

National Center for Complementary and Integrative Health

Guidelines for Developing a Manual of Operations and Procedures (MOP)

TABLE OF CONTENTS

	Page
WEB LINKS	4
1. INTRODUCTION	5
2. OVERVIEW	5
3. MOP CONTENTS AND ORGANIZATION	6
3.1 Study Protocol.....	7
3.2 Study Organization and Responsibilities.....	7
3.2.1 Roster.....	7
3.2.2 Coordinating Center	7
3.2.3 Study Sites	8
3.2.4 Pharmacy Activities	8
3.2.5 Steering Committees.....	8
3.2.6 Other Study Committees	9
3.2.7 NCCIH	9
3.3 Training Plan	9
3.4 Communications Plan	9
3.5 Study Intervention	10
3.6 Recruitment Plan.....	10
3.7 Participant Retention.....	10
3.8 Study Flow	11
3.9 Screening and Eligibility Criteria.....	11
3.9.1 Screening Log	13
3.9.2 Eligibility Criteria.....	13
3.10 Informed Consent and HIPAA.....	13
3.10.1 HIPAA Authorization.....	13
3.11 Randomization	14
3.12 Blinding and Unblinding (Masking and Unmasking).....	14
3.13 Study Measurements and Procedures	15
3.13.1 Timeline and Visit Schedule	15
3.13.2 Scope/Schema	15
3.13.3 Final Study/Early Discontinuation Evaluations	15
3.14 Concomitant Medication.....	16
3.15 Safety Reporting	16
3.16 Study Compliance	16
3.17 Data Collection and Study Forms.....	17
3.17.1 Source Documentation.....	17
3.17.2 Participant Binder	17
3.17.3 Study Forms	17
3.17.4 General Instructions for Completing Forms.....	17
3.18 Data Flow	19

3.19	Administrative Forms	19
3.20	Retention of Study Documentation.....	20
3.21	Data Management.....	20
	3.21.1 External Data	21
3.22	Quality Control Procedures	22
	3.22.1 Standard Operating Procedures.....	22
	3.22.2 Data and Form Checks	22
	3.22.3 Double Data Entry	22
	3.22.4 Site Monitoring	23
3.23	Reports	23
3.24	Data and Safety Monitoring Activities.....	24
3.25	Study Completion and Closeout Procedures	24
	3.25.1 Participant Notification.....	25
	3.25.2 Site Procedures.....	25
3.26	Policies.....	25
	3.26.1 Confidentiality Procedures	25
	3.26.2 Publications.....	26
3.27	MOP Maintenance	27
4.	REFERENCES	28
	APPENDIX A. SAMPLE SCREEN LOG.....	30
	APPENDIX B. SAMPLE SCHEDULE OF EVENTS.....	31
	APPENDIX C. SAMPLE PROTOCOL DEVIATION LOG	32
	APPENDIX D. SAMPLE MOP MODIFICATION LOG	33

WEB LINKS

Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials
(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>)

Implementation of NCCIH Policies for Clinical Studies
(<http://nccih.nih.gov/grants/policies>)

NIH Policy for Data and Safety Monitoring
(<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>)

Guidelines for Writing Informed Consent Documents
(<http://ohsr.od.nih.gov/info/sheet6.html>)

Clear and to the Point: Guidelines for Using Plain Language at NIH
(<http://oma.od.nih.gov/ma/customer/customerserviceplan/attachment2.htm>)

1. INTRODUCTION

The purpose of this document is to provide a Manual of Operating Procedures (MOP) template for principal investigators (PIs) of multisite clinical trials. The role of the MOP is to 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. Investigators of single-site studies are encouraged to consider the template's contents. However, a MOP is not mandatory for these studies.

In preparing the MOP, the PI (study chair) must be aware of the terms of award with respect to required reporting, data and safety monitoring, and Institutional Review Board (IRB) approval (see Grantee Policies and Resources). <http://nccih.nih.gov/grants/policies>

2. OVERVIEW

A MOP is a handbook that details a study's conduct and operations. It transforms the study protocol into a guideline that describes a study's organization, operational data definitions, recruitment, screening, enrollment, randomization, followup procedures, data collection methods, data flow, case report forms (CRFs), and quality control procedures. The MOP is intended to serve as a study "cookbook" that facilitates adherence to study procedures. The MOP is developed before the study can commence.

During a study's planning phase, the PI and study staff drafts the protocol. The protocol must be approved by the IRBs of all Institutions participating in the study and by the Data and Safety Monitoring Board (DSMB). Prior to developing the MOP, the final protocol, CRFs, informed consent documents, and administrative forms (e.g., screening and enrollment log, protocol deviation log, etc.) should be finalized. Additionally, if the study is to be submitted to the Food and Drug Administration (FDA) under an Investigational New Drug Application (IND), an Investigator's Brochure (for investigational products) or Package Insert (for marketed drugs) must be included. The timeline for development of study materials must be planned for and typically takes approximately 6 months.

Development of the MOP requires the involvement of the PI and study staff to ensure that the MOP accurately describes how the study procedures will be performed. A Steering Committee comprised of study site and Coordinating Center investigators, often finalizes the protocol and develops or oversees development of the MOP.

The MOP is a dynamic document that will be updated throughout the conduct of a study to reflect any protocol or consent amendments as well as the refinement of the CRFs and study procedures. The MOP should be maintained in a format that allows it to be easily updated, and is typically filed in a three-hole binder. For ease of organization, it is recommended that the MOP be subdivided into various sections separated by dividers or sheets of

color paper between each section. Further, each page of the MOP should contain the version number and date. As pages are revised, an updated version number and associated date will replace the original page(s) in the MOP. All previous versions should be archived.

3. MOP CONTENTS AND ORGANIZATION

The MOP details the study procedures and describes the study-specific documents and must be adapted to each study's specific needs. It often includes the following sections:

- a. Study Protocol or Synopsis
- b. Staff Roster
- c. Study Organization and Responsibilities
- d. Training Plan
- e. Communications Plan
- f. Recruitment and Retention Plan
- g. Study Design Diagram
- h. Screening and Eligibility Criteria and Processes
- i. Informed Consent and HIPAA
- j. Study Intervention
- k. Blinding and Unblinding (Masking or Unmasking)
- l. Evaluations and Followup
- m. Concomitant Medications
- n. Safety Reporting
- o. Data and Safety Monitoring Responsibilities
- p. Study Compliance
- q. Data Collection and Study Forms
- r. Data Management
- s. Quality Control Procedures
- t. Study Completion and Closeout Procedures
- u. Policies
- v. MOP Maintenance

The MOP should include all of the relevant sections from this list that apply to the specific study. If a section does not apply (e.g., randomization for a study with no randomization), it is not included in the MOP. Additionally, if the study involves a drug intervention, either the Package Insert for an approved drug or the Investigator's Brochure for an investigational product must be included as an appendix.

3.1 Study Protocol

The study protocol provides scientific rationale of the proposed investigation. See the [NCCIH Protocol Template](#) for protocol development details. The final version of the study protocol with the date of IRB approval and version number is included in the MOP or can accompany the MOP as an appendix.

3.2 Study Organization and Responsibilities

The study organization, staff roster, roles, and responsibilities are described in this section.

Members of the Coordinating Center and other centers as relevant study sites, study committees, laboratories, etc. are delineated along with their roles and responsibilities. Large studies are generally depicted by an organizational chart.

3.2.1 Roster

The roster includes the names, roles, addresses, phone numbers, fax numbers, pager numbers and e-mail addresses of study staff members, NCCIH staff, and DSMB or safety officer.

A notation of whom to contact regarding special situations and study-related questions should also be included. Examples of questions include:

- Protocol requirements
- Reporting an adverse event (AE)
- Request for additional supplies
- Randomizing a participant
- Unblinding a participant (should not be done lightly).

3.2.2 Coordinating Center

The responsibilities of the Coordinating Center may include:

- Development and maintenance of the MOP
- 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
- Quality control procedures
- Reports (e.g., enrollment, AEs, participant status, site performance, quality control, and DSMB)

- Distribution of all changes, updates and policies of reports and documents to all participating study sites, NCCIH, and the DSMB, as necessary.

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

3.2.3 Study Sites

The roles and responsibilities of the investigators and study sites may include:

- Maintenance of study binder
- Participation in protocol finalization and preparation of study materials
- Compliance with protocol, MOP, IRB, Federal and state regulations
- Membership in a Steering Committee and other committees
- Recruitment, screening, and enrollment of participants
- Protection of participants' rights
- Data collection and participant followup through study completion
- Transfer of data to Coordinating Center and resolution of all queries
- Compliance with and accountability of administration of study intervention
- Retention of specific records (e.g., laboratory or drug distribution records)
- Communication of questions, concerns, and/or observations to the Coordinating Center.

When developing this section of the MOP, please include all roles and responsibilities of the sites, not just the examples given above.

3.2.4 Pharmacy Activities

“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.

This section of the MOP describes how the investigational agent is to be prepared, dispensed, stored, and returned to the Coordinating Center, the Sponsor, or other designated organization. It provides instructions for completing drug accountability records and administrative records.

3.2.5 Steering Committees

The Steering Committee often assumes the leadership role in large, multicenter studies, and is responsible for the overall direction of a study.

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

- Design and conduct of the study
- Preparation of the essential study documents, including the protocol, protocol amendments, MOP, and data collection forms

- 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
- Review and response to other general advice and/or recommendations (e.g., from the NCCIH program director or project officer)

3.2.6 Other Study Committees

In large studies, there may be an Executive Committee that is responsible for reviewing study progress and identifying and resolving issues. The NCCIH program director/project officer may be a member of this committee. The Executive Committee is the small study leadership group that guides the study implementation and operations. Studies often include a number of other committees (e.g., Recruitment and Retention, Safety, Quality Control, Publications, etc.)

All relevant study committees should be briefly described.

3.2.7 NCCIH

Many interventional multicenter studies sponsored by NCCIH are funded under a cooperative agreement (U01), an "assistance" mechanism, in which substantial NCCIH programmatic involvement with the awardees is anticipated during the study. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and NCCIH. NCCIH supports and stimulates the awardees' activities in a partnership role. However, NCCIH does not assume direction, prime responsibility, or a dominant role in the study's activities. NCCIH's role and responsibilities in the conduct of the trial should be delineated in this section.

3.3 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.

3.4 Communications Plan

Ongoing communications among study site investigators and members of the committees are essential to assure study progress and address emerging study issues. The Coordinating Center should document these communications. This section describes the study communications plan.

Regular communication with the NCCIH Program Officer should also be described in this section.

3.5 Study Intervention

A study intervention can be defined as administration of a test article to prevent or change the natural course of a disease or condition. Interventions include drugs, nutritional supplements, surgery, devices, behavioral activities (e.g., coping mechanisms, cognitive training), and/or lifestyle changes (e.g., diet, exercise). A clinical trial has an intervention that is assessed for efficacy and/or safety.

This section should include a detailed description of the type of intervention and how it will be implemented.

Intervention must be thoroughly described so that all participants have the same exposure:

- 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
- **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).
- **Biobehavioral 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.

3.6 Recruitment Plan

To assist study sites in recruiting study participants, this section of the MOP describes the target population and suggests recruitment 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.

3.7 Participant Retention

Participant retention requires careful planning and continuous efforts and helps to ensure a successful study. Every effort should be made to retain study participants without coercion. During enrollment, it is important to obtain the names and contact information for several individuals closely related to

the participant (e.g., next of kin, friends, etc.). Such individuals can be contacted in the event that a participant does not return for followup visits.

Plans and suggestions for participant retention should be described and may include strategies such as:

- Monthly phone calls
- Birthday and holiday cards
- Reminder postcards.

An action plan for correcting retention problems should also be provided in this section.

3.8 Study Flow

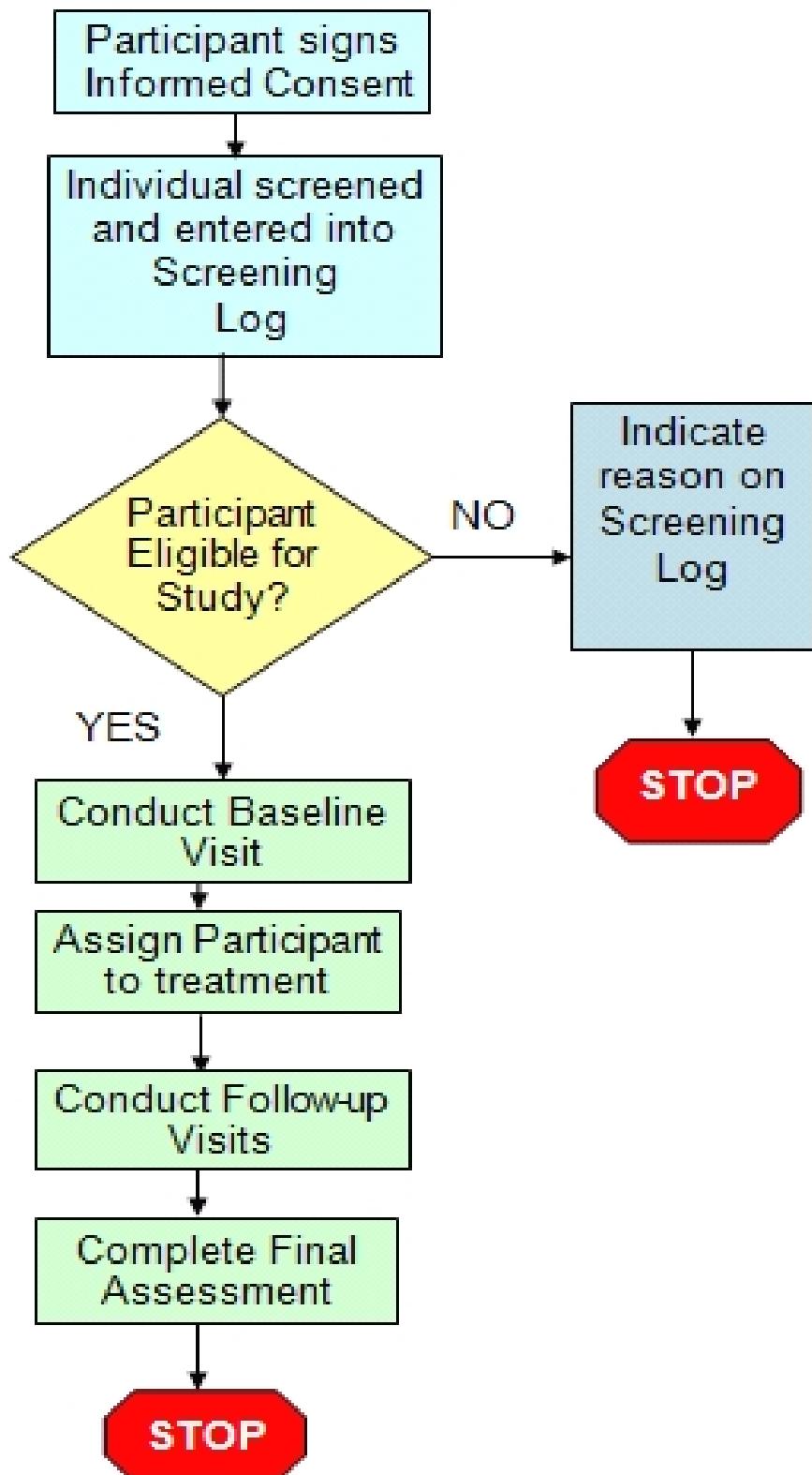
It is useful to provide an overview of the study's major steps in a flow diagram, as shown in Figure 1. This flow should be uniquely tailored to the study and is useful in describing it to new staff members.

3.9 Screening and Eligibility Criteria

To help assure that study sites accrue participants with the required characteristics, this section provides 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.

Frequently, there is a prescreening phase during which the study coordinator responds to initial telephone calls from interested individuals or physicians. With consideration for the Health Insurance Portability and Accountability Act (HIPAA) regulations, as interpreted by the site's institution, the PI/study coordinator may access their clinic's medical records, hospital admission, or discharge notes, if necessary, to identify potential candidates for screening.

Figure 1: Sample Study Flow Diagram



3.9.1 Screening Log

A Screening Log provides documentation of all individuals that are reviewed for study eligibility. Usually, it contains an identification number (ID) and individuals' initials, age, gender, race and ethnicity, screening date, and eligibility status:

- Eligible for study participation and date enrolled
- Ineligible for study participation and reason
- Source of participant (i.e., advertising, referral, etc.)

It may also contain the randomization number. The MOP describes the contents of the Screening Log and maintenance procedures, including frequency of updates and processes for secure storage. A sample Screening Log is included in [Appendix A](#).

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

3.9.2 Eligibility Criteria

Study eligibility is determined by a set of specific inclusion and exclusion criteria that are outlined in the study protocol. Individuals must meet all entry criteria prior to treatment assignment. This section of the MOP defines the criteria, method for determination (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).

3.10 Informed Consent and HIPAA

This section of the MOP describes the specific instructions for obtaining informed consent. If there are multiple consent documents (e.g., collecting data from additional sources, participation in ancillary studies), then each informed consent form should be outlined in the MOP and accompanied by detailed instructions. A template of the Informed Consent(s) should be included in the MOP.

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.

This section should indicate who receives a copy of the informed consent form and where the original will be held.

[NCCIH Informed Consent guidelines](#) and [NCCIH Informed Consent Checklist](#) should be accessed for additional details.

3.10.1 HIPAA Authorization

The HIPAA authorization form may be a separate document from the informed consent, and must be reviewed and signed by the study participant in addition to reviewing and signing the consent form. The format of the HIPAA authorization is established by the local IRB. Investigators should

review information provided in Impact of the HIPAA Privacy Rule on NIH Processes Involving the Review, Funding, and Progress Monitoring of Grants, Cooperative Agreements, and Research Contracts

(<http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>) and contact their appropriate institutional officials to learn how the Privacy Rule applies to them, their organization, and their specific research project.

Another helpful resource is Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, NIH Publication 03-5388 at <http://privacyruleandresearch.nih.gov>.

If the study is collecting any personal identifiable health information, this should be explained in this section of the MOP. Additionally, the IRB-approved HIPAA form should be included in the appendix.

3.11 Randomization

Randomization is used to reduce bias in assignment to treatment. In randomized, controlled clinical trials, participants are assigned to a treatment group based upon a predetermined randomization scheme developed by the study statistician. 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.

3.12 Blinding and Unblinding (Masking and Unmasking)

In most studies with randomization, participants and the treating physician are "blinded" or "masked" to the treatment and do not know if the participant is receiving the study intervention or placebo. The study statistician and/or a designated study staff member securely maintains the randomization codes so that the treatment assignments are not revealed. Randomization and

blinding/unblinding procedures are typically determined prior to the enrollment of the first participant.

Unblinding is a serious action and should be limited to reduce potential bias. In the event that 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

The investigators' procedures for unblinding should be clearly specified in the MOP.

3.13 Study Measurements and Procedures

To ensure that assessments and measures are conducted consistently across study participants and sites, this section describes procedures for performing assessments and outcome measures. For example, in a weight loss study, the procedure for capturing weight and blood pressure might be described as follows:

- Weigh participant between 7 a.m. and 9 a.m. while fasting and without shoes.
- Measure blood pressure while participant is in a sitting position.

All outcome and safety evaluations (e.g., blood chemistries) should be delineated in this section.

3.13.1 Timeline and Visit Schedule

A useful study tool included in the MOP is 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. An example of a schedule is provided in [Appendix B](#).

3.13.2 Scope/Schema

In this section of the MOP, each visit should be explained in enough detail so that a new or substitute team member can 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.

3.13.3 Final Study/Early Discontinuation Evaluations

Participants should be actively followed through all study visits until the final visit.

It is important to note that if a study participant is discontinued from treatment, he/she should still be followed to the end of the study.

Evaluations for the final study/early discontinuation visit should be described in this section.

3.14 Concomitant Medication

The MOP provides a rationale for the concomitant medications that are required and restricted in the protocol. Please list all required and/or excluded concomitant medications in this section.

3.15 Safety Reporting

This section of the MOP details the definitions of and procedures for reporting AEs.

The Guidelines provide:

- Definitions of AEs, serious AEs, and unanticipated problems
- Responsibilities of NCCIH and investigators
- Reporting processes
- Description of terms used in reporting.

This section should delineate the AEs, as related to the study, serious AEs, and safety reporting procedures.

3.16 Study Compliance

Clinical trials are expensive endeavors and every effort should be made to maximize adherence to the protocol and minimize noncompliance.

Comprehensive training on the study protocol, early review of the data, and routine communications with the sites help to minimize protocol deviations. However, there should be a mechanism in place to track protocol deviations and procedures to notify appropriate parties about their occurrence.

Protocol deviations include, but are not limited to the following:

- Randomization of an ineligible participant
- 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
- Outcome measurement not performed

This section should describe what constitutes protocol deviations and the process for reporting such deviations to appropriate parties, including the study chair and site investigator, the Coordinating Center, NCCIH, and the DSMB or safety officer, within 24 hours of occurrence if possible, or as soon as they are discovered. Investigators need to follow their IRB requirements for reporting protocol deviations to the Board. In addition, if monitors discover any of these deviations during a site visit, they should list any such occurrence in their monitoring report. The Coordinating Center (for the study) and the study coordinator (for the site) should maintain a log of all protocol deviations and should report them routinely to the DSMB or safety officer.

While there may be rational clinical reasons for an occasional deviation, a site with continuous problems is at risk for losing its funding. A log for recording protocol deviations should also be included in this section. A sample log is presented in [Appendix C](#).

3.17 Data Collection and Study Forms

This section describes the study's data collection and data management procedures and should include copies of all forms. Alternatively, they could be maintained in a separate binder.

3.17.1 Source Documentation

A source document is any document on which study data are initially recorded. Source documents include laboratory reports, EKG tracings, medical records, standardized test forms, etc. These data are then transcribed to a paper CRF or electronic CRF (eCRF) to document study-specific data elements.

3.17.2 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 and generally include the following:

- Source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- Signed consent forms
- Questionnaires completed by the participant
- CRFs
- Data correction forms
- Workbooks

3.17.3 Study Forms

Data must be collected consistently across participants and sites so that any variability is limited to participants' individual responses to the intervention. Study CRFs provide the vehicle for consistent data collection. In this section of the MOP, please provide:

- Study forms and their collection schedule
- Description of each study form and questionnaire
- Format for forms production and distribution along with contact person
- Forms maintenance.

3.17.4 General Instructions for Completing Forms

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). Instructions for completing CRFs ensure quality and consistency

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

- **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).
- **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.
- **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.
- 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.

3.18 Data Flow

It is the site's responsibility to ensure that all forms are complete, intact, and transmitted to the data manager in a single site study or to the Coordinating Center, as appropriate. More recently, in some studies, data are directly entered into an 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
- Data flow, data entry, and data correction procedures.

3.19 Administrative Forms

Administrative forms provide documentation of study processes and assist with study operations. They may include the following, as relevant:

- **Facsimile Transmittal Sheet**—serves as a cover page for all faxes.
- **Telephone Contact Log**—serves as a record of all conversations regarding the study and study participants.
- **Screening Log**—is a record of all individuals screened for participation in the study. It should be arranged chronologically and be kept up to date at all times.
- **Participant Identification Code List**—is a record of the participant's name, medical record number, randomization number, and study entry and exit dates. Due to the confidential nature of this information, it should be maintained in a secure location, apart from other forms and data files at the study site. The information contained in the list must be maintained by

the site for a period stipulated by NCCIH, the site institution, or other relevant body.

- **Protocol Deviation Log**—is used to document deviations from the protocol as they are identified by participants.
- **Study Drug Accountability Record**—should be maintained in the Pharmacy by the research pharmacist and must not be shared with other members of the study team.
- **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 Record.
- **CRF Transmittal Sheet**—serves as a cover page for each packet of CRFs submitted for data entry. It provides an inventory of the forms that are included in each mailing.
- **Signature Log**—contains the signature of all members of the site study team. It is the responsibility of the PI and/or clinical research coordinator to:
 - Designate individuals authorized to perform outcome measurements, make form entries and changes, and
 - Note the date when any study team member is removed from the team for any reason.
- **Site Visit Log**—records individuals visiting the site. The most common reasons for visits are site initiation, monitoring, training, and closeout.

3.20 Retention of Study Documentation

The length of time all study files are to be maintained is specified in this section. NIH policy requires that studies conducted under a grant retain participant forms for 3 years, while studies conducted under contract must retain participant forms for 7 years. 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.

3.21 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. For studies that involve a large number of sites and/or participants, the investigators may wish to consider a computerized approach for data collection.

Whether using a computerized approach or manual procedures, investigators should consider utilizing systems or procedures that encompass the following functions:

- **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
- **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).

Investigators should involve staff or colleagues with data management experience to assist with the determination of the 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. These areas should be discussed in this section.

A Users Guide may need to be developed as a separate document to aid the study staff with data management tasks.

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>.

3.21.1 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.

3.22 Quality Control Procedures

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol, obtaining complete followup information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality. A quality control plan should be developed before the study starts and adhered to through completion. It may include standard operating procedures (SOPs), data and forms checks, onsite monitoring, numerous reports, and problem correction procedures. This section should detail the various aspects of the plan and describe any training and certification procedures.

3.22.1 Standard Operating Procedures

One aspect of site quality control is a set of SOPs. They describe a site's generic procedures that may have been developed to assist with standardization across studies. SOPs may include laboratory and pharmacy procedures, and storage of study documents. As relevant, SOPs should be developed by a site to ensure quality studies and study staff should be trained on them. The SOPs should be located in a central location and made easily available to staff for reference.

SOPs that 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, as printed versions of SOPs should be limited in order to maintain version control. The location of each SOP (i.e., electronic file name) can be included in this section.

3.22.2 Data and Form Checks

Data and form checks depend upon the complexity of the study. Data quality control checks may identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical over-time dates
- Fields on a "completed form" actually not completed; or no reason for missing data is provided.

If the study is using electronic data forms, provide a summary of data and form checks that will be implemented for data quality control.

3.22.3 Double Data Entry

In recent years, there have been several articles written on the value of double data entry. While conventional wisdom used to insist upon double data entry, it may be of questionable value, especially if the data entry system provides edits as data are entered. Double data entry is still recommended for cases in which data entry staff enters data "heads down" or with no edits flagged as the data are entered.

3.22.4 Site Monitoring

In multisite studies, a Coordinating Center may conduct periodic site monitoring visits during the course of the study.

The purposes of monitoring visits are to:

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

During monitoring visits, the data recorded on CRFs are reviewed and verified against source documents to ensure:

- Informed consent has been obtained and documented in accordance with IRB/FDA regulations
- 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 when exiting the study is accurately recorded.

Site investigators must ensure that the monitor has access to all study documents, including informed consent forms, intervention accountability records, and source documents.

Once the site visit is complete, a site monitoring report is drafted to provide feedback regarding any problems or issues that may have been uncovered during the visit. The report should state the problems uncovered during the visit and describe recommendations to correct them. A timeline should be agreed upon and included in the report to ensure that followup of the issues is completed and implemented into the study's procedures.

In this section of the MOP, please describe the monitoring plan, including a planned monitoring timeline.

3.23 Reports

Once a study begins, routine reports prepared by the Coordinating Center or study statistician are an important quality control tool. Monthly reports may describe target and actual enrollment by site and in aggregate, individuals screened with reasons for screen failure, and participant disposition (enrolled; active, completed, and discontinued treatment; and lost to followup). Monthly reports can also list or summarize AEs and SAEs. Administrative reports can list the forms completed, entered, and missing and/or erroneous data and

forms. DSMB/independent monitor(s) and NCCIH will specify the type and frequency of reports they wish to receive. Other reporting requirements (e.g., to local IRBs and other regulatory bodies) should also be described.

In this section of the MOP, please discuss the types and frequency of the reports that will be prepared, and the members of the study team who are responsible for their completion.

3.24 Data and Safety Monitoring Activities

The roles and responsibilities of the entities monitoring participant safety and study quality are described in this section. All clinical trials supported by NCCIH must have a data and safety monitoring plan. The type of safety monitoring is determined by the size and/or nature of the study and is specified in the Notice of Grant Award. Small, single-site studies usually have an Independent Monitoring Committee, while large multicenter studies require an independent (of the study, investigators, and participating institutions) DSMB that is advisory to the NCCIH Director. However, if a small, single site study is determined to pose a significant risk to participants, a DSMB may be required by NCCIH.

Safety monitoring activities by the DSMB or independent monitor(s) include: reviewing the protocol with emphasis on data integrity and participant safety issues, monitoring AEs, protecting the confidentiality of the data, and making recommendations to NCCIH and the PI regarding the study and its progress. This section of the MOP should present a data and safety monitoring plan and name the members of the monitoring body.

To assist in preparing a monitoring plan, generic monitoring plans for studies requiring a DSMB or independent monitor(s) are available on the NCCIH Web site. The generic plans describe the monitoring procedures required by NCCIH.

3.25 Study Completion and Closeout Procedures

Study closeout activities are performed to confirm that the site investigator's study obligations have been met and post-study obligations are understood. This section of the MOP should briefly outline the study completion and closeout procedures. Details should be included in the subsequent sections. Examples of closeout activities include, but are not limited to, the following:

- Verification that study procedures have been completed, data have been collected, and study intervention(s) and supplies are returned to the responsible party or prepared for destruction
- Comparison of the investigator's correspondence and study files against the Coordinating Center's records for completeness
- Assurance that all data queries have been completed
- Assurance that correspondence and study files are accessible for external audits

- Reminder to investigators of their ongoing responsibility to maintain study records and to report any relevant study information to NCCIH
- Assurance that the investigator will notify the IRB of the study's completion and store a copy of the notification
- Preparation of a report summarizing the study's conduct
- Participant notification of the study completion

3.25.1 Participant Notification

The PI and study staff or Coordinating Center should develop a letter to notify participants that the study is completed, ask whether they would like to be informed of the results, and thank them for their participation.

In this section of the MOP, please describe a plan for notifying participants about completion of the study.

3.25.2 Site Procedures

The study leadership may also wish to provide certificates of appreciation to sites that met or exceeded their recruitment goals, provided high quality data, and ensured adequate participant retention.

3.26 Policies

The MOP also contains the study's policies, such as confidentiality and publication policies.

Please provide these policies in this section of the MOP.

3.26.1 Confidentiality Procedures

It is the responsibility of the study leadership to outline and enforce participant and study data confidentiality policies. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals, unless such a release is approved by the study leadership and NCCIH and is not in violation of applicable Federal and state laws.

This section of the MOP will discuss the safeguards that have been put in place by the Steering Committee to ensure participant confidentiality and data security.

The following is a list of study participant confidentiality safeguards:

- **Data flow procedures:** Data identifying participants should not be transmitted from study sites to the Coordinating Center.
- **Electronic files:** Data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file.
- **Forms;** Forms or pages containing personal identifying information should be separated from other pages of the data forms.

- **Data listings:** Participant name, name code, hospital chart, record number, Social Security Number, or other unique identifiers should not be included in any published data listing.
- **Data distribution:** Data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- **Data disposal:** Computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
- **Access:** Participant records should not be accessible to persons outside the study without the express written consent of the participant.
- **Storage:** Study forms and related documents retained both during and after study completion should be stored in a secure location. If computers are used to store and/or analyze clinical data, the Coordinating Center or the investigator should address the following elements of computer security to ensure that the data remain confidential:
 - **Passwords:** Passwords provide limitations on general access to computer systems and to the functions that individuals can use. Passwords should be changed on a regular basis.
 - **User training:** Study staff with access to clinical computer systems should be trained in their use and in related security measures. Training should include explanations of how to access the system and a discussion of the need for, and importance of, system security.
 - **System testing:** Prior to the use of a new computer system, and subsequent to any modifications, the system should be tested to verify that it performs as expected. Testing should verify that the password-activated access system performs as intended.
 - **System backups:** Backup copies of electronic data should be made at specified intervals. Backups should be stored in file cabinets or secure areas with limited access. Storage areas should have controlled temperature and humidity so that the backup tapes are not damaged.

3.26.2 Publications

Investigators have a responsibility to the public to make study results available as soon as possible. The MOP should detail the publication policy so that data are not released inappropriately, authorship is predetermined, and manuscripts are subjected to rigorous review before they are submitted for publication.

The Coordinating Center or PI must check with NCCIH if there are plans to publish data before the study is over.

Effective September 27, 2008, responsible parties are required to report basic results of clinical trials in ClinicalTrials.gov within 12 months of trial completion, or within 30 days of FDA approval of a new drug or device.

3.27 MOP Maintenance

The MOP is maintained and updated throughout a study. This section describes the procedures for updating and distributing updated MOP versions as well as staff members responsible for this activity. The MOP should be available to site staff in looseleaf form. Each page of the MOP should be numbered and dated, and contain a version number to facilitate any changes and/or additions. The MOP may serve as a history of the project, documenting the time and nature of any changes in procedures and policies.

The MOP should be continuously reviewed by the Coordinating Center to ensure that the operating procedures described are accurate. If any procedures have been changed or modified, the MOP should be updated—and the appropriately modified pages distributed, with instructions, for replacement in the MOP. A MOP template for changes is included in [Appendix D](#).

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APPENDIX A. SAMPLE SCREEN LOG

Study: _____

Site: _____

Investigator: _____

Screening Number	Date of Birth	Gender	Screening Date	Screening Status (use codes below)	Consent Obtained	Enrolled (if no, indicate reason from codes below)	Date Enrolled
□□□□□	/ / mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	/ / mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	/ / mm/dd/yyyy
□□□□□	/ / mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	/ / mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	/ / mm/dd/yyyy
□□□□□	/ / mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	/ / mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	/ / mm/dd/yyyy
□□□□□	/ / mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	/ / mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	/ / mm/dd/yyyy
□□□□□	/ / mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	/ / mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	/ / mm/dd/yyyy

Sample Screen Status Codes: 1-Eligible
2-Eligible, declined participation
3-Not Eligible
4-Eligible, lost to followup
5-Other, specify in space provided

If not eligible, reason:

1-Inclusion # (specify)
2-Exclusion# (specify)
3-Other (specify)

APPENDIX B. SAMPLE SCHEDULE OF EVENTS

Visit Description	Screening	Treatment Phase							Followup						
		Visit 1 Day 14 to Day 1	Visit 1 Day 0	2 W1	3 W2	4 W3	5 W4	6 W8	Final Visit W10	8 W12	9 W14	10 W16	11 W18	12 W20	13 W22
Study Visits/ Study Days (or Weeks)															
Informed Consent	X														
12-lead EKG	X					X				X	X				X
Medical History	X														
Prior Medications	X														
Physical Exam	X									X					
Vital Signs	X									X					
Chemistries	X		X	X	X					X	X				X
Liver Function Tests	X		X	X	X					X	X				X
Hematology	X		X	X	X					X	X				X
Pregnancy Test	X				X					X	X				X
Investigational Agent Administration		X	X	X	X	X	X	X							
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

APPENDIX C. SAMPLE PROTOCOL DEVIATION LOG

Protocol Name: _____

Protocol Deviation Code:	Participant Initials	Participant ID#	Date Deviation Occurred: mm/dd/yyyy	Date Protocol Deviation Form Completed: mm/dd/yyyy	Contact Person (if applicable)

SAMPLE PROTOCOL DEVIATION CODES

Consent Form:

1. Missing or not obtained
2. Not signed and dated by participant
3. Does not contain all required signatures
4. Outdated, current IRB-approved version not used
5. Not protocol-specific
6. Does not include updates or information required by the IRB

Randomization:

7. Ineligible participant enrolled and/or randomized
8. Participant randomized prior to determining whether eligible for study
9. Occurs outside protocol window

IRB:

10. Not reporting a serious complication within 24 hours;
11. Approvals not kept up to date
12. Enrollment and/or treatment occurs prior to IRB approval or during period when on “on hold”
13. Reportable serious adverse events not reported to IRB

Participant

14. Receives wrong treatment
15. Visits occur outside expected follow-up window
16. Entered into another study

Study Data and/or Forms

17. Missing data and/or forms
18. Missing radiology and/or operative reports
19. Forms or data not sent from clinical site to coordinating center

APPENDIX D. SAMPLE MOP MODIFICATION LOG

MOP MODIFICATION LOG					
Section #	Version #	Date Modified	Page #	Text Location	Brief Modification Summary