National Institute of Arthritis and Musculoskeletal and Skin Diseases

Revised Guidelines for Developing a Manual of Operations and Procedures (MOOP)

July 2007

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1.0 INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH) must ensure compliance with Federal laws and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. In preparing a study protocol and a Manual of Operating Procedures (MOOP), the investigators must be aware of the terms of award with respect to required reporting, data and safety monitoring, and Institutional Review Board (IRB) approval (*NIAMS: Data and Safety and Monitoring Guidelines for Investigator-Initiated Clinical Trials,* http://niams.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.doc.

The purpose of this document is to assist investigators in the preparation of a study Manual of Operating Procedures (MOOP) by providing them with a template. The role of the MOOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Use of the MOOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that patient safety and scientific integrity are closely monitored.

2.0 OVERVIEW

A MOOP 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, follow-up procedures, data collection methods, data flow, Case Report Forms (CRFs), and quality control procedures. The MOOP is intended to serve as the study "cookbook" to facilitate researchers in following study procedures. All investigators develop this guideline and submit to NIAMS before the study can commence.

During a study's planning phase, the investigators and their institutional colleagues delineate the protocol. The protocol must be approved by the IRBs of all Institutions participating in the study.

The MOOP development requires that the final protocol, CRFs, informed consent documents, and administrative forms (e.g., patient screening log, patient enrollment log, delegation of responsibilities log, etc.,) be completed. 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 must be included. The timeline for development of study materials must be planned for and typically takes at least six months.

Development of the MOOP requires the involvement of the Investigator and study staff to ensure the guidelines are written to accurately reflect how the study procedures will be performed In multi-site clinical studies, a Steering Committee,

comprised of the Principal Investigators from each of the sites, is often appointed to finalize the protocol and elements of the MOOP before it is sent to NIAMS.

The MOOP 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 MOOP should be maintained in a format that allows it to be easily updated, and typically filed in a three-hole binder. For ease of organization, it is recommended that the MOOP be subdivided into various sections separated by dividers or sheets of paper between each section.

Further, it is helpful to have each page of the MOOP 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 MOOP. All previous versions should be archived.

3.0 MOOP CONTENTS AND ORGANIZATION

A MOOP is useful for clinical intervention trials (e.g., drug, surgery, behavioral, device, etc.) and also for multi-center observational studies. The MOOP sections outlined below and further described in later sections provide a recommended guideline rather than a prescription and must be adapted to each study's specific needs. In studies where a section does not apply (e.g., randomization in a study with no randomization), it is not included in the MOOP.

The MOOP details the study procedures and describes the study-specific documents. It often includes the following sections:

a. Study Protocol
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
i. Informed Consent and HIPAA
j. Study Intervention
k. Blinding and Unblinding (Masking or Unmasking)
l. Participant Evaluations and Follow-up
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. MOOP Maintenance

The MOOP submitted to NIAMS must include all of the elements listed above.

3.a Study Protocol

The study protocol provides a brief, scientific rationale of the proposed investigation. It generally begins with a statement of the problem, followed by background information which helps the reader understand the general scientific problem. The research question and study hypotheses are also stated and the primary and secondary aims of the study are defined. In addition to these areas, the study target population is introduced, study procedures and interventions are described, primary and secondary endpoints along with the statistical plan are stated. Plans for protecting patient safety and well-being are also explained. A clinical protocol that meets both scientific and ethical standards is a fundamental requirement of clinical investigations.

In addition, the following items should be clearly articulated in the ensuing sections:

- Study design
- Primary and secondary endpoints
- Type and number of sites and centers, e.g., coordinating center
- Patient population, including type of patient groups and associated numbers
- Inclusion and exclusion criteria
- Randomization plan
- Screening process, baseline evaluation, study treatment and final evaluation
- Definition of evaluable patients
- Blinding/unblinding issues

- Statistical plan
- Data management
- Safety issues
- Confidentiality/privacy issues
- Institutional Review Board (IRB) approval procedures
- Informed consent procedures
- Plans for and responsibilities of the internal and/or external Data and Safety Monitoring Board (DSMB) or safety monitor

The final version of the study protocol with the date of IRB approval and version number is included in the MOOP or can accompany the MOOP as an appendix.

3.b Schedule of Visits and Evaluations

A useful component of the MOOP is the schedule of study visits and evaluations. This schedule delineates every clinical (or non-clinical) procedure to be performed throughout the study. An example of a schedule is provided in Figure 1.

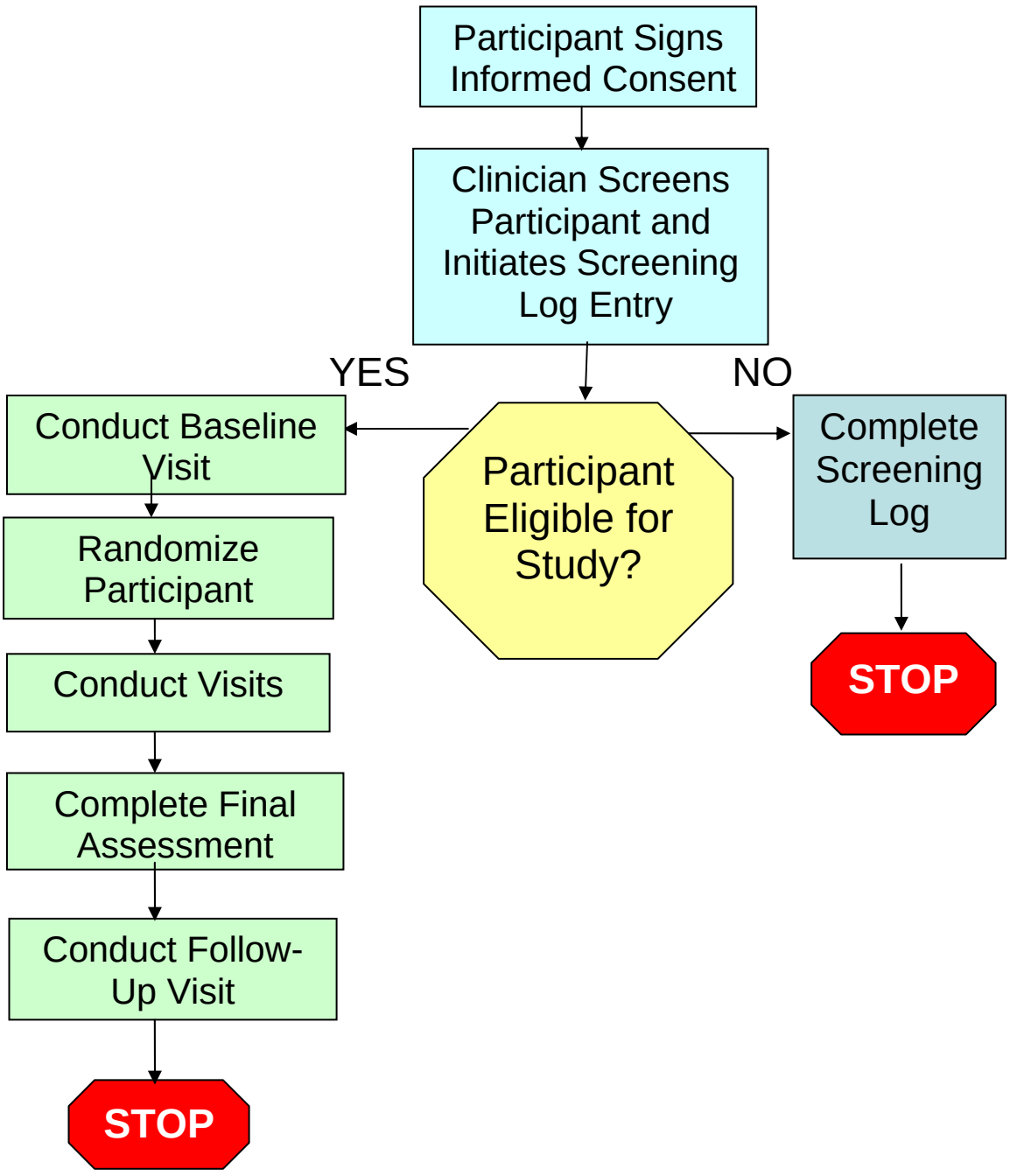
FIGURE 1:
Sample Schedule of Study Events

Visit Description	Screening	Treatment Phase							Follow-Up					
Study Visits/ Study days (or weeks)	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
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
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
PK		X	X	X	X			X	X					X

3.c Study Flow

It is useful to provide an overview of the study process in a flow diagram, as shown in Figure 2, which describes each of the study's major steps. It is uniquely tailored to the study and is helpful in describing the study to new staff members.

Figure 2. Sample Study Diagram



3.d Study Organization and Responsibilities

This section describes the study's organizational scheme and provides a roster of members of the Coordinating and Clinical Centers and study committees. The study organization for large studies is generally depicted by an organizational chart. This section also describes the roles and responsibilities of the Clinical Centers, Data Management, Coordinating and/or Statistical Center, laboratories and committees.

3.d.1 Roster

The roster includes the names, roles, addresses, phone numbers, fax numbers, pager numbers and e-mail addresses of study staff members, committee members, the Safety Officer, and NIAMS staff.

A notation of whom to contact regarding special situations as well as study-related questions should also be included, for example,:

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

3.d.2 Coordinating Center

The responsibilities of the Coordinating Center may include:

- Development and maintenance of the MOOP
- Randomization scheme and procedures
- Development and implementation of the data flow, schedules for transferring data from sites, and data tracking
- Development of procedures for data entry, error identification, and error correction
- Adverse event monitoring and reporting
- Communications with clinical sites, scheduling of meetings and training sessions, responding to and documenting ad hoc communications
- Site visits to ensure adherence to the protocol and procedures
- Quality control procedures
- Creating reports - enrollment, adverse events, participant status (e.g., withdrawals) by site
- Distribution of all changes, updates and policies of above mentioned

reports and documents to all participating clinical sites

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

3.d.3 Clinical Sites

The roles and responsibilities of the Investigators and Clinical Sites may include:

- Maintaining the study binder (regulatory and clinical documents)
- Participating in protocol finalization and preparing study materials
- Assuring the study is conducted according to the protocol and MOOP
- Participating in a Steering Committee and other committees
- Identifying, recruiting, screening and enrolling participants
- Protecting participants' rights
- Obtaining informed consent from each participant
- Collecting study data and following participants through study completion
- Compliance and accountability of administration of study intervention
- Retaining specific records, (e.g., laboratory or drug distribution records)
- Preparing and sending required reports to the coordinating center (e.g., 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

When writing this section of the MOOP, please be sure to include all roles and responsibilities of the sites, not just the example given above.

3.d.4 Pharmacy Activities

“Pharmacy” refers to the unit responsible for the storage and dispensation of the investigational agent. An actual pharmacy may be directly involved in a study, or the investigational agent may be delivered directly to the study site in pre-labeled, sealed packages.
This section of the MOOP describes how the investigational agent is to be stored, prepared, dispensed, and returned to the Coordinating Center, the Sponsor or other designated organization. It provides instructions for completing drug accountability records and administrative records.

3.d.5 Steering Committees

The Steering Committee often fills the leadership role of large, multi-center studies, and is responsible for the overall direction of a study.
The following areas typically fall under the purview of the Steering Committee:

- Responsibility for the general design and conduct of the study
- Preparation of the essential study documents, including the protocol, protocol amendments, MOOP, and data collection forms
- Review of data collection practices and procedures
- Changes in study procedures as appropriate
- Appointments to and disbanding of study implementation 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 NIAMS Program Officer)

3.d.6 Executive Committees

In large, multi-center studies with multiple coordinating centers (e.g., clinical, data, and statistical centers), there is often an Executive Committee that is responsible for reviewing study progress and identifying and resolving issues. The NIAMS Program Officer is a member of this committee. The Executive Committee is the small study leadership group that guides the study's implementation and operation.

3.e Training Plan

Procedures for training study staff, including the clinical site investigators, should be described in this section. The Investigators' meeting or other training formats can be utilized to introduce the study protocol and procedures. This section of the MOOP should clearly detail the specific training plan, including timelines and meeting schedules, the Investigator has created to train all those involved in the study.

3.f Communications Plan

In addition to routine administrative communications with clinical sites, scheduling meetings and training sessions, there should be a plan to ensure ongoing communication among site investigators, especially during protocol finalization and as part of the Steering and other Committees. Once a study is operational, routine telephone calls among the clinical site coordinators are useful to build an

esprit de corps, discuss issues, and share successful strategies. The coordinating center should document these communications. The Steering Committee and Executive Committees will also participate in routine calls once the study is implemented to discuss progress, issues, and potential solutions.

Routine reports required by the NIAMS Program Officer can also be described in this section.

3.g Recruitment, Screening, and Eligibility Criteria

This section of the MOOP is aimed at assisting clinical sites to quickly and efficiently enroll eligible patients into the study. The section should describe the target population, recruitment strategies, screening procedures and eligibility criteria. The target population defines the patients to be identified during the recruitment and screening process and describes the disease status or condition. The inclusion and exclusion criteria are specifically defined and delineated to capture the target population.

3.g.1 Recruitment Plan

This section of the MOOP characterizes the target population and suggests recruitment strategies such as identifying primary care referral practices, grand rounds, and advertising through media. It is suggested that each site develop a recruitment plan that documents the primary approach and alternatives.

3.g.2 Screening

This section describes in details the screening procedures outlined in the protocol to determine if an individual is eligible to participate in the study. Frequently, there is a *pre-screening* phase during which the study coordinator responds to initial telephone calls from interested patients or physicians. With consideration for HIPAA regulations, as interpreted by the site's institution, the PI/study coordinator may access their clinic's medical records, hospital admissions or discharge notes, if necessary, to identify potential patients for screening.

3.g.3 Screening Log

A screening log provides documentation of all individuals that are evaluated for study eligibility. It generally contains the patient's initials and study identification number (screening number), age, gender, race and ethnicity, screening date, and eligibility status:

- Eligible for study participation and date enrolled
- Ineligible for study participation and reason
- Refused consent and why

It may also contain the randomization number if different from the screening number. This section of the MOOP describes the contents of the screening log and the process for filling it out. A sample screening log may be submitted in this section or included as part of the Appendix. (Note: this information is usually part of the reporting requirements for data and safety monitoring.)

3.g.4 Eligibility Criteria

Study eligibility is determined by a set of protocol-specific inclusion and exclusion criteria that are outlined in the study protocol. Potential participants must meet all entry criteria prior to enrollment. This section of the MOOP defines the criteria, method for determination (e.g., blood pressure sitting down), and the specific forms needed to document eligibility (e.g., medical history form, physical examination form).

All data captured on the CRFs to support a participant's enrollment in the study must be verifiable in the source documents.

3.h Informed Consent and HIPAA

Informed consent is a process that gives individuals the opportunity to decide whether they want to participate in a study. During this process, individuals should be informed of all aspects of the study that are relevant to their decision. The participants then confirm their willingness to participate in a particular research study by signing the Informed Consent form.

Once a clinical site coordinator, investigator, or other staff member identifies an individual that appears to meet the pre-screening criteria, the informed consent process is initiated, and the individual must sign an informed consent form prior to undergoing a physical examination, medical history, laboratory procedures, or other eligibility assessments that are outside the routine care procedures.

The Health Insurance Portability & Accountability Act (HIPAA) provides guidelines for investigators for the protection of participant confidentiality. According to the Privacy Rule, participants must authorize investigators, IRBs, research administrators, and others to use and disclose their Protected Health Information (PHI) for research purposes. In order to obtain HIPAA authorization, the informed consent may contain language that satisfies the HIPAA requirements and outline the protection of health information utilized in the study

Informed consent document requires:

- Disclosure of relevant information to prospective participants about the research;
- The participant's comprehension of the information;
- The participant's voluntary agreement to participate in a research study without coercion or undue influence.

The informed consent procedure involves:

- Providing patients with adequate information concerning the study procedures and scope
- Providing adequate opportunity for the patient to consider all available options
- Responding to the patient's questions and concerns
- Ensuring that each patient understands all information provided
- Obtaining the patient's written voluntary consent to participate.

Additional items that should be included in an informed consent document include:

- Complete disclosure of any appropriate alternative procedures and their risks and benefits
- Disclosure of the extent of confidentiality that will be maintained
- Statement of compensation and/or medical treatment available if injury occurs
- Name, address, and telephone number of the Principal Investigator

The informed consent regulations are administered by the Office of Human Research Protections (OHRP). Their Web site (http://www.hhs.gov/ohrp/policy/index.html#informed) also provides a number of tips to guide investigators in developing informed consent documents.

3.h.1 Informed Consent Process

When writing the MOOP, the process by which the sites obtain informed consent should be explained in as much detail as possible. The process should include:

- When will consent be obtained?
- Who from the study staff will discuss the nature of the study with the patient (including voluntary participation and risks/benefits of the trial)?
- How long will the patient be given to read the consent and have questions answered?
- Which of the parties involved will sign the consent form, and will a copy of the signed form be given to the patient?

- Where will informed consent forms be housed and who will have access to these forms?
- When will patients be required to be re-consented?

An individual must be informed that he/she is not obligated to participate in the study and that it is strictly voluntary. The informed consent process should ensure that there is no penalty for not participating in a clinical trial and that treatment will not be compromised if individuals do not participate or if they cease participation at any time.

3.h.2 Informed Consent Document

The written Informed Consent form should be short and written in plain language so that an individual who has not graduated from high school can understand the contents. It is recommended that the information materials be written on a 4th – 8th grade reading level. Sample consent forms for clinical investigations and observational studies are found at http://niams.nih.gov/Funding/Clinical_Research/invest_form.asp.

The Principal Investigator, the participant, and a witness must each sign and date the Informed Consent Document. NIAMS recommends that the Principal Investigator, the study nurse and/or a witness be present when the patient signs the informed consent document. The International Committee on Harmonization (ICH) Good Clinical Practice (GCP) guidelines require that the patient or legal representative receive a copy of the signed and dated informed consent form. OHRP and the FDA both require that the participant receive a copy, although it need not necessarily be a signed copy. Additionally, the investigator must maintain a signed copy of the informed consent document for each patient in the study. The source documents should indicate that informed consent was obtained, along with the date of signing.

If there is a change in any of the study procedures that may affect the participant, the informed consent document must be revised and approved by the IRB. Any patients enrolled in the study prior to a change in procedures must sign the amended consent form.

NIH policy requires that studies conducted under a grant retain participant forms for three years and studies conducted under contract retain participant forms for seven years. Individual IRBs may have different requirements for record retention. The FDA requires that informed consent forms be retained for two years after a marketing application is approved for a product or, if an application is not approved, until two years after shipment and delivery of the product is discontinued for investigational use and the FDA is notified. Investigators should retain forms for the longest applicable period, and this period should be stated in the MOOP.

The IRB approved Informed Consent form should be included as an appendix in the MOOP. If it is not IRB approved at the time the MOOP is submitted to NIAMS, it can be submitted at a later date. If amended consent forms are generated after the study begins, they should be submitted to NIAMS.

3.h.3 HIPAA Authorization

The HIPAA authorization form may be a separate document from the informed consent, which 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 dictated 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 MOOP. Additionally, the IRB approved HIPAA form should be included in the appendix. If it is not IRB approved when the MOOP is submitted to NIAMS, it can be submitted at a later date.

3.i Randomization

Randomization is introduced in the study design in order to reduce bias in treatment selection. In randomized, controlled clinical trials, participants are assigned to a treatment group based upon a pre-determined randomization scheme developed by the study statistician. This section of the MOOP 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 the study computer system while other studies maintain the assignment in a randomization log. In either case, the method for documenting randomization must be described, and if relevant, a person named who will be responsible for completing the randomization log at each site.

3.j Blinding and Unblinding

In most studies with randomization, participants and the treating physician are "blind" or "masked" to the treatment and do not know if the participant is receiving drug or placebo. The study statistician and/or a designated study staff member securely maintains the randomization codes so that the treatment assignments are not known. 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. The DSMB or Safety Officer and the NIAMS Project Officer must be involved in the decision and must grant approval for unblinding. In the event that unblinding occurs, the following should be recorded:

- The ID of the unblinded patient,
- The reason for unblinding,
- The study staff person responsible for unblinding
- A list of person(s) who are not blinded.

The Investigators' procedures for unblinding should be clearly specified in the MOOP.

3.k Study Intervention

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

Clinical trial phases are described as follows:

- ***Phase I:*** Safety studies test a treatment for the first time in humans with a small group of participants in order to determine a safe dose range, identify side effects, and observe the treatment's effect on the participants. Phase I studies usually test the intervention using normal healthy volunteers and often do not involve a comparison group.
- ***Phase II:*** The study treatment is given to a larger group of participants with the disease or condition of interest to estimate effectiveness and further evaluate safety data. The main purpose is to provide preliminary information on treatment efficacy and to supplement information on safety obtained from Phase I trials. Phase II studies may be randomized and controlled.
- ***Phase III:*** Clinical trial done to determine efficacy of a treatment. Such a trial is usually designed to include a control treatment, some form of investigator and patient blinding, random allocation to treatment, and usually involve a few hundred participants.
- ***Phase IV:*** A study of an intervention that is designed to evaluate the long-term safety and efficacy of a treatment for a given indication after it has been approved by the FDA for use following phase III trials. These studies are not usually funded by the NIH.

The MOOP must state the phase of the study. In addition, this section will include a detailed description of the type of intervention and how it will be implemented.

The intervention, whether medical treatment, surgical procedure, device or behavioral intervention, must be thoroughly described so that all sites, investigators and participants have the same exposure:

- For ***drug intervention*** studies, 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 at http://www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB
- ***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).
- ***Surgical studies*** require a detailed description of the procedure.

- ***Biobehavioral*** and ***life style*** studies describe how the intervention is to be carried out as well as documentation of the process.

3.l Participant Evaluations and Follow-Up

Once a participant is enrolled in the study, there are typically baseline and follow-up assessments. The MOOP helps to ensure that study procedures are administered in the same way for all participants across all sites. All assessments, as well as their schedule and the procedures for obtaining data, must be clearly stated in this section. All endpoint or outcome evaluations (e.g., improvement in symptoms) and safety evaluations (e.g., blood chemistries) should be delineated. The schedule of when evaluations take place must also be specified (e.g., five hours after the last dose of study drug/placebo administration).

3.l.1 Timeline and visit schedule

A useful study tool included in the MOOP 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 Figure 3. In this section of the MOOP, the investigator should include a visit schedule, as seen in Figure 3, for the study.

3.l.2 Scope

In this section of the MOOP, each visit should be explained in enough detail so that a new or substitute team member can perform the visit. Step by step procedures should be documented for all study procedures.

3.l.3 Follow-up

Participants should be actively followed through all study visits through the study completion visit. This section can detail strategies sites can use to follow participants, such as:

- Monthly phone calls
- Sending birthday cards
- Sending postcards

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.

FIGURE 3: Generic Time and Events for a Clinical Research Study

	Screening	Enrollment and/or Randomization	Baseline Visit	Follow-up Visits			
Study Visits	**-14 days to Day 0**			**2**	**3**	**4**	**Final Visit**
Informed Consent	X						
Medical History	X	X					
Prior Medications	X	X	X				
Physical Exam	X	X	X				X
Vital Signs	X		X				X
Chemistries	X			X	X	X	X
Liver Function Tests	X			X	X	X	X
Hematology	X			X	X	X	X
Pregnancy Test	X				X	X	X
Endpoint Assessment			X	X	X	X	X
Investigational Agent Administration			X	X	X	X	X
Concomitant Medications			X	X	X	X	X
Adverse Events			X	X	X	X	X
Study Completion Form							X

3.m Participant Retention

Effective participant retention and adequate recruitment are both key to ensuring a successful study. Participant retention requires careful planning and continuous efforts. Many NIH Institutes require at least a 95% retention rate.

Every effort should be made to retain study participants without coercive measures. Thus, it is important that several contacts be made during the screening and enrollment process, including next of kin, friends, and other potential contacts, in the event that a participant does not return for follow-up visits. Suggestions for participant retention should be provided in this section.

The following are the major principles and commonly used strategies to maximize retention and minimize loss to follow-up:

- Stressing that retention efforts begin with recruitment and are an ongoing process
- Following, a proactive plan for retention, including placing ongoing telephone calls to participants to see how they are doing, sending birthday and holiday cards, and providing transportation and child care, as needed.
- Building patient relations and patient satisfaction, with the study coordinator taking a central role on this effort
- Emphasizing the importance of congeniality, respectfulness and friendliness in interactions with participants
- Giving patients and their families the opportunity to address questions and concerns pertaining to their condition
- Enhancing participant's understanding of the study's mission and the protocol
- Stressing the idea that participants have an active role in the research and are part of the research team
- Using strategies to sustain ongoing communication with patients and their families including specific programs and events
- Distributing newsletters to provide feedback on the status of the study
- Surveying participants on a regular basis, understanding their expectations, and measuring their experiences and satisfaction
- Identifying potential problems and key retention factors and developing intervention strategies regarding retention
- Assessing each patient's drop out potential and intervening as needed to keep patients interested in continuing to participate

In this section of the MOOP, the sites' plan for participant retention, as well as an action plan for correcting retention problems, should be explained.

3.n Concomitant Medications

The MOOP provides a rationale for the concomitant medications that are allowed and restricted in the protocol. Please list all allowable or excluded concomitant medications in this section of the MOOP.

The form used to collect concomitant medication information and the period of time for which this information will be collected should be described. The form should be included as part of this section or the appendix. Concomitant medication information must be verifiable in the source documents.

3.n.1 Safety Reporting

This section of the MOOP details the definitions of and procedures for reporting adverse events.

- ***Adverse Event (AE)*** - An AE is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period which have increased in severity.
- ***Serious Adverse Event (SAE)*** - An SAE is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.
- ***Unexpected Adverse Event*** - An unexpected adverse event is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product/device or package insert/summary of product characteristics for an approved product or device).

3.n.2 Adverse Event Reporting

All AEs are collected, analyzed, and monitored by using an Adverse Event Form, a sample of which is shown in Figure 4. AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety must be reported. All AEs experienced by the participant during the time frame specified in the protocol

FIGURE 4: SAMPLE ADVERSE EVENT FORM

Has the patient had any Adverse Events during this study? ☐ **Yes** ☐ **No** ***(If yes, please list all Adverse Events below)***

Severity	**Study Intervention Relationship**	**Action Taken Regarding Study Intervention**	**Other Action Taken**	**Outcome of AE**	**Serious**
1 = Mild 2 = Moderate 3 = Severe	1 = Unrelated 2 = Related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = None 2 = Remedial Therapy – pharmacologic 3 = Remedial Therapy- non-pharmacologic 4 = hospitalization	1 = Resolved, No Sequela 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-no treatment 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No (If yes, complete SAE form)

Event	Start Date	Stop Date	Severity	Relatedness	Action Taken with Intervention	Other Action Taken	Outcome	Serious?	Initials

(e.g., from the time study drug administration through the end of the study) are to be reported, as outlined in the protocol.

In this section of the MOOP, the procedure for collecting and reporting AEs should be detailed, including the role of the PI in assigning severity and relationship of the AE to study drug or intervention. In addition, a sample AE form should be part of this section or included in the appendix. Requirements for reporting AEs to the study's safety monitor, NIAMS and the independent data and safety monitoring body [i.e., Data and Safety Monitoring Board (DSMB) or Safety Officer] is described in this section.

3.n.3 Serious Adverse Event Reporting

All SAEs, unless otherwise specified in the protocol and approved by the IRB and NIAMS (as applicable), require expedited reporting by the Principal Investigator to the study's safety monitoring bodies. SAEs must be reported to the independent safety monitoring body (i.e., DSMB or Safety Officer) and the NIAMS, through the NIAMS, contractor within 24 hours of being reported to the Investigator. The immediate reports should be followed by detailed, written reports as soon as possible. Follow up information may be required. All interventional studies, independent of phase or type, must report SAEs.

In this section of the MOOP, a plan for SAE reporting to NIAMS and its contractor will be established. The role of the investigator and study coordinator and all others involved in SAE reporting should be explained in detail. In addition, the sites' SAE reporting form should be included in this section or in the appendix of the MOOP. [Note: multiple reporting requirements, e.g., to the FDA and IRB(s), which are separate from the reporting requirements for NIAMS and the independent monitoring body, are the responsibility of the Investigator(s) and should be described in this section.]

A sample of the SAE form used for NIH Intramural Programs is shown in Figure 5.

FIGURE 5:
SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

1. Protocol number: Protocol title:
2. Principal Investigator:
   Institution: Office:
   Phone: Fax:
   E-mail:
3. Date of serious adverse event:
4. Location of serious adverse event:
5. Was this an unexpected adverse event? Yes [ ] No [ ]
6. Brief description of participant(s) with no personal identifiers: Sex: Age:
   Diagnosis:
7. Brief description of the nature of the serious adverse event (attach description if more space needed):
8. Category (outcome) of the serious adverse event:

   [ ] death
   [ ] life-threatening
   [ ] hospitalization-initial or prolonged
   [ ] disability / incapacity
   [ ] congenital anomaly / birth defect
   [ ] required intervention to prevent permanent impairment
   [ ] other:

9. Relationship of Serious Adverse Event to research:

   [ ] 1 = Unrelated (clearly not related to the research)
   [ ] 2 = Unlikely (doubtfully related to the research)
   [ ] 3 = Possible (may be related to the research)
   [ ] 4 = Probable (likely related to the research)
   [ ] 5 = Definite (clearly related to the research)

10. Have similar adverse events occurred on this protocol? Yes [ ] No [ ]
    If "Yes", how many? ____ Please describe.

11. What steps do you plan to take as a result of the adverse event reported above? Provide documentation to the IRB for review and approval of any of the steps checked below.

    [ ] no action required
    [ ] amend consent document
    [ ] terminate or suspend protocol
    [ ] other (describe)
    [ ] amend protocol
    [ ] inform current participants

Signature of Principal Investigator: _____ Date: _____

3.o Data and Safety Monitoring Activities

The roles and responsibilities of the entities monitoring participant safety and study quality are described in this section. To ensure proper monitoring, NIAMS has established Data and Safety Monitoring Guidelines. These guidelines may be found at: http://niams.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.doc.

All clinical trials supported by NIAMS must have a Safety Officer or a Data and Safety Monitoring Board (DSMB) that is independent of the study. The type of independent safety monitoring is dependent on the size and/or nature of the study and is determined by NIAMS. Small, single-site studies usually have a Safety Officer, while multi-center studies require a DSMB. However, if a small, single site study is determined to have high risk, a DSMB may be required. In addition, NIAMS requires Observational Study Monitoring Boards (OSMBs) for large multi-site observational studies that entail risk or burden to participants.

The individual(s) identified to monitor a study possess the appropriate expertise necessary for analysis and interpretation of data to ensure participant safety and the study is conducted in an ethical and scientifically, rigorous manner. The NIAMS selects the individual(s) for the DSMB, OSMB, or Safety Officer and may solicit suggestions from the Principal Investigator.

DSMB activities include reviewing the protocol with emphasis on data integrity and patient safety issues, monitoring adverse events, protecting the confidentiality of the data and monitoring results, and making recommendations to NIAMS and Principal Investigator to continue or conclude the study. The Sample DSMB Charter (http://niams.nih.gov/Funding/Clinical_Research/dsmb_charter.asp) describes the safety monitoring board activities and is drafted by NIAMS and approved by the monitoring body. The charter can be modified throughout the study, as appropriate. This section of the MOOP is an introduction to the following Data and Safety Monitoring sections and should briefly outline the monitoring activities.

3.o.1 Generic Monitoring Plans

This section of the MOOP should describe the specific monitoring plans. A monitoring plan must be submitted to and approved by the NIAMS Program Officer prior to the award for a clinical trial. It may contain sample reports the investigator will provide to the Safety Officer or DSMB/OSMB.

To assist in preparing a monitoring plan, generic monitoring plans for studies requiring a Data and Safety Monitoring Board or a Safety Officer are available at http://niams.nih.gov/Funding/Clinical_Research/NIAMS_sample_documents.asp.

These documents describe the monitoring procedures required by NIAMS for clinical studies.

3.o.2 Safety Officer and DSMB Membership

The independent Safety Officer or members of the DSMB/OSMB are appointed by the NIAMS. The investigators may recommend individuals with appropriate background and expertise. DSMB/OSMB members and Safety Officers are selected to reflect a mix of appropriate clinical expertise and methodological knowledge regarding the design, monitoring, analysis and ethical issues of the clinical research project necessary to protect participant safety and the conduct of the study. All DSMB/OSMB members must attest that they have no conflicts of interest by signing the *Conflict of Interest (COI) Statement* (http://niams.nih.gov/Funding/Clinical_Research/conflict_of_interest.asp). The NIAMS contractor will provide and track the COI statements prior to providing study materials and on an annual basis. This section outlines the process for identifying the monitoring body and for reviewing and collecting the COI statements.

3.p Study Compliance

Clinical trials are expensive endeavors, and procedures should be implemented to maximize adherence to the protocol and minimize non-compliance. 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 to track protocol deviations and procedures to notify appropriate parties that are described in this section.

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

- Randomization of an ineligible participant
- Failure to obtain Informed Consent
- Entering a participant into another study
- Failure to keep IRB approval up to date
- Wrong treatment administered to participant

This section of the MOOP should describe relevant deviations and the reporting process to appropriate parties, including the Principal Investigator at the study site and at the Coordinating Center, the NIAMS, and the DSMB or Safety Officer, within 24 hours of occurrence or as soon as they are discovered. In addition, if monitors discover any of these deviations during a monitoring visit, they should notify NIAMS of the occurrence in writing. The study coordinator should maintain a log of all protocol deviations and should report them routinely to the DSMB or Safety Officer. A sample log is presented as Figure 6. While there may be rational clinical reasons for an occasional deviation, a site with serious, continual

problems is at risk for losing its funding.

FIGURE 6:
SAMPLE PROTOCOL DEVIATION LOG

Protocol Name:_____

Protocol Number: Site: Principal Investigator:

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 is 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

The requirements for reporting protocol deviations are described in this section of the MOOP. A log for recording protocol deviations should also be included in this section 3.q Data Collection and Study Forms

This section describes the study's data collection and data management procedures and should include copies of all forms.

3.q.1 Source Documentation

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

This section describes how study data are initially collected and maintained for the study. All essential study documents must be retained by the investigator as described in Section 3.t below. The following are considered to be part of the participant file documents:

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

3.q.2 Study Forms

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

- Study forms and their collection schedule
- Description of each study form and questionnaire
- How forms are produced and distributed
- Participant binder setup

- Maintenance of forms

- The contact person responsible for sending additional forms to sites or answering questions

3.q.3 General Instructions for Completing Forms

All data recorded on study forms must be verifiable in the source documents maintained by the clinical site(s), according to FDA and ICH Good Clinical Practice (GCP) guidelines. Instructions for completing CRFs ensure quality and consistency in data collection. In this section of the MOOP, please provide a set of instructions for completing CRFs. Some useful and frequently used examples are listed below:

Sample instructions:

When completing 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 identification (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 2:00 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.
- ***Extraneous Writing***: Comments written extraneously on forms cannot be captured in the database; thus, write only in the spaces indicated.
- ***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 checked when necessary.

- ***Incomplete data***: Data may not be available to complete the form for various reasons. Circle the item for which data 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 MOOP, a set of guidelines for incomplete or illegible form must be included.

Below is an example:

- If an entire page of the forms 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.r Data Flow

It is the site's responsibility to ensure that all forms are complete, intact, and transmitted to the Coordinating Center, as appropriate. More recently, in some studies data are directly entered into an electronic CRF (eCRF).
This section of the MOOP describes:

- The disposition of study forms or data entry into the computer system (see Section 3.v)

- The schedule for completion and transmission of forms

- Lists of forms for which copies are to be maintained at the site and forms to be submitted for data entry.

- The data flow, data entry, and data correction procedures

3.s 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 three years, while studies conducted under contract must retain participant forms for seven years. Researchers should pay special attention to studies involving children, as study documentation retention procedures are often longer in duration and more comprehensive. The FDA, individual IRBs, institutions, sponsors, 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 period should be stated in the MOOP.

3.t Administrative Forms

The MOOP should contain a complete set of administrative forms. Administrative forms assist study documentation and 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* patients screened for participation in the study. It should be arranged chronologically and be kept up-to-date at all times.
- ***Record of Request for Exemption to Entry Criteria*** - is used to document a participant's exemption to an entry criterion.
- ***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 is recommended that it be maintained in a secured 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 the NIAMS, site institution, FDA, or other government body.
- ***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*** - this log is used to document the destruction of any unused study drug. The date and time of incineration as well as how many vials 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 Principal Investigator and/or Clinical Research Coordinator to:
  - designate individuals approved to 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 close-out.

3.u Data Management

This section of the MOOP describes the data management approach that will support the study and details how data are to be entered (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.

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 multi-center study, handling of error identification and resolution, identification of useful reports, and deriving a frozen, analytic database from edited or "clean" records. These areas should be discussed in this section.

As relevant, the MOOP should also include a description of the computer system used to support the study and the investigator should develop a Users Guide to aid the study staff with data management tasks.

Investigators should be aware that systems of 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/ora/compliance_ref/part11/.

3.u.1 External Data

External data refers to data sent to or collected at a laboratory or imaging facility (e.g., blood samples, MRIs, etc.) This section of the MOOP 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 new Health Insurance Portability and Accountability Act (HIPAA) guidelines, personal identifiers such as name, geographic location, social security number, and fifteen other specific individual identifiers should not be used. Therefore, it is important to specify how participant materials will be identified (e.g., by participant identification number) during transmission.

3.v Quality Control Procedures

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

3.v.1 Standard Operating Procedures

One aspect of site quality control is a set of standard operating procedures (SOPs). SOPs 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 clinical staff should be trained on them. The SOPs should be located in a central location and made easily available to staff for reference.

SOPs which relate to conduct of clinical trials should be listed in this section of the MOOP. Note: printed SOPs should not be inserted in the MOOP, 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.v.2 Data and Form Checks

Data and form checks depend upon data flow and computer procedures. Data quality control checks may identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Consistent and logical dates over time
- 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

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

3.v.3 Double Data Entry

In recent years, there have been several articles written on the value of double data-entry. While conventional wisdom is used to insist upon double data-entry, it is recognized that 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.v.4 Clinical Monitoring

Site monitoring can take place through periodic site visits conducted during the course of the study. The frequency of visits depends upon the site's performance and the number of participants enrolled.

The purpose of monitoring visits is to:

- Ensure the rights and safety of participants
- Confirm that the study’s conduct follows 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

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 clinical monitor has access to all study documents, including informed consent forms, drug accountability records, and source documents, including pertinent hospital or medical records.

Once the site visit is complete, a site monitoring report is drafted to provide feed-back regarding any problems or issues that may have been uncovered during the visit. The report should be straightforward, stating the problems uncovered and describing recommendations to deal with them. A timeline should be agreed upon and included in the report to ensure that follow-up of the issues is completed and implemented into the study's procedures.

In this section of the MOOP, please discuss the sites' plan for monitoring, including a planned monitoring timeline.

3.w Reports

Once a study begins, routine reports prepared by the data management 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 enrollment status (enrolled, active, completed, discontinued treatment, and lost to follow-up). 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. NIAMS will specify the type and frequency of reports it wishes to receive. Other reporting requirements to local IRBs and study officials should also be described in this section. Reports are also provided to the DSMB, OSMB, or Safety Officer, as applicable, who can specify the format and content of the reports they wish to receive.

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

3.x 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 MOOP should briefly outline the study completion and close-out 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 the NIAMS.
- 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.x.1 Participant Notification

The Principal Investigator and study staff or Coordinating Center should develop a plan to notify participants that the study is over, ask whether they would like to be informed of the results, and thank them for their participation. It may include either the first article or a reference to the article.

In this section of the MOOP, please include the sites' plan for participant notification for when the study is over.

3.x.2 Site Procedures

The study leadership may also wish to provide certificates of appreciation to sites that enrolled adequately, had data of high quality, and ensured that most participants completed the study.

3.y Policies

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

Please provide these policies in this section of the MOOP.

3.y.1 Confidentiality Procedures

It is the responsibility of the study leadership to outline and enforce participant confidentiality and data security guidelines. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals without checking with NIAMS.

This section of the MOOP will discuss the safeguards which have been put in place by the PI 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 clinical 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 stored in the data center should not be accessible to persons outside the center 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.y.2 Publications

Investigators have a responsibility to the public to make study results available as soon as possible. The MOOP 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 PI must check with NIAMS if there are plans to publish data before the study is over.

3.z MOOP Maintenance

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

The MOOP should be continuously reviewed by study staff to ensure the operating procedures described are accurate. If any procedures have been changed or modified, the MOOP should be updated and the appropriately modified pages distributed, with instructions, for replacement in the MOOP.

4.0 SUMMARY

The development of a study MOOP is an important process that yields a product that is critical in ensuring a study with high quality results. Development of the MOOP forces investigators to consider the details of a study and to develop procedures that are understood and can be followed by multiple clinical centers.

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RELEVANT WEB SITES

Food and Drug Administration:

http://www.fda.gov/cber/guidelines.htm

http://www.fda.gov/ora/compliance_ref/part11/

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Gene Therapy, Stem Cells and Fetal Tissue

http://grants.nih.gov/grants/policy/gene_therapy_20000307.htm

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-050.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-026.html

Information Required in NIH Grant Applications:

http://grants.nih.gov/grants/policy/policy.htm

NIH Policies for Monitoring Clinical Research:

http://grants.nih.gov/grants/guide/notice-files/not99-044.html

http://grants.nih.gov/grants/guide/notice-files/not98-084.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

http://grants.nih.gov/grants/guide/notice-files/not99-107.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html