

**National Institute of Arthritis and
Musculoskeletal and Skin Diseases**

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

June 5, 2002

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WEB LINKS

NIH and the Academic Research Community: Partnerships for Clinical Trials
<http://www.nih.gov/about/director/Speeches/aamc57.htm>

Guidelines for Submission of Applications for Investigator-Initiated Clinical Trials
<http://www.nih.gov/niams/grants/gsaiict.htm>

NIAMS Policy: Request for a Planning Phase in Clinical Trial Applications
<http://grants.nih.gov/grants/guide/notice-files/NOT-AR-01-002.html>

Data and Safety Monitoring for Investigator-Initiated Clinical Trials
<http://www.nih.gov/niams/grants/datasafe.htm>.

WEB LINKS (Cont'd)

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>)

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/finfo_6.php3)

Clear and to the Point: Guidelines for Using Plain Language at NIH
(<http://www1.od.nih.gov/execsec/guidelines.htm>)

Sample Clinical Study Consent Forms
(http://www.niams.nih.gov/rtac/clinical/invest_form.htm and
<http://www.niams.nih.gov/rtac/clinical/observ.htm>)

ICH E6 Good Clinical Practice Guidelines (<http://www.ifpma.org/pdfifpma/e6.pdf>)

Code of Federal Regulations (CFR) Title 21, Parts 800 – 1299
(http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfrv8_00.html)

Guidance for Industry – Medical Device Reporting – Alternative Summary Reporting
(ASR)
Program (<http://www.fda.gov/cdrh/osb/guidance/315.html>)

Interim Guidelines for NIH Intramural Principal Investigators and for NIH
Institutional Review Boards on Reporting Adverse Events
http://ohsr.od.nih.gov/info/Adverse_Events/Adverse_Events_Guidelines.htm

Data and Safety Monitoring Guidelines for Investigator-Initiated Clinical Trials
(http://www.niams.nih.gov/rtac/clinical/safe_monitoring_plan.htm)

Guidelines for NIH Intramural Investigators and Institutional Review Boards on Data
and Safety Monitoring (http://ohsr.od.nih.gov/info/rinfo_18.php3)

Conflict of Interest Statement for DSMB Members
(<http://www.nih.gov/niams/grants/clinres/ciform.htm>)

DSMB Charter <http://www.nih.gov/niams/grants/clinres/dsmbchar.htm>

Generic Monitoring Plan for Trials Requiring a Safety Officer
(<http://www.nih.gov/niams/clinical/dsmb4.html>)

Generic Monitoring Plan for Trials Requiring a Data Safety Monitoring Board
<http://www.nih.gov/niams/clinical/dsmb3.html>

Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records;
Electronic Signatures (http://www.fda.gov/ora/compliance_ref/part11/Default.htm)

1.0 INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is the primary agency within the National Institutes of Health (NIH) for research on rheumatic diseases, musculoskeletal system disorders and diseases of muscle, bone, and skin. As part of its mandate, NIAMS supports numerous clinical research activities. As our understanding of disease processes has grown along with an expanded armament of potential interventions, the numbers of clinical studies NIAMS supports have increased in recent years. In addition to the increased numbers of clinical studies, their complexity has also increased. The large numbers of complex studies that involve human participants has stimulated a focus on the protection of human participants and on study integrity. Thus, this revised document includes recent policies and guidelines on protection of human participants and conducting studies of the highest quality. A recent talk entitled *NIH and the Academic Research Community: Partnerships for Clinical Trials* by Acting Director of the NIH, Ruth Kirchstein, M.D., summarized the human participant protection issues and strategies of the NIH [<http://www.nih.gov/about/director/Speeches/aamc57.htm> (5/00)].

A clinical study is a planned systematic investigation of a particular problem (e.g., a disease or risk factors). A clinical trial is a planned prospective human experiment that compares the outcomes of one or more treatment, device, or behavioral interventions in a group of participants with the outcomes of a control or comparison group (Friedman, Furberg, and Demets, 1996). An investigator can initiate a clinical trial through an Investigator-Initiated Clinical Trial grant application. NIAMS also supports clinical trials through the Request for Applications (RFA), Request for Proposals (RFP), and Cooperative Agreement mechanisms. Guidelines for Submission of Applications for Investigator-Initiated Clinical Trials (<http://www.nih.gov/niams/grants/gsaict.htm>) assists investigators in preparing an application for a clinical trial. Because of the complexity of clinical trials, NIAMS recommends that Investigators include a planning phase of up to nine months in their application [*NIAMS Policy: Request for a Planning Phase in Clinical Trial Applications* (<http://grants.nih.gov/grants/guide/notice-files/NOT-AR-01-002.html>)].

NIAMS must ensure compliance with Federal law and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. In preparing a grant application, investigators must be aware of the terms of award with respect to required reporting, data safety and monitoring, and Internal Review Board (IRB) approval (NIAMS: *Data and Safety and Monitoring Guidelines for Investigator-*

Initiated Clinical Trials, <http://www.nih.gov/niams/grants/datasafe.htm>). Funded applicants must meet and adhere to the **terms of award** that are incorporated into the Preaward Letter. This process is summarized in Figure 1.

NIH monitoring policies for Phase I and II studies are described in the NIH policy *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>] (6/00). *NIH Policy for Data and Safety Monitoring* describes requirements for Phase III studies [<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>] (6/98). As of October 2000 grant applicants are required to include the following:

- **Data Safety and Monitoring Plan** - The Principal Investigator must include a data safety and monitoring plan in each new protocol.
- **Institutional Review Board (IRB) Approval** - The IRB must approve the data safety and monitoring plan and must determine what kind of safety monitoring process (if any) is required.
- **Independent Monitor** - The NIAMS Program Director/Project Officer is responsible for appointing an independent monitor or convening a Data Safety and Monitoring Board (DSMB) if one does not already exist.
- **Provision of Data** - The Principal Investigator is responsible for providing all required data to the study monitor or DSMB and for responding to any of their findings.

The clinical trial protocol provides a brief scientific rationale of proposed investigation, defines the study objectives and target population, provides a detailed description of all study procedures and interventions, defines end points, outlines the statistical plan, and establishes procedures aimed to ensure patients safety and wellbeing. Frequently, clinical trials are conducted at multiple clinical centers in order to enroll an adequate number of participants into the study. A study Manual of Operating Procedures (MOOP) is developed to facilitate consistency in protocol implementation and data collection across patients and clinical sites. Further, the MOOP provides reassurance to all participants that scientific integrity and patient safety are closely monitored and increases the likelihood that the results of the study will be scientifically credible. The NIAMS recognizes the importance of a MOOP. Thus, the purpose of this document is to assist investigators that are conducting clinical studies by providing them with a template for the preparation of a

FIGURE 1:

General Clinical Study Process Flow with Relevant Guidelines and Policies



2.0 OVERVIEW

During a study's planning phase, the investigators and their institutional colleagues delineate the protocol. The study overview and justification, study objectives, patient population and numbers, patient eligibility, randomization, end points, assessments, treatment regimens, definitions, data to be collected, statistical plan, endpoints, data management plans, and data safety monitoring plans may be expanded and refined. The protocol must be approved by the IRBs of all Institutions that are participating in the study.

The MOOP is analogous to a cookbook in that it details the study conduct and operations. It transforms the study protocol into a guideline that describes the study organization, operational definitions of the data, patient recruitment, screening, enrollment, randomization, and follow-up procedures, data collection methods, data flow, case report forms (CRFs), and quality control procedures.

MOOP development requires that the final protocol, CRFs, informed consent documents, and administrative forms such as Patient Screening Log, Patient enrollment Log, Delegation of Responsibilities Log, etc., be completed. Additionally, if the study is conducted with a pharmaceutical sponsor and is to be submitted to the Food and Drug Administration (FDA), an Investigator's Brochure must be included. Parenthetically, the timeline for development of study materials must be planned for and typically takes at least six months.

The MOOP development process must involve the investigators and study staff to ensure that the study will be performed as intended. In multiple 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.

The MOOP must be 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, typically in a three-hole notebook. 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

The MOOP details the study procedures. It should include the following sections:

- a. Study Protocol
- b. Schedule of Visits and Evaluations
- c. Study Organization, Centers, Committees
- d. Recruitment, Screening, and Eligibility Criteria
- e. Informed Consent
- f. Randomization
- g. Blinding and Unblinding
- h. Study Intervention
- i. Participant Evaluations and Follow-up
- j. Study Completion
- k. Concomitant Medications
- l. Adverse Events
- m. Data Safety and Monitoring Activities
- n. Study Compliance
- o. Data Collection and Study Forms
- p. Data Management
- q. Good Clinical Practice
- r. Reports
- s. Policies
- t. MOOP Maintenance

The above sections apply not only to drug treatment trials, but also to surgery, behavioral, and device trials. In studies where a section does not apply (e.g., randomization in a study with no randomization), the study investigators need not include it in the MOOP. Each of the above MOOP sections is now described.

3.a Study Protocol

The protocol describes a statement of the problem, objectives, research questions and hypotheses and should clearly articulate:

- the 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
- safety issues
- confidentiality/privacy issues
- internal review board (IRB) approval procedures
- informed consent procedures
- plans for and responsibilities of internal and/or external data and safety monitoring board (DSMB) or safety monitor
- statistical plan

The final version of the study protocol with the date of approval and version number is included in the MOOP.

3.b Schedule of Visits and Evaluations

A useful component of the MOOP is a schedule of visits and evaluations. This schedule delineates what is to be done at each study phase and at each contact with the patient. An example of a schedule is provided in Figure 2.

FIGURE 2: Generic Time and Events for Clinical Research Study

Study Visits	Screening	Treatment Phase													
	-14 days to Day 0	Visit 1	2	3	4	5	6	7	8	9	10	11	12	13	Final Visit
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	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
Investigational Agent PK		X	X	X	X				X				X		X

3.c Study Organization, Centers, Committees

This section describes the study organization and provides a roster of the coordinating and clinical centers, and study committees. The study organization for large studies generally includes an organizational chart and describes the roles of the clinical centers, data management, coordinating and/or statistical center, laboratories and committees.

3.c.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, Safety Office, and NIAMS staff.

A notation of whom to contact regarding the following special situations should also be included:

- reporting an adverse event
- request for an exemption to entry criteria
- request for additional supplies
- randomizing a participant
- unblinding a participant

3.c.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 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
- reports - enrollment, adverse events, participant status (e.g., drop-outs)
- distribution of all changes, updates and policies of above mentioned reports and documents to all participating clinical sites

3.c.3 Clinical Sites

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

- assuring that the study is conducted according to the protocol and MOOP
- identifying, recruiting, screening and enrolling participants
- protecting participants' rights
- obtaining informed consent from each participant
- collecting study data and following participants through study completion
- for drug treatment studies, controlling the distribution of the drug intervention under study
- retaining specific records, (e.g., laboratory drug distribution records)
- preparing and sending required reports to 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

3.c.4 Pharmacy Activities

“Pharmacy” refers to the unit responsible for the storage, dispensing and accountability for the investigational agent. An actual pharmacy may or may not be directly involved in a study at the clinical level (e.g., the investigational agent may be delivered directly to the clinic or office participating in the study 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 Sponsor. It provides instructions for completing drug accountability records and administration records.

3.c.5 Steering Committees

In multicenter studies, the Steering Committee is generally responsible for the overall direction of a study and is the main leadership committee of the study. Frequently, the Steering Committee is comprised of the clinical and coordinating center Principal Investigators.

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

- Responsibility for the general design and conduct of the trial and preparation of the essential study documents, including the protocol, manual of operations, 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 enhance the likelihood of achieving those goals
- Review and implementation of recommendations from the DSMB for protocol treatment amendments (e.g., termination of treatment due to lack of efficacy)
- Review and respond to other general advice and/or recommendations from the DSMB

3.d Recruitment, Screening, and Eligibility Criteria

The goals of participant recruitment and screening are to quickly and efficiently enroll eligible patients into the study. This section of the MOOP describes 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 amplifies the disease or condition. The eligibility and exclusion criteria are specifically defined and delineated to capture the target population.

3.d.1 Screening

This section provides a detailed discussion of all screening procedures outlined in the protocol to determine if a participant is eligible to participate in the study. Frequently, there is a *pre-screening* phase during which the study coordinator reviews medical records, hospital admissions or discharges, or responds to initial patient or physician telephone inquiries. *Pre-screening* of participants may be performed prior to obtaining the participant's informed consent.

A Screening Log must be used to monitor recruitment and document the enrollment status of prospective study participants. The Screening Log generally contains the patient's initials, age, gender, race, date and time of hospitalization or office visit, participant status (whether the participant is eligible for study participation, ineligible for study participation and reason, or refused consent) and screening and randomization number (if applicable). The MOOP describes how sites will maintain the Screening Log and its contents.

3.d.2 Eligibility Criteria

Inclusion and exclusion criteria are protocol specific and are outlined in the study protocol. Participants must meet all entry criteria prior to being enrolled in the study. This section of the MOOP must clarify any of the eligibility criteria that may not be specifically defined in the protocol or are participant to interpretation and the situations in which an exception to an entry criteria may be sought. It should also delineate the necessary procedures in seeking an exception, who is responsible for granting the exemption, and the relevant forms used to document eligibility (e.g., medical history form, physical examination form, laboratory form). All data captured on the forms to support the participant's enrollment in the study must be verifiable in the source documents.

If the patient appears to be eligible for participation in the study, informed consent must be obtained in order to accomplish screening procedures, such as performing a physical exam and obtaining the participant's demographic information, medical history and laboratory results.

3.e Informed Consent

According to the *Guidelines for Writing Informed Consent Documents*, [http://ohsr.od.nih.gov/info/finfo_6.php3 (08/00)], informed consent gives patients the opportunity to choose whether they want to participate in a study.

Informed consent requires:

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

Informed consent is a process that 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.

As required by 21 CFR 50.25, when obtaining informed consent, the following eight basic elements must be addressed:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental
- A description of any reasonably foreseeable risks or discomforts to the participant
- A description of any benefits to the participant or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and that notes the possibility that authorized persons may inspect the records
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical

treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled

3.e.1 Informed Consent Process

Specific instructions regarding the process of obtaining informed consent must be detailed in this section. In offering participation in the study to a patient, there should be ample time should be provided for the patient to read the informed consent form. Additionally, the investigator, coordinator or individual obtaining informed consent must discuss the nature of the study, randomization and blinding, study procedures, importance of compliance, potential risks and benefits, and duration of the study. The patient must be informed that he/she is not obligated to participate in the study. 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 patients do not participate or cease participation at any time. Further, there should be adequate time for the patient to ask questions. The instructions must discuss the following:

- *Describing study withdrawal* - the study withdrawal process based on the specific protocol, emphasizing that study participation is voluntary.
- *Signing the Informed Consent Form* - the necessary signatures based on the site's IRB requirements (i.e. the patient's signature/legal representative, the investigator or person actually obtaining the consent, and a witness).
- *Maintaining the Informed Consent Form* - where the informed consent form should be maintained and to whom a copy of the form should be provided.

3.e.2 Informed Consent Document

The written Informed Consent should be short and written in plain language so that an individual or patient who has not graduated from high school can understand the contents. According to *Clear and to the Point: Guidelines for Using Plain Language at*

NIH [<http://www1.od.nih.gov/execsec/guidelines.htm> (8/00)], it is recommended that public information materials be written on a 4th – 8th grade reading level. Sample consent forms for clinical investigations and observational studies are found at (http://www.niams.nih.gov/rtac/clinical/invest_form.htm and <http://www.niams.nih.gov/rtac/clinical/observ.htm>).

The Investigator, patient, and witness must each sign and date the Informed Consent Document. NIAMS recommends that the Principal Investigator, 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. 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.

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, while studies conducted under contract must 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.

3.f Randomization

The MOOP should describe the randomization approach for the study. In randomized, controlled clinical trials, participants are assigned to a treatment group based upon a pre-determined randomization scheme developed by the study statistician. Randomization is introduced to reduce bias in treatment selection.

Simple randomization assigns treatment groups without regard for previous assignments. This approach can yield imbalance among groups. For example, in a recent small two-arm study that used simple random assignment, among the first twenty participants

enrolled, the men were all assigned to one group and the women another. The following is a brief description of randomization approaches.

3.f.1 Blocked Randomization

Blocked randomization reduces the likelihood of imbalance between treatment groups. A block, which is an exact integer multiple of the number of treatment groups, contains a balance of treatment assignments. The order of the assignments is randomly assigned within the block, but the block maintains a balanced assignment among groups.

3.f.2 Stratified Randomization

To balance factors that may influence treatment outcome, such as age, gender, or disease severity, randomization can be stratified. Each combination of factors form a Stratum, and randomization is allocated within each stratum. Thus, if age and gender are the factors upon which to stratify, study stratum could include:

- men under age 60
- men ages 60 and older
- women under 60
- women ages 60 and older

Within these study stratum, treatment allocation can be blocked to assure balance.

3.f.3 Blocked and Stratified Randomization

Blocking and stratification can also be combined to assure adequate, relative size of treatment groups.

3.f.4 Cross-Over Studies

An alternative to the parallel independent treatment group design is a cross-over design. This design incorporates two treatment periods. Participants are randomized to receive Treatment A followed by Treatment B or visa versa.

3.f.5 Randomization Procedures

This section of the MOOP provides a full discussion of the randomization procedures including:

- **Process Responsibilities:** An 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 randomized files.
- **Procedure for Randomizing a Participant:** At each site, an 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).
- **Documentation of Randomization:** The person who will be responsible for completing the randomization log must be named at each site.

3.g 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 keeps the randomization assignment under "lock and key" so that the study 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 to unblind and must grant approval for unblinding. In the event that unblinding occurs, the following should be recorded:

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

Procedures for unblinding should be clearly specified in the MOOP.

3.h Study Intervention

This section describes the study intervention in clinical trials. A study intervention can be described as an effort to change the natural course of a disease or condition by attempting to alter the risk factors or precursors associated with that disease or condition.

Interventions include drugs, surgery, devices, biobehavioral activities (e.g., coping mechanisms), and/or lifestyle changes (e.g., diet, exercise).

All intervention studies require valid scientific evidence in order to determine if the intervention is safe and effective. Types of intervention studies are summarized 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 accepted for use following phase III trials.

Two other types of studies, pharmacokinetics or PK studies and pharmacodynamics or PD studies are typically Phase I or Phase II studies that may not be considered clinical trials by some NIH Institutes. However, these studies are important in pediatric populations. PK studies focus on the action of drugs in the body at a point in time or over a period of time, including the processes of absorption, distribution, tissue localization, biotransformation, and excretion. PD studies focus on the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure and interactions with another drug.

The intervention, whether medical treatment, device or behavioral intervention, should be described comprehensively:

- 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.ifpma.org/pdfifpma/e6.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).
- For *surgical studies*, the procedure is delineated.
- *Biobehavioral* and *life style* studies describe how the intervention is to be carried out.

3.i Participant Evaluations and Follow-Up

This section describes the baseline and follow-up evaluations and tests for enrolled participants. All evaluations, as well as their schedule and procedures for obtaining data, must be clearly stated in this section. All efficacy (e.g., visual analog scales) and safety evaluations (e.g., blood chemistries) should be delineated. The schedule of when evaluations are to be obtained must be specific (e.g., five hours after the last dose of study drug/placebo).

3.j Study Completion

This section of the MOOP must describe the evaluations that take place at study completion, along with follow-up of participants who stop study treatment or drop out of the study. Some studies are designed to follow participants who stop treatment through the end of the study. The approach to following participants who discontinue treatment and the data that are to be collected should be detailed. A discussion of the forms that are to be completed at each visit is discussed in Section 3.o.2, Study Forms.

3.k Concomitant Medications

The MOOP should discuss which concomitant medications are allowed or restricted in the protocol. The form used to collect concomitant medication information and the period of time for which this information will be collected must be described. Concomitant medication information must be verifiable in the source documents.

3.1 Adverse Events

This section of the MOOP details the definitions of and procedures for reporting adverse events. Relevant definitions, based on FDA Guidelines for drug treatments (21CFR312.32, 21CFR314.80, ICH E6), guidances (ICHE6, Good Clinical Practices), and devices (21CFR803 SubpartB and 21CFR803.20; *Guidance for Industry - Medical Device Reporting - Alternative Summary Reporting (ASR) Program 21CFR 803 Subpart B-End 803.20-End*) may be found at (<http://www.fda.gov/cdrh/osb/guidance/315.html>); and in *Interim Guidelines for NIH Intramural Principal Investigators and for NIH Institutional Review Boards on Reporting Adverse Events* (http://ohsr.od.nih.gov/info/Adverse_Events/Adverse_Events_Guidelines.htm).

Definitions include the following:

- ***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, whether or not related to the intervention.
- ***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).

3.1.1 Adverse Event Reporting

Procedures for reporting adverse events are described in this section of the MOOP. All

adverse events are collected, analyzed, and monitored by using an Adverse Event Form, a sample of which is shown in Figure 3. All adverse events experienced by the participant during the timeframe specified in the protocol (e.g., from the time study drug administration to thirty days following the last administration of study drug) should be reported. AEs include new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported as specified in the protocol.

3.1.2 Serious Adverse Event Reporting

Procedures for reporting serious adverse events are described in this section of the MOOP. All SAEs, unless otherwise specified in the protocol and approved by the IRB, must be immediately reported by the Principal Investigator to the study's responsible group, e.g., DSMB or safety monitor, and NIAMS. All interventional studies, independent of phase or type, must report SAEs. The immediate reports should be followed promptly by detailed, written reports.

As shown on the sample SAE form in Figure 4 that is used for NIH Intramural Programs, the following information must be provided with the initial adverse event report:

- Protocol number and title
- Name of principal investigator and site where SAE occurred
- Participant's I.D. number (site-specific reports only – not to be submitted to IRB/DSMB)
- Date and time of onset of the event
- Description of the event and attribution to study drugs or intervention
- Brief description of participant, including gender and age

FIGURE 3: 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 = Unlikely 3 = Possible 4 = Probable 5 = Definitely	1 = None 2 = Discontinued Perm. 3 = Discontinued Temp. 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = None 2 = Remedial Therapy-pharm 3 = Remedial Therapy-nonpharm 4 = hospitalization	1 = Resolved, No Sequela 2 = AE still present- no tx 3 = AE still present-being tx 4 = Residual effects present-no tx 5 = Residual effects present- tx 6 = Death 7 = Unknown	1 = Yes 2 = No (If yes, complete SAE form)

Event	Start Date	Stop Date	Severity	Relatedness	Action Taken W/Study Drug	Other Action Taken	Outcome	Serious?	Initials

**FIGURE 4:
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 disability / incapacity
 life-threatening congenital anomaly / birth defect
 hospitalization-initial or prolonged 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 protocol
 amend consent document inform current participants
 terminate or suspend protocol
 other (describe)

Signature of Principal Investigator: _____ Date: _____

3.m Data Safety and Monitoring Activities

With the increased concerns for patient safety, NIAMS has established Data and Safety Monitoring Guidelines. These guidelines may be found at:

(http://www.niams.nih.gov/rtac/clinical/safe_monitoring_plan.htm).

All clinical trials supported by NIAMS must have a Safety Officer or a Data Safety Monitoring Board (DSMB), that are independent of the study. Phase I studies, which may be small single site studies, often have a Safety Officer, while multi-center studies require a DSMB. For Phase II and III studies, the monitoring group is responsible for reviewing the study data at regular intervals, including the interim analysis, and determining if it is safe to continue with the study according to the protocol.

DSM activities are established in order to protect the safety of human participants and maintain and ensure the scientific integrity of the study. The individual or group selected to monitor a study should reflect the appropriate clinical expertise and knowledge of the design, monitoring, and analysis of the project necessary to conduct an ethical and scientifically rigorous study.

DSM activities include a review of the protocol with emphasis on data integrity and patient safety issues, monitoring of adverse events, protection of the confidentiality of the data and monitoring results, and recommendations to the NIAMS and Principal Investigator regarding continuation or conclusion of a study.

A description of the roles and responsibilities of the Safety Officer and/or Data Safety and Monitoring Board (DSMB) should be described in this section and generally include the following:

- review protocol, informed consent documents, plans for data safety and monitoring;
- evaluate study progress, including periodic assessments of data quality, participant recruitment and retention, participant risk versus benefit, site performance, and other factors that may affect study outcome;
- consider external factors such as scientific or therapeutic developments that may impact on the safety of the participants or the ethics of the trial;
- protect the safety and scientific progress of the trial;
- make recommendations to the Principal Investigator, NIAMS, and, if required, to the FDA regarding continuation, termination, or other modifications to the study based on observed beneficial or adverse effects

of the treatment under study; Recommendations should be in accordance with stopping rules, which are clearly defined prior to data analysis and have the approval of the DSMB;

- ensure data integrity;
- ensure the confidentiality of the trial data and the monitoring results; and
- assist NIAMS by providing recommendations on any problems with study conduct, enrollment, sample size, and/or data collection.

3.m.1 Generic Monitoring Plans

Also available are generic monitoring plans for studies requiring a Data and Safety Monitoring Board (<http://www.niams.nih.gov/rtac/clinical/dsmb3.html>) or a Safety Officer (<http://www.niams.nih.gov/rtac/clinical/dsmb4.pdf>). These documents describe the monitoring procedures required by NIAMS for clinical studies. This section of the MOOP should describe the specific study plans. A monitoring plan must be submitted to and approved by the NIAMS Program Director prior to the award for a clinical trial.

3.m.2 DSMB Membership

Members of a DSMB (and Safety Officers) are selected to reflect a mix of appropriate clinical expertise and knowledge of the design, monitoring, analysis and ethical issues of the clinical research project necessary to protect patient safety and conduct a scientifically rigorous study. NIAMS has developed a general letter to formally invite individuals to become a member of the. The DSMB members must also assure that they have no conflict of interest by signing the *Conflict of Interest Statement for DSMB Members* (<http://www.nih.gov/niams/grants/clinres/ciform.htm>).

3.m.3 DSMB Charter

To assist the DSMB in carrying out its advisory role to the Institute, NIAMS has prepared a draft *DSMB Charter* (<http://www.nih.gov/niams/grants/clinres/dsmbchar.htm>). The DSMB members may recommend charter amendments to NIAMS.

3.n Study Compliance

Clinical trials are expensive endeavors, and procedures should be implemented to maximize adherence to the protocol, minimize participant non-compliance and enhance participant retention in the study. Drug accountability and other study procedures, such as ongoing communication between study staff and participant, participant visits, etc. to encourage patient compliance are described in this section. Likewise, protocol violations

and deviations as well as procedures to track them and notify appropriate parties must also be described in this section.

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

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

The MOOP should state that these violations will be reported to the Principal Investigator at the Coordinating Center and to the NIAMS and DSMB or Safety Officer within 24 hours of occurrence or as soon as they are discovered. In addition, if monitors discover any of these violations during a monitoring visit, they should notify the NIAMS in writing of the occurrence.

The study Coordinating Center or responsible person in a single site study should maintain a log of all protocol deviations and violations and should report them routinely to the DSMB or Safety Officer. A sample log is presented as Figure 5. While it is assumed that there may be rational clinical reasons for an occasional violation, a site with serious continual problems is at risk for losing its funding. Similarly, subcontractors of the awarder may be made aware of repetitive violations or deviations in this section.

3.0 Data Collection and Study Forms

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

3.0.1 Source Documentation

Patient data are collected on source documents, such as lab reports, ECG tracings, etc., and these data are then transcribed to a paper case report form (CRF) or electronic CRF (eCRF). All study documents must be retained by the investigator as described in Section 3.0.6 below. The following are considered participant file documents:

**FIGURE 5:
SAMPLE PROTOCOL VIOLATION LOG**

Protocol Name: _____

Protocol Number:

Site:

Principal Investigator:

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

SAMPLE PROTOCOL VIOLATION CODES:

- | | |
|--|---|
| <ol style="list-style-type: none"> 1. Randomization of an ineligible participant 2. Failure to obtain informed consent 3. Entering a (trial name) participant in another type of study 4. Failure to keep IRB approval up to date 5. Participant receives wrong treatment 6. Participant is randomized prior to Baseline Diagnosis, Imaging Report Form, Baseline Assessment, etc. 7. Participant seen outside window of normal follow-up visits 8. Missing radiology and/or operative report 9. Registration and/or treatment of participant prior to IRB approval 10. Registration of participant on protocol during a period of delayed re-approval 11. Reportable monitored events not reported to IRB 12. Consent form missing 13. Consent form not signed and dated by participant 14. Consent form does not contain all required signatures | <ol style="list-style-type: none"> 15. Consent form used was not current IRB-approved version at time of participant 16. Registration 17. Consent form was not protocol specific 18. Consent form does not include updates or information required by IRB |
|--|---|

ADDITIONAL POTENTIAL PROTOCOL VIOLATION CODES:

19. Not reporting a serious complication within 24 hours
20. Completing a survey outside the acceptable window for that survey
21. Missing data
22. Enrollment of an ineligible patient
23. Randomization occurring outside normal window
24. Center fails to submit and transport data from their onsite computer to the Coordinating Center
25. Baseline Data (e.g. x-rays) for participants were not obtained

- Case report forms
- Data correction forms
- Workbooks
- Source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- Signed participant consent forms

Source documents are any documents on which study data are recorded for the first time. Source documents include but are not limited to medical records, study-specific source documents supplied by the coordinating center or sponsor, standardized test forms and laboratory reports.

3.o.2 Study Forms

This section details how study forms (also called case report forms) are to be completed on a question-by-question (Q by Q) basis. Each of the study forms are included in the section with explanatory comments.

It also identifies who is responsible for producing and distributing forms, how they are packaged (e.g., placed in a binder for each participant), how the forms are to be maintained, and who should be contacted in the event additional forms are needed. In addition, a list of all study forms and the collection schedule is included.

This section should also describe where the forms are to be sent or transmitted once they are complete.

3.o.3 General Instructions for Completing Forms

All data recorded on forms must be verifiable in the source documents maintained by the clinical site(s) according to FDA Guidelines and good clinical practice. Examples of specific instructions for completing paper forms follow.

When completing the 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 I.D. number.

Header: Complete the header information on **EVERY** page, including pages for which no study data are recorded.

Participant I.D.: The participant I.D. must be recorded on **EVERY** page, including pages for which no study data are recorded.

Participant Initials: Record participant's first, middle and last initials. If a participant has no middle name, place a dash (-) in the designated space. If the participant has a hyphenated last name, record the first letter of the first part of the name.

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. Estimates are **not** acceptable unless specifically indicated in instructions.

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. If an

entire page of the forms cannot be completed (i.e., 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.o.4 Performing a Quality Control (QC) Check

This section of the MOOP describes the study quality control procedures. With increased emphasis on scrutiny of clinical data, it is important to conduct a quality control check of the study forms before entering the data or submitting the forms to the coordinating center. Part of Good Clinical Practice, discussed below in Section 3.q, is establishing quality control procedures. The Coordinating Center and sites should develop quality control procedures. Such procedures may specify the following types of checks:

- Numbers are not transposed in the site I.D and participant's I.D. number.
- Same participant I.D. number and initials recorded on all forms.
- There are no illegible handwritten items, spelling errors, etc.
- Placement of responses are clearly within designated spaces.
- All fields of a "completed form" are actually completed with participant data or reason for no data is noted in or near the field.

All required forms have been completed or reason for no data collection is noted on the form.

3.o.5 Submitting Forms

Forms should not be submitted for data entry until all data are recorded and verified against source documents. It is the sites' responsibility to ensure that all forms are complete. Identify which copies of forms are to be maintained at the site and which copies are to be submitted for data entry. In addition, identify the data flow, data entry, and data correction procedures.

3.o.6 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. Individual IRBs may have different requirements for record retention.

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 (see Code of Regulations (CFR) Title 21, Parts 312.62c, revised April 1, 2001). Investigators should retain forms for the longest period in accordance with the applicable regulatory requirements or by an agreement with the sponsor. This period should be stated in the MOOP.

3.0.7 Administrative Forms

The MOOP should contain a complete set of administrative forms. Administrative forms may include the following:

Facsimile Transmittal Sheet - This form serves as a cover page for all faxes, as required by a study.

Telephone Contact Log - This form serves as a record of all conversations regarding the study and study participants.

Screening Log - This form is a record of all patients who are 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 - This form is used to document a participant's exemption to an entry criterion.

Participant Identification Code List – According to the ICH Guidelines, it is recommended that the investigator or lead site maintain a confidential participant identification code list. This form is a record of the participant's name, medical record number, randomization number, and study entry and exit dates. The purpose of the code list is to “document that the investigators/institutions keep a confidential list of names of all participants allocated to trial numbers on enrolling in the trial. It allows the investigators/institutions to reveal identity of any participant” (ICH E6 section 8.3.21). Due to the confidential nature of this information, it is recommended that it be maintained in a secured location apart from forms and

other participant data files. Although this form is not mandated by regulations, the information contained on it must be maintained by the site.

Study Drug Accountability Record - This form 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 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 - This form 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 - All members of the site study team must sign the log. It is the responsibility of the Principal Investigator and/or Clinical Research Coordinator to:

- indicate individuals approved to make forms entries and changes; and
- note the date when any study team member is removed from the team for any reason.

Site Visit Log - Visiting individuals should always complete the Site Visit Log. Most common reasons for visits are: site initiation, monitoring, training and close-out.

3.p Data Management

This section describes the data management approach that will support the study. An issue that transcends clinical studies is how to collect data accurately, quickly and cost-effectively from multiple sites. Each study requires decisions regarding data handling options as discussed in this section.

3.p.1 Data Collection Options

Traditionally, data have been collected on paper forms. Recently, however, technological advances support data entry directly into a computer using electronic forms at clinical sites. While the use of paper forms is familiar, it is a time consuming and an error-prone process.

Electronic forms can eliminate the step of entering data from the paper forms into a computer format. Further, since data are entered where they are collected, errors can easily be corrected. Copies of paper forms and/or printed electronic forms should be included in the MOOP.

3.p.2 Data Transmission Options

In multicenter studies, data are sent from the clinical centers to a Coordinating Center. With paper forms, data are mailed, faxed or scanned. The fax option is used with packages that allow data to be directly entered into a computer database management system. Some of these systems require a line by line review at the Coordinating Center unless each item can be completed by darkening circles. Furthermore, this option may not eliminate the need to send paper back and forth between the Clinical Centers and the DMC to correct errors. With electronic forms, encrypted data can be sent electronically to the DMC over the Internet.

3.p.3 Locus of Computing

Another issue for clinical trials data management is where the software and data are stored. In the last decade, remote data entry (RDE) gained some popularity as data could be entered close to the source. However, with this version of RDE, software was typically distributed to the clinical centers, and data were entered locally and mailed to the Data Coordinating Centers on diskettes. A major problem with this approach was that if there were software corrections, the software had to be reinstalled at each of the sites and often the sites were not using the correct version.

An option, only recently available, is the use of "application hosting" technology. With this approach, data are entered into a personal computer at the site and the mouse clicks and keystrokes are electronically transmitted to a central server over the Internet. Thus, the site's computer acts like a "dumb terminal" and the server replicates the "main frame." The advantage to this approach is that the software and data are stored centrally in one place, assuring that the current software is always utilized, and that the data are adequately backed up and secure.

Each of these options may be useful for specific studies. When small numbers of participants are accrued at a large number of sites, paper forms that are transmitted to the Coordinating Center for central entry may be the most cost-effective approach. However, when large numbers of participants are enrolled at the sites telefax or electronic forms may be more cost-effective approaches. Investigators should be aware that if they are conducting studies that will also be submitted to the Food and Drug Administration (FDA), the systems will need to be documented and validated. Guidance for electronic

systems is found on the FDA website, *Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures* (http://www.fda.gov/ora/compliance_ref/part11/Default.htm).

3.p.4 System Functions

Investigators should consider utilizing systems that perform the following functions:

- **Data Tracking** - to provide the status of participant enrollment, forms completed at the sites and forms at the coordinating center.
- **Randomization** - of participants to treatment arms.
- **Data Entry** - for either a “paperless” approach or that has screens that are facsimiles of the forms.
- **Data Editing** - that identifies out-of-range and missing entries, errors in dates (e.g., first treatment date precedes protocol start date), and logical inconsistencies (e.g., protocol specifies an examination before randomization, but there is no examination form).
- **Updating module** - to correct data and maintain an audit trail of all changes to the data [21 CFR 11.10(e)].
- **Reporting** - to describe and account for patients accrued, entered, completed, etc.
- **Export module** - to transmit data to statistical analysis packages, i.e. 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 data base from edited or "clean" records. These areas should be discussed in this section. The MOOP should also include a description of the computer system used to support the study and a copy of the Users Guide.

3.p.5 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 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 enter data “heads down” or with no edits flagged as the data are entered. However, if there are edit procedures in place during data entry, double data-entry may not be necessary.

3.q Good Clinical Practice

The integrity and ultimate credibility of the study depends 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. The quality assurance plan should be developed before the study starts and should be implemented over the life of the study. This section should detail the various aspects of that plan and describes training and certification procedures and the site monitoring and data monitoring procedures.

3.q.1 Standard Operating Procedures

One aspect of site quality control is standard operating procedures (SOPs). SOPs describe a site's generic procedures such as the maintenance of a screening log or quality control.

3.q.2 Monitoring

This section should describe any site monitoring that will take place during a study by the coordinating center. Monitoring typically takes place through periodic site visits conducted during the study.

Periodic visits will be conducted throughout the course of the study. The frequency of visits is dependent on the site's performance and the number of participants enrolled. The purpose of monitoring visits is to:

- assure the rights and safety of participants
- confirm that study conduct follows the guidelines of Good Clinical Practice
- assure maintenance of required documents
- verify adherence to the protocol
- monitor the quality of data collected
- assure accurate reporting and documentation of all AEs

During the monitoring visits, the data recorded on the CRF's are reviewed and verified against source documents to assure:

- informed consent has been obtained and documented in accordance with 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

The investigator must allow the clinical monitor access to all study documents, including informed consent forms, drug accountability records, as well as source documents, including pertinent hospital or medical records.

3.r Reports

Once a study begins, the Coordinating Center, lead center in a multi-site study, or Investigator in a single site study produces a series of monthly reports. The reports describe enrollment of participants at each site and in aggregate form. The reports describe participants screened, enrolled, refused participation, dropouts, adverse and unexpected reactions to therapies, and participants completing the study. Additionally, administrative reports can enumerate the forms received at the Coordinating Center for multi-site studies, forms entered, and missing and/or erroneous data and forms.

Data are also provided to DSMB. DSMBs can specify the format and content of the reports they wish to receive.

3.s Policies

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

3.s.1 Confidentiality Procedure

It is the responsibility of the study leadership to outline and enforce patient confidentiality and data security guidelines for the study. Study staff should be instructed in their responsibilities regarding data safeguards and cautioned against the release of data to any unauthorized individuals before they are allowed access to any study data.

The following is a list of study participant confidentiality safeguards:

- **Data flow procedures** - participant identifying information should not be transmitted from clinical site to the Coordinating Center.
- **Electronic files** - participant identifying information stored electronically should be maintained in an enciphered 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 distribution** - data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- **Data listings** - patient name, name code, hospital chart or record number, or other unique identifiers, such as Social Security number, should not be included in any published data listing.
- **Data disposal** - computer output from aborted runs that contain patient identifying information should be disposed of in an appropriate manner.
- **Access** - patient 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, sponsors should address the following elements of computer security to ensure that the data remain confidential:

- **Passwords** - Passwords provide limitations on general access to the systems and to the functions that individuals can use on the system. Passwords should be changed on a regular basis.
- **User Training** - Study staff who have 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 if it is modified, the system should be tested to verify that it performs as expected. Testing should verify that password activated access system performance is 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.s.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 participated to rigorous review before they are submitted for publication.

3.t MOOP Maintenance

This section describes the procedures for updating and distributing updated MOOP versions as well as staff responsible for this activity. The MOOP should be reproduced and distributed to appropriate 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 that 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 study MOOP is an important process that yields a product that is critical in helping to assure a study that will yield 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. Further, the MOOP assists with ensuring regulatory compliance for those studies that will be submitted to the FDA.

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RELEVANT WEB SITES

Food and Drug Administration:

<http://www.fda.gov/regguide.htm>

<http://www.fda.gov/cdrh/ggmain.htm>

<http://www.fda.gov/drug.htm>

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

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

International Conference on Harmonization (ICH) Guidelines

<http://www.ifpma.org/pdfifpma/e6.pdf>

<http://www.ifpma.org/ich1.html>

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/guide/notice-files/NOT-OD-00-031.html>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>

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>