaire*
* *A set of instructions for completing the paper CRFs*
* *Format for forms production and distribution along with contact person*
* *Forms maintenance*

### 20.3.1 General Instructions for Completing Forms

*In this section of the MOP, please provide a set of instructions for completing CRFs.*

*According ICH Good Clinical Practice (GCP) guidelines, all data recorded on study forms must be verifiable in the source documents maintained by the study site(s). Study data should be recorded without specific patient identifying information on both the paper and digital formats. Patient identifiers are sequestered in a separate code book that is kept in a locked cabinet in the Principal Investigator’s office. Instructions for completing CRFs ensure quality and consistency in data collection.*

*Some useful and frequently used examples are listed below:*

**[Sample instructions:**

When completing paper study forms, PRINT IN CAPITAL LETTERS using black ink. Note, participants must not be identified by name on any study document submitted with the forms (e.g., ECG tracing, lab reports). Replace the participant name with the participant initials and ID number (per institutional policy).

* **Header:** Complete the header information on EVERY page, including pages for which no study data are recorded.
* **Participant ID:** The participant ID must be recorded on EVERY page, including pages for which no study data are recorded.
* **Time:** Use a 24-hour clock (e.g., 14:00 to indicate 2 p.m.) unless otherwise specified.
* **Dates:** All dates must be verifiable by source documents. Historical dates are sometimes not known (e.g., date of first symptom); therefore, conventions for missing days and/or months should be described (e.g., UNK or 99). Provide as much information as known (e.g., unk/unk/2011).
* **Abbreviations:** Use of abbreviations not specifically noted in the instructions for completing the forms can be problematic and should be held to a minimum.
* **Correcting errors:** If an error has been made on the study forms, place a single line through the erroneous entry and record the date and your initials. Indicate the correct response as close to the original entry as possible. It is important to not obstruct any original data. Do not use white out or throw a form away and start over.
* **Skipping items:** Do not skip any items. Some items may carry "Unknown" or "Not Applicable" response choices which should be selected when necessary.
* **Incomplete data:** Data may not be available to complete the form for various reasons. Circle the item for which information is not available and indicate the reason near the appropriate field:
* If an evaluation was not done, write ND and provide a reason.
* If the information is not available, but the evaluation was done, write NAV.
* **Note: Only in rare circumstances, as in the case of lost documentation,** should NAV be recorded on the form. Every effort should be made to obtain the information requested.
* If an evaluation is not applicable, write NA.
* **Incomplete or Illegible forms:** Incomplete forms that do not have adequate explanation (as described above) compromise the integrity of the entire study. Errors, such as incomplete or illegible forms, are problems that require time and energy to resolve.]

*In this section of the MOP, a set of guidelines for incomplete or illegible forms must be included. For example:*

* [If an entire page of the form cannot be completed (e.g., no parts have any responses), and it is unlikely that it will be completed, draw a diagonal line through the form and write NOT DONE, NOT AVAILABLE, or NOT APPLICABLE, as appropriate. Add your initials and the date that the form was crossed out.
* The header information must be completed even though no data are recorded on the form. If a form can only be partially completed at the time of monitoring, but will be completed when the information becomes available, follow the direction of the clinical monitor.
* Do not leave forms incomplete or unused without explanation.]

**20.3.2 Data Flow**

*This section of the MOP describes data flow, data entry, and data correction procedures. Specifically describe how the team will ensure that all forms are complete, intact, and transmitted to the data manager or how the data are directly entered into an electronic CRF (eCRF). This section of the MOP describes the:*

* *Disposition of study forms or data entry into the computer system*
* *Schedule for completion and transmission of forms*
* *List of forms for which copies are to be maintained at the site and forms to be submitted for data entry*

### 20.3.3 Study Tracking Documentation

*This section lists the study logs, forms, and/or documents that will be used to provide documentation of study processes and assist with study operations.*

*This section should reference documents that serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. For additional examples of study documentation, logs, and forms, please go to* ***provide link to the Web Toolbox****.*

* **[Delegation of Authority Log**—serves as the record of appropriately qualified individuals as delegated by the PI to perform study-related tasks. It is the responsibility of the PI to delegate study team members and maintain the log.
* **Screening Log**—provides a comprehensive list of all subjects who were screened for eligibility. It should be arranged chronologically and be kept up to date at all times.
* **Enrollment Log**— documents chronological enrollment of subjects by trial number.
* **Adverse Event Log**—is used to document adverse events as they are identified. It is the responsibility of the PI and delegated study investigators to assess for adverse events at each subject visit, including those conducted via telephone or electronically. A subject-specific and study-wide Adverse Event Log should be maintained to facilitate safety monitoring and help identify adverse event trends across subjects.
* **Protocol Deviation Log**—is used to document deviations from the IRB-approved protocol as they are identified. A subject-specific and study-wide Protocol Deviation Log should be maintained to facilitate compliance monitoring and reporting to regulatory authorities.
* **Study Drug Dispensation and Accountability Log**—provides documentation of the precise amount of study drug given to and returned by subjects, the compliance rate, and the individual responsible dispensing the study drug.
* **Record of Destruction of Clinical Product**—is a log used to document the destruction of any unused study drug. The date and time of incineration as well as how many vials/pills were incinerated must be recorded. This record should be attached to the Study Drug Accountability Log.
* **Site Visit Log**—records individuals visiting the site. The most common reasons for visits are site initiation, monitoring, training, and closeout.
* **Training Logs**—provides a record of study-specific training.]

#### 20.3.4 Retention of Study Documentation

*The length of time all study files are to be maintained should be specified in this section and should be responsive to NIH policy (see below). Individual IRBs, institutions, states, and countries may have different requirements for record retention. Investigators should adhere to the most rigorous requirements and should retain forms and all other study documents for the longest applicable period. This section should outline the length of time of retention of study files and where they will be located. If subject files are to be sent off-site for long-term storage, the files must be completely de-identified.*

*(NIH Grants Policy 8.4.2;* [*https://grants.nih.gov/grants/policy/nihgps/HTML5/section\_8/8.4\_monitoring.htm*](https://grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.4_monitoring.htm)*)*

*(NIH grants under an IND/IDE (FDA regulations 21CFR312.62);* [*https://www.ecfr.gov/cgi-bin/text-idx?SID=c2fdba244d645ddda8a2c9647156683c&mc=true&node=pt21.5.312&rgn=div5#se21.5.312\_162*](https://www.ecfr.gov/cgi-bin/text-idx?SID=c2fdba244d645ddda8a2c9647156683c&mc=true&node=pt21.5.312&rgn=div5#se21.5.312_162) *)*

# 21.0 Data Management

*This section should describe the computer system and data management approach that will be used to support the study and details on how data are to be collected, entered (e.g., if eCRFs are used), edited, and corrected. The procedures to address the following functions should be described:*

* **[Data Tracking**—to provide the status of enrollment, number of forms completed at the sites and number of forms transmitted to a Coordinating Center or lead site, as appropriate
* **Data Entry**—that is easy to use and minimizes errors, such as facsimiles of the forms. In addition, data are double-entered, checked, and a log maintained for any alteration to the database (audit trail).
* **Data Editing**—that identifies out-of-range and missing entries, errors in dates and logical inconsistencies (e.g., first treatment date precedes protocol start date or protocol specifies an examination before randomization, but the examination form is missing)
* **Updating**—to correct data and maintain an audit trail of all data changes
* **Reporting**—to describe and account for accrual, forms entered and completed, etc.
* **Statistical Analysis**—mechanism to transmit data to statistical analysis packages (e.g., SAS).
* **Access to the Database**—e.g., password protected
* **Back**-**up of Database**— e.g., the frequency and location of back-ups]

*Discussion should cover data flow, transfer of data from sites in a multicenter study, error identification and resolution, development of useful reports, and deriving a frozen, analytic database from edited or "clean" records.*

*If a Users’ Guide to data management will be used, it can be referenced in the MOP, but the information in the guide does not need to be duplicated in the MOP.*

*Investigators should be aware that computerized systems used in studies that will be submitted to the FDA must be documented and validated. Guidance for electronic systems is found on the FDA Web site, Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures* [*http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm*](http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm)*.*

**21.1 Data Quality Checks**

*This section of the MOP should also provide a summary of the checks that will be implemented for data quality control, who will conduct these, and on what timeframe. The following items should be included in the review:*

* [Missing forms or data
* Unique identification (ID) number for each study participant is consistent across all forms and visits
* Correct numbers in the site ID and participant’s ID number
* Legible data
* Consistent and logical dates over time
* Data within acceptable ranges
* Data consistent across forms and visits
* All fields of a "completed form" actually completed or reason for no data noted
* All required forms completed or reason for no data noted
* Assure the rights and safety of participants
* Confirm that study conduct follows the guidelines of Good  
  Clinical Practice (GCP)
* Assure maintenance of required documents
* Verify adherence to the protocol
* Monitor the quality of data collected
* Assure accurate reporting and documentation of all adverse events
* Informed consent has been obtained and documented
* Adverse events have been identified and recorded
* The information recorded on the forms is complete and accurate
* There are no omissions in the reports of specific data elements
* Missing examinations are indicated on the forms
* Participant disposition at study exit is accurately recorded]

## 21.2 Computerized Patient Record System

*If a site’s computer patient record system is being used as part of study procedures, describe what activities are being conducted through that system, and instructions for conducting those activities. Also note if this system is being utilized as a study database, and describe relevant study procedures for activities such as:*

* [Placing lab orders for subjects
* Getting lab results
* Reviewing subject records
* Reviewing subject progress notes
* Obtaining consults
* Accessing study outcome data]

## 21.3 Training on the Data Management System

*This section should articulate how study staff will be trained on the study data management system(s).*

## 21.4 External Data

*External data refers to data sent to or collected at a study organizational component other than a clinical site (e.g., central laboratory, imaging facility, etc.) This section of the MOP should describe how this information will be collected, labeled, handled, shipped, tracked and reconciled, so that study data are not lost. As stated in the HIPAA guidelines, personal identifiers such as name, geographic location, social security number, and 15 other specific individual identifiers should not be used. Therefore, it is important to specify how participant materials will be coded (e.g., by participant identification number) during transmission.*

# 22.0 SITe-SPECIFIC STANDARD OPERATING Procedures

*Site-specific Standard Operating Procedures (SOPs) which relate to conduct of clinical trials should be listed in this section of the MOP. Note: Printed SOPs should not be inserted in the MOP. The location of each SOP (i.e., electronic file name) can be included in this section for staff to reference.*

# 23.0 STUDY COMPLETION AND CLOSEOUT PROCEDURES

*This section of the MOP should briefly outline the Study Completion and Close-out procedures. Examples of Close-out activities include, but are not limited to, the following:*

* [Verification that study procedures have been completed, data collected, and study drug and supplies are returned to the responsible party or prepared for destruction
* Review of all correspondence and study files against sub-contracted site records for completeness
* Ensure that all data queries have been completed
* Ensure that all correspondence and study files are accessible for external audit
* Ensure study records retention policies are followed
* Ensure the IRB/DSMB is notified of study completion and obtaining a copy of the notifications
* Preparation of a report summarizing study conduct to the DSMB]

## 23.1 Participation Notification

*This section should include the plans developed by the Principal Investigator and study staff to notify participants that the study is over, ask whether they would like to be informed of the overall results of the study, and thank them for their participation.*

# 24.0 POLICIES

*This section of the MOP should discuss the safeguards which have been put in place to ensure participant confidentiality and data security. It is the responsibility of the Principal Investigator to outline and enforce participant confidentiality and data security guidelines.*

[The following policies shall be in place in order to protect subject safety and privacy:

* ***Data flow procedures*** - participant identifying information will not be transmitted from clinical site to the Coordinating Center.
* ***Electronic files*** *-*participant identifying information stored electronically will be maintained in an encrypted form or in a separate file.
* ***Forms*** *-*forms or pages containing personal identifying information will be separated from other pages of the data forms.
* ***Data listings*** *-*participant name, name code, hospital chart or record number, or other unique identifiers, such as Social Security number, will not be included in any published data listing.
* ***Data distribution*** - internally utilized data listings that contain participant name, name code, or other identifiers easily associated with a specific participant will not be distributed.
* ***Data disposal*** - computer listings that contain participant identifying information will be disposed of in an appropriate manner.
* ***Access*** - participant records stored in the data center will not be accessible to persons outside the center without the express written consent of the subject.
* ***Storage*** *-*study forms and related documents retained both during and after study completion will be stored in a secure location.
* ***Computer Passwords*** - Passwords provide limitations on general access to the systems and to the functions that individuals can use on the system. Passwords will be changed on a regular basis per Institutional policy. Passwords should not be shared with other study team members. If subjects are completing self-report forms electronically, each subject should have individual log-in credentials.]

# 25.0 MOP MAINTENANCE

*This section should describe the procedures for updating and distributing updated MOP versions, as well as staff members responsible for this activity. Each page of the MOP should be numbered and dated, and contain a version number to facilitate any changes and/or additions. The MOP should be continuously reviewed by the PI and/or Coordinating Center to ensure that the operating procedures described are accurate. If any procedures have been changed or modified, the MOP should be updated distributed.*

**26.0 APPENDICES**

*The following documents can be included in the MOP appendices: study forms, standard operating procedures, recruitment flyers, letters to participants, and other documents included in the study regulatory binder or used in study operations and implementation. Templates that can be included in the MOP appendices can be found at* ***provide a link to the OCR Web Toolbox****. These templates can be utilized by the study team and modified to meet the needs of the study.*

*For a comprehensive list of essential study documents, it is recommended that a site(s) reference ICH GCP E6 Section 8 (*[*http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial*](http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial)*).*

*Note: If the study involves drug intervention, either the Package Insert for an approved drug or the Investigator’s Brochure for an investigational product should be included as an appendix.*