

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

**Guidelines for Developing a Multi-Site
Manual of Operations and Procedures (MOOP)**

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ACRONYM GLOSSARY

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to capture all protocol-required information for a study.

Code of Federal Regulations (CFR) is an annual codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government.

Coordinating Center (CC) – A group organized to coordinate the planning and operational aspects of a multi-center clinical trial. CCs may also be referred to as Data Coordinating Centers (DCCs) or Data Management Centers (DMCs).

Clinical Research or Study Coordinator (CRC) – An individual that handles the administrative and day-to-day responsibilities of a clinical trial and acts as a liaison for the clinical site. This person may collect the data or review it before it is entered into a study database.

Conflict of Interest (COI) – A conflict of interest occurs when individuals involved with the conduct, reporting, oversight, or review of research also have financial or other interests, from which they can benefit, depending on the results of the research.

Data and Safety Monitoring Board (DSMB) – A group of individuals independent of the study investigators that is appointed by the NIAMS to monitor participant safety, data quality and to assess clinical trial progress.

Food and Drug Administration (FDA) – An agency within the U.S. Department of Health and Human Services (DHHS) responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

Good Clinical Practice (GCP) – A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – The first comprehensive Federal protection for the privacy of personal health information. The Privacy Rule regulates the way certain health care groups, organizations, or

businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI).

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – An independent body consisting of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and material to be used to obtaining and documenting informed consent of the trial participant.

International Conference on Harmonization (ICF)- Is an international collaboration between the United States, the European Union and Japan working in conjunction to harmonize the testing requirements of pharmaceutical products intended for human use.

Investigational New Drug Application (IND) – An IND is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application (21 CFR 312).

Manual of Operating Procedures (MOOP)/Manual of Procedures (MOP) – A “cook book” that translates the protocol into a set of operational procedures to guide study conduct. A MOOP/MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

Not Applicable (NA) - When recording data on a study form, if the information is not applicable, then the acronym NA should be used to fill out the field.

Not Available (NAV) - When recording data on a study form, if the information is not available, then the acronym NAV should be used to fill out the field.

Not Done (ND) - When recording data on a study form, if the evaluation required for a field is not done, then the acronym ND should be used to fill out the field.

Observational Study Monitoring Boards (OSMBs) - A group of individuals appointed by the NIAMS to provide ongoing review for an observational study to help assure the integrity of the study. The OSMB closely monitors data acquisition for comprehensiveness, accuracy, and timeliness; and monitors other concerns such as participant safety and confidentiality

Office for Human Research Protection (OHRP) – A federal government agency within the Department of Health and Human Services (DHHS) charged with the protection of human subjects participating in government funded research. It issues assurances and oversees compliance of regulatory guidelines by research institutions.

Principal Investigator (PI) - The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial and administrative policies and regulations associated with the award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the sponsored research award rests with the Principal Investigator.

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.).

Safety Monitoring Plan (SMP) – A plan that outlines the oversight of a clinical trial.

Safety Officer (SO) - The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single site clinical studies. The Safety Officer advises the NIAMS Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Serious Adverse Event (SAE) – Any adverse event that:

- Results in death;
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred;
- Requires or prolongs hospitalization;
- Causes persistent or significant disability or incapacity;
- Results in congenital anomalies or birth defects; or
- Is another condition which investigators judge to represent significant hazards.

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Unknown (UNK)- When recording data on a study form, if the information is unknown, then the acronym UNK should be used to fill out the field.

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 to implement a study, the Principal Investigator must be aware of the terms of award outlined in their Notice of Grant Award (NGA) with respect to required reporting, data and safety monitoring oversight, and Institutional Review Board (IRB) approval.

The purpose of this document is to assist investigators of multi-site studies in the preparation of a study Manual of Operating Procedures (MOOP) by providing them with a guideline. A multi-site study is defined as a single protocol involving more than one clinic (i.e., performance site) and one or more centers (e.g., data coordinating center) to receive and process data. The performance site and coordinating center may or may not be in the same location. The role of the MOOP is to facilitate consistency in study implementation and data collection across study visits and participants. Use of the MOOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

The NIAMS website houses many links and references to helpful policies, procedures and templates related to clinical research (see http://niams.nih.gov/Funding/Clinical_Research/clinical_main.asp). All staff members participating in the conduct of this study at participating institutions should have ready access to the MOOP and be familiar with its contents.

2.0 OVERVIEW

Once a grant application is funded, the investigator transforms it into a study protocol, which then must be approved by the Institutional Review Board (IRB).

A MOOP is useful for clinical interventional trials (e.g., drug, surgery, behavioral, device, etc.). The MOOP transforms the study protocol into a handbook and provides the operational detail to run the study consistently. The MOOP should serve as the study manual to help study staff follow study procedures. The study team (investigators, coordinators, statisticians, etc.) develops the MOOP and submits it to the NIAMS for approval 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 clinical site institutions participating in the study.

The MOOP development requires that the final protocol, study forms (often called case report forms [CRFs]), Investigator Brochure (IB) or Device Manual, and informed consent forms be completed. The timeline for development of study materials must be planned for and typically takes several 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, can be appointed to finalize the protocol and elements of the MOOP before it is sent to the NIAMS.

The MOOP is a dynamic document that will be updated throughout the study to reflect any protocol or informed 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 referenced and updated such as in a three-hole binder. For ease of organization, it is recommended that the MOOP be subdivided into sections separated by dividers. It is helpful to have each page of the MOOP contain the version number and date. Revised pages with an updated version number and associated date should replace the original page(s) in the MOOP. All previous versions should be archived. Any revisions to the MOOP should be submitted to the NIAMS with tracked changes for easy reference before finalization.

3.0 MOOP CONTENTS AND ORGANIZATION

The NIAMS recognizes that clinical studies vary in terms of complexity. Thus, the MOOP sections outlined below and further described in subsequent 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 (include as an appendix)
- b. Study Flow Diagram
- c. Staff Roster, Organization, and Responsibilities
- d. Recruitment and Retention Plan
- e. Screening and Eligibility Criteria
- f. Informed Consent and HIPAA process
- g. Study Intervention
- h. Blinding and Unblinding
- i. Participant Evaluations and Follow-up
- j. Concomitant Medications
- k. Safety Reporting
- l. Data and Safety Monitoring Activities

- m. Study Compliance
- n. Data Collection and Study Forms
- o. Data Management
- p. Quality Control Procedures
- q. Study Completion and Close-out Procedures
- r. Policies
- s. MOOP Maintenance

The MOOP submitted to the NIAMS should include all of the elements listed above, if relevant.

3.a Study Protocol

The study protocol, typically presented as an appendix, provides a brief, scientific rationale of the proposed investigation. There are many protocol templates available from a variety of resources. 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 target population, study procedures and interventions, primary and secondary endpoints, and the statistical plan are all described. Plans for protecting participant safety and well-being are also explained. A clinical protocol that meets both scientific and ethical standards is a fundamental requirement of clinical investigations.

The protocol should clearly articulate the following components:

- Study phase (e.g., Pilot and feasibility, Phase I – IV)
- Study population (sample size, gender, age, demographic group, general health status, geographic location)
- Description of the intervention
- Study design (e.g., blinding, randomized, control groups, treatment and follow-up duration)
- Primary and secondary endpoints
- Study duration (total time for the study from open to close with a timeframe for all components – e.g., screening, active treatment, follow up, close out)
- Inclusion and exclusion criteria
- Randomization plan, if applicable
- Screening process, baseline evaluation, intervention/treatment phase, and final evaluation. This section also describes the duration required for each individual participant
- Definition of evaluable participants and anticipated dropout rate

- Blinding/masking and unblinding/unmasking procedures
- Statistical analysis plan
- Data management plan
- Human subjects risk and safety considerations
- Confidentiality/privacy considerations
- Institutional Review Board (IRB) review and approval procedures
- Informed consent/assent procedures
- Plans for and responsibilities of the internal and/or independent safety monitoring body (Safety Officer (SO) or Data and Safety Monitoring Board (DSMB)).

The final version of the study protocol with the date of IRB approval and version number should accompany the MOOP as an appendix.

3.b Study Flow Diagram

An overview of the study processes presented in a flow diagram, as shown in Figure 1, 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.

3.c Staff Roster, Organization and Responsibilities

This section provides a roster of the study staff and a brief description of their roles as well as an overview of the organization.

In a multi-site study, the clinical site staff may perform the duties of both a center (e.g., data coordinating center) and one of the clinics (i.e., performance sites), or there could be a separate center handling the data coordinating activities. The following are responsibilities that may either be conducted by the center or the clinics:

- Development and maintenance of all study materials including the MOOP and study forms
- Reporting and monitoring of adverse events
- Maintenance of the study binder (regulatory and study documents)
- Identification, recruitment, screening, and enrollment of participants
- Obtaining informed consent from each participant
- Collection of study data and follow-up of participants through study completion
- Compliance with and accountability of study intervention administration
- Retaining specific records, (e.g., laboratory or drug distribution records)
- Randomization of participants
- Development and implementation of data management including the data flow and procedures for data entry, error identification and correction
- Quality control procedures
- Creation of reports - enrollment, adverse events, participant status (e.g., withdrawals), independent safety monitoring body reports
- Ensuring compliance with human subjects regulations and policies
- Submitting documents to regulatory bodies (i.e., IRB or FDA)

3.c.1 Organization

The study organization chart is a diagram that shows the structure of the study and the relationships among the staff members.

3.c.2 Pharmacy Activities

“Pharmacy” refers to the unit responsible for the storage and dispensation of the investigational agent if it is a drug or supplement. An actual pharmacy may be

directly involved 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 or destroyed. It provides instructions for completing drug accountability records and administrative records.

3.d Recruitment and Retention Plan

This portion of the MOOP is aimed at describing how the sites will quickly and efficiently identify and enroll eligible individuals into the study. The section should describe the target population, recruitment strategies, screening procedures and eligibility criteria. The target population defines the individuals 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.d.1 Participant Retention

Effective participant retention and adequate recruitment are both key to ensuring a successful study. Participant retention requires careful planning and continuous efforts.

Every effort should be made to retain study participants without coercive measures. In the event that a participant does not return for study visits, it is important that several contacts be made using all methods of contact provided. Strategies and 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 the idea that retention efforts begin with recruitment, and informed consent is an ongoing process
- Following a proactive plan for retention, including calling participants to see how they are doing, sending birthday and holiday cards, and providing transportation and child care, as needed
- Building participant relations and participant 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 participants and their families the opportunity to ask questions and express concerns pertaining to their condition
- Enhancing participant's understanding of the study's objectives 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 participants 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 participant's drop-out potential, and intervening as needed to keep participants interested in continuing to participate

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

3.e Screening and Eligibility Criteria

3.e.1 Screening

This section 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 individuals or physicians. With consideration for HIPAA regulations, as interpreted by the site's institution, the investigator or study coordinator may access their clinic's medical records, hospital admissions or discharge notes, if necessary, to identify potential participants for screening.

3.e.2 Screening Log

A Screening Log provides documentation of all individuals evaluated for study eligibility. It generally contains the individual's initials and study identification number (screening number), age, gender, race and ethnicity, screening date, and eligibility status (e.g., 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.e.3 Eligibility Criteria

Study eligibility is determined by a set of inclusion and exclusion criteria outlined in the study protocol. Potential participants must meet all entry criteria prior to enrollment. This section of the MOOP defines the method for determination

(e.g., blood pressure sitting down) of eligibility, and the specific forms needed to document eligibility (e.g., medical history form, physical examination form).

3.f 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 relevant to their decision. They are often encouraged to take the informed consent form home to discuss the study with family members and/or friends. Individuals then confirm their willingness to participate in the research study by signing the Informed Consent form.

A clinical site coordinator, investigator, or other staff member identifies an individual that appears to meet the pre-screening criteria. The pre-screening assessment may not require informed consent; however, this policy varies and should be checked with each institution's local IRB. The individual must sign an informed consent form prior to undergoing any screening assessments that are outside routine care procedures (e.g., physical examination, medical history, laboratory procedures). Thus, some studies have two informed consent forms: one for the screening process and one for the study entry. Other studies divide one informed consent form into two parts--one that describes the screening process and its assessments, and the other that describes the processes once a participant enrolls in the study.

The informed consent form requires:

- Disclosure of relevant information about the research;
- Comprehension by the individual of the information;
- Agreement to voluntarily participate in a research study without coercion or undue influence.

The informed consent procedure involves:

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

Additional items that should be included in an informed consent form 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

Figure 2 provides a checklist of basic and optional elements that should be included in the informed consent form.

FIGURE 2: INFORMED CONSENT CHECKLIST

(Please refer to DHS HHS OHRP 45 CFR 46 for details http://www.hhs.gov/ohrp/policy/consentckls.html)	Indicate	
	Yes	No
Basic Elements		
Statement that the study involves research	<input type="checkbox"/>	<input type="checkbox"/>
Explanation of the purposes of the research	<input type="checkbox"/>	<input type="checkbox"/>
Expected duration of the individual's participation	<input type="checkbox"/>	<input type="checkbox"/>
Description of the procedures to be followed	<input type="checkbox"/>	<input type="checkbox"/>
Identification of any procedures which are experimental	<input type="checkbox"/>	<input type="checkbox"/>
Description of any reasonably foreseeable risks or discomforts to the participant	<input type="checkbox"/>	<input type="checkbox"/>
Description of any benefits to the participant or to others which may reasonably be expected from the research	<input type="checkbox"/>	<input type="checkbox"/>
Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant	<input type="checkbox"/>	<input type="checkbox"/>
Statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained	<input type="checkbox"/>	<input type="checkbox"/>
For research involving more than minimal risk, an explanation as to whether any compensation will be provided, 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	<input type="checkbox"/>	<input type="checkbox"/>
Explanation of whom to contact for answers to pertinent questions about the research and participant's rights, and whom to contact in the event of a research-related injury to the participant	<input type="checkbox"/>	<input type="checkbox"/>
Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the individual is otherwise entitled, and the individual may discontinue participation at any time without penalty or loss of benefits, to which he/she is otherwise entitled	<input type="checkbox"/>	<input type="checkbox"/>
Optional Items, as Relevant		

(Please refer to DHS HHS OHRP 45 CFR 46 for details http://www.hhs.gov/ohrp/policy/consentckls.html)	Indicate	
	Yes	No
Basic Elements		
Statement that the intervention may involve risks to the individual (or to the embryo or fetus, if the individual is or may become pregnant), which are currently unforeseeable	<input type="checkbox"/>	<input type="checkbox"/>
Anticipated circumstances under which the individual's participation may be terminated by the investigator without regard to the subject's consent	<input type="checkbox"/>	<input type="checkbox"/>
Any additional costs to the individual that may result from participation in the research	<input type="checkbox"/>	<input type="checkbox"/>
Consequences of an individual's decision to withdraw from the research and procedures for orderly termination of participation by the individual	<input type="checkbox"/>	<input type="checkbox"/>
Statement that significant new findings developed during the course of the research, which may relate to the individual's willingness to continue participation, will be provided to the individual	<input type="checkbox"/>	<input type="checkbox"/>
Approximate number of study participants and research sites	<input type="checkbox"/>	<input type="checkbox"/>

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

3.f.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 consent will be obtained
- Who from the study staff will discuss the nature of the study with the participant (including voluntary participation and risks/benefits of the trial)
- Length of time the individual will be given to read the consent and have questions answered
- Who will sign the consent form and whether a copy of the signed form will be given to the participant
- Where the informed consent documents will be stored and who will have access to these forms
- Under what circumstances will participants be required to be re-consented
- Process to follow if a subject wants to withdraw consent
- Any applicable training required or recommended for study personnel

An individual must be informed that study participation is strictly voluntary and there is no obligation to participate. The informed consent process should ensure there is no penalty for not participating in a clinical trial and that medical treatment will not be compromised if an individual does not participate or if he/she chooses to withdraw at any time. Obtaining informed consent is an ongoing, educational process and should not be limited to a one-time read, review and signature of the document.

3.f.2 Informed Consent Form

Under HHS regulations ([45 CFR 46.101\(i\)](#)), legally effective informed consent of individuals must be obtained before involving them in research. [Food and Drug Administration (FDA) regulations at [21 CFR part 50](#) may also apply if the research involves a clinical investigation regulated by FDA.] 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.

The Principal Investigator, the participant, and a witness must each sign and date the Informed Consent form. Once it is signed, it is called the Informed Consent

Document. The NIAMS recommends that the Principal Investigator, the study nurse and/or a witness be present when the participant signs the form. The International Committee on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines recommend that the participant or legal representative receive a copy of the signed and dated Informed Consent Document. 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 study participant. The source documents should indicate that informed consent was obtained, along with the date it was signed. (See section 3.n.1 for a description of source documentation.)

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

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

3.f.3 HIPAA Authorization

The Health Insurance Portability and 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 form may contain language that satisfies the HIPAA requirements and outlines the protection of health information utilized in the study.

Alternatively, the HIPAA authorization form may be a separate document from the informed consent form. However, both must be reviewed and signed by the study participant. 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/pdf/HIPAA_Booklet_4-14-2003.pdf.

If the study is collecting any personally identifiable health information, these items 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 the NIAMS, it can be submitted at a later date.

3.g Study Intervention

A study intervention can be defined as a drug, vitamin, or other supplement, biologic, gene transfer, vaccine, device, procedure (e.g., surgery), behavior (e.g., Internet-based education) and/or lifestyle change (e.g., diet, exercise) introduced to prevent or change the natural course of a disease or condition. A clinical trial has an intervention that is assessed for efficacy and/or safety.

NIH-defined clinical trial phases are described as follows:

Phase I: Tests a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).

Phase II: Study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.

Phase III: Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions, as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely.

NIH-Defined Phase III: A broad-based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such an investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Phase IV: Studies conducted after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

The protocol and/or 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.

To ensure the intervention is administered properly and consistently, it must be thoroughly described in the MOOP so that all participants are exposed in the same manner:

- **For drug, vitamin, or other supplement, biologic, gene transfer, and vaccine intervention studies**, the distribution, preparation and handling, labeling, and administration are detailed along with the duration of treatment and criteria for treatment discontinuation. This section must include the regulatory approval status of the drug, whether it's a new indication/population or approved for the disease/condition under study. A detailed description of the information that must be provided is documented in the ICH E6 Guideline for Good Clinical Practice. This document is available on the Internet at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf
- **Device studies** require a detailed description of the device and its intended use. This section must include the regulatory approval status of the device, whether it has an investigational device exemption. Information on device studies is provided in the Code of Federal Regulations (CFR) Title 21, Part 812, revised as of April 1, 2011, at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=812&showFR=1>.
- **Procedure studies** (e.g., surgery) require a detailed description of the process.
- **Behavior and life style studies** require a detailed description of how the intervention is to be carried out as well as documentation of the process.

3.g.1 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 to assign participants into treatment groups is described.
- **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 whom 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.h Blinding and Unblinding

Unblinding is a process by which one is made aware of the participant's treatment allocation in a clinical trial. Unblinding must be undertaken by a pre-determined process to ensure it does not occur unnecessarily and the study results are not compromised. In some cases, unblinding should occur in a responsive manner when it is clinically indicated. A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a control (placebo or another therapy) is considered a double-blind study. The study sponsor (e.g., the grantee Institution), the funding agency (e.g., NIAMS) and the monitoring body also can be "blind" or "masked" to the intervention. Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome (Clinical Trials.Gov).

A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking is called a single-blind study (Clinical Trials.Gov). In studies where the intervention cannot easily be blinded such as surgery, some exercise and behavioral interventions, blinded raters may be assigned to administer the outcome assessments so that the study can still maintain a single- or double-blinded design.

The study statistician and/or a designated study staff member securely maintains the randomization codes so the treatment assignments are not known. Randomization and blinding/unblinding procedures are determined prior to the enrollment of the first participant.

Unblinding is a serious action and should be limited to reduce potential bias. The MOOP should clearly state who is blinded/unblinded on the study team.

Additionally, the handling of the blinded data including preparation of blinded reports should be described.

Unblinding may be required when:

- Clinical treatment decisions are necessary or when a serious adverse event occurs and the treatment allocation must be made known. This is called emergency unblinding.
- During an unmasked analysis in accordance with the study Statistical Analysis Plan (e.g., an interim analysis)
- At the request of the Data and Safety Monitoring Board (DSMB) or Safety Officer
- At the conclusion of the study to determine the effect of the intervention.

Emergency unblinding due to undue risk or safety concerns should be left to the discretion of the Principal Investigator and/or party(ies) responsible for the protection of the research participants. Any action requiring emergency unblinding should be promptly reported to the NIAMS and Safety Officer, but does not require pre-approval. If unblinding does not require immediate action and is not part of the pre-specified plans to unblind, the DSMB or Safety Officer and the NIAMS Program Officer must be involved in the decision.

In the event that unblinding occurs, the following should be recorded:

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

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

3.i 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 consistently 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.i.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 **Appendix A**.

3.i.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.i.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.

3.j Concomitant Medications

The MOOP provides a rationale for the concomitant medications that are allowed and restricted in the protocol, if relevant. 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.

3.k Safety Reporting

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

- ***Adverse Event*** - An adverse event (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 increased in severity.
- ***Serious Adverse Event*** – A serious adverse event 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.

3.k.1 Adverse Event Reporting

All AEs are collected, analyzed, and monitored by using an Adverse Event Form, a sample of which is shown in **Appendix B**. AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety must be reported to the NIAMS and the independent safety monitoring body. All AEs experienced by the participant during the time frame specified in the protocol (e.g., from the time of 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 Principal Investigator and study Medical Monitor (if applicable, a Medical Monitor who is different than the independent safety monitoring body, provides safety review and determinations during the execution of the clinical trial and is usually a member of the Investigator's study team) 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 NIAMS and the study's independent data and safety monitoring body (i.e., Data and Safety Monitoring Board (DSMB) or Safety Officer (SO)) is described in this section.

3.k.2 Unanticipated Problems

Unanticipated Problems are not included in the 45 CFR part 46, but are defined by the OHRP as any incident, experience or outcome that meets all of the following requirements:

- (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- (2) Related or possibly related to participation in the research. Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- (3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document, or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects; modification of inclusion or exclusion criteria to mitigate the newly identified risks; implementation of additional procedures for monitoring subjects; suspension of enrollment of new subjects; suspension of research procedures in currently enrolled subjects; modification of informed consent documents to include a description of newly recognized risks; and provision of additional information about newly recognized risks to previously enrolled subjects.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. For further information see <http://www.hhs.gov/ohrp/policy/advevntguid.html>.

3.k.3 Serious Adverse Event Reporting

All serious adverse events (SAEs), unless otherwise specified in the protocol and approved by the IRB and the NIAMS, require expedited reporting by the Principal Investigator to the study's safety monitoring bodies. SAEs must be reported to the independent safety monitoring body and the NIAMS, through the NIAMS contractor within 48 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 the NIAMS and its contractor will be established. The role of the investigator and study coordinator and any 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 the 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 is shown in **Appendix C**.

3.1 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, the NIAMS has established Data and Safety Monitoring Guidelines. These guidelines may be found at http://www.niams.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.docx.

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

Safety monitoring activities performed by an independent monitoring body appointed by the NIAMS include reviewing the protocol with emphasis on data integrity and participant risk and safety issues, monitoring adverse events, protecting the confidentiality of the data and monitoring results, and making recommendations to the NIAMS and Principal Investigator to continue or conclude the study. Since the independent monitoring body is advisory to the NIAMS, the NIAMS must provide final approval of the study materials and initiation of recruitment, participant treatment, or any clinical procedures.

3.1.1 Data and Safety Monitoring Plans

This section of the MOOP should describe the specific Data and Safety Monitoring Plan that the investigator will be using. These plans are required as part of the grant application process and reviewed during Peer Review. However, after a study has been awarded, they are developed in more detail with NIAMS' guidance following the guidelines referenced below and must be approved by the NIAMS Program Officer and monitoring body.

To assist in preparing a Data and Safety Monitoring Plan, guidelines for developing monitoring plans for studies requiring a Data and Safety Monitoring Board or a Safety Officer are available at

http://www.niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp.

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

3.1.2 Independent Safety Monitoring Body

The independent safety monitoring body is selected and appointed by the NIAMS. The investigators may recommend individual(s) with appropriate background and expertise necessary for understanding the scientific area of study; study design; analyzing and interpreting the data to ensure participant safety; and ethical, scientifically rigorous study conduct. All safety monitoring body member(s) must attest that they have no conflicts of interest by signing the *Conflict of Interest (COI) Statement* (See **Appendix D**). The NIAMS contractor will provide and track the COI statements prior to providing study materials and on an annual basis. This section of the MOOP outlines the process for identifying the monitoring body and for reviewing and collecting the COI statements.

3.m Study Compliance

Clinical trials are expensive endeavors, and procedures should be implemented to maximize adherence to the protocol and minimize non-compliance.

Comprehensive training with all sites on the study protocol, and early review of the data help to minimize protocol deviations and/or violations. However, there should be a mechanism to track protocol deviations and violations, and procedures to notify appropriate parties that are described in this section.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB. A protocol violation is a deviation from the IRB-approved protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data.

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

- Enrollment or randomization of an ineligible participant
- Follow-up visit at a time point different from that specified in the protocol.
- Failure to obtain Informed Consent
- Entering a participant into another clinical study
- Failure to keep IRB approval up-to-date
- Wrong treatment administered to participant

This section of the MOOP should describe relevant deviations/violations and the reporting process to appropriate parties, including the Principal Investigator, the NIAMS, and the independent safety monitoring body. The study should adhere to its local IRB policies for reporting these protocol deviations/violations. In addition, the reporting of deviations/violations should be discussed with the NIAMS and the safety oversight body prior to study start and clearly outlined in the safety monitoring plan. Protocol deviations/violations impacting participant safety are generally reported to the NIAMS and the independent safety monitoring body in an expedited manner (e.g., 48 hours). All events should be reported at the time of the biannual DSMB meeting or submission of the safety report. The study coordinator should maintain a log of all protocol deviations/violations and should report them routinely to the independent safety monitoring body. A sample log is presented as **Appendix E**. This section should also describe the internal actions that will be taken should serious violations occur.

The requirements for reporting protocol deviations/violations are described in this section of the MOOP. A log for recording protocol deviations should also be included in this section.

3.n Data Collection and Study Forms

This section describes the study's data collection and data management procedures and should include copies of all 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 case report forms (CRFs), provide the vehicle for consistent data collection. In this section of the MOOP, please provide:

- 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.n.1 Source Documentation

A source document is any document on which study data are initially recorded. Source documents include laboratory reports, Electrocardiography (ECG) tracings, medical records, standardized test forms, etc. These data are then transcribed to a 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.n.3 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.n.2 General Instructions for Completing Forms

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:

Print using black ink when completing study forms. 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 forms must be included.

Below is an example:

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

3.n.3 Retention of Study Documentation

The length of time all study files are to be maintained is specified in this section. In general, federal regulation requires that studies conducted under a federal grant retain participant forms for three years, while studies conducted under a federal 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. Details about the federal policies surrounding record retention and access can be found at [2 CFR Part 215](#). 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.n.4 Administrative Forms

The MOOP should contain a complete set of administrative forms. Administrative forms assist study documentation and may include the following, as relevant:

- **Telephone Contact Log** - serves as a record of all conversations regarding the study and study participants.
- **Screening Log** - is a record of *all* participants screened for participation in the study. It should be arranged chronologically and be kept up-to-date at all times.
- **Participant Identification Code List** – is a record of the participant's name, medical record number, randomization number, and study entry and exit dates. Due to the confidential nature of this information, it 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** – as relevant, 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.
- **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.o 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.

Investigators are encouraged to utilize computer systems that encompass the following functions:

- **Data Tracking** - to provide the status of enrollment, number of forms completed at the sites.
- **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., Statistical Analysis Software (SAS)].

Investigators should involve staff or colleagues with data management experience to assist with the determination of the data flow, 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.

The MOOP should also include a description of the computer system used to support the study.

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 website, Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures-Scope and Application <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm>

3.o.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 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 (see the comprehensive list in Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, NIH Publication 03-5388 at http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf.)

Therefore, it is important to specify how participant materials will be identified (e.g., by participant identification number) during transmission.

3.p 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.p.1 Standard Operating Procedures

One aspect of site quality control is a set of SOPs. SOPs describe a site's generic procedures that may have been developed to assist with standardization across studies. SOPs may include storage of study documents. As relevant, SOPs should be developed to ensure quality studies and 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; 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.p.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 consistency across forms and visits
- Completion of all fields of a "completed form" or reason noted for no data
- Completion of all required forms or reason noted for no data

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.p.3 Double Data Entry

In recent years, there have been several articles written on the value of double data-entry. While conventional wisdom insists on 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” (such as those who are strictly data entry personnel and not the personnel who collect the clinical data. Staff who is strictly data entry personnel typically does not address data edits or flags).

3.p.4 Clinical Monitoring

The following section describes site monitoring which is separate from the data and safety monitoring activities described in *Section 3.1 Data and Safety Monitoring Activities*.

Site monitoring may take place through periodic site visits conducted during the course of the study and is typically conducted by a Clinical Research Associate (CRA) or other designated individual who is not directly involved with the day-to-day aspects of the study, but is assigned to monitor the study to ensure proper study conduct (i.e., protocol adherence) and the timely generation and collection of quality data. The frequency of visits depends upon the site's performance and the number of participants enrolled. Frequency is generally pre-specified, but visits can also be done ad hoc depending on site issues and circumstances.

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 feedback regarding the activities that were accomplished and any problems or issues that may have been uncovered during the visit. The report should be straightforward, stating any problems uncovered, and describing recommendations to address them. A timeline should be agreed upon and included in the report to ensure that follow-up of any 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 monitoring timeline.

3.g 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. The 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.r Study Completion and Closeout Procedures

Study close-out 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 Close-out 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

- 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

Additional close-out activities can be found in **Appendix F**.

3.r.1 Participant Notification

The Principal Investigator and study staff 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.r.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.s 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.s.1 Confidentiality Procedures

It is the responsibility of the Principal Investigator 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 the NIAMS.

This section of the MOOP will discuss the safeguards that 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:

- ***Electronic files*** – data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file.

- **Forms** - forms or pages containing personal identifying information should be separated from other pages of the data forms.
- **Data listings** - participant name, name code, hospital chart, record number, Social Security Number, or other unique identifiers should not be included in any published data listing.
- **Data distribution** - data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- **Data disposal** - computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
- **Access** - participant records should not be accessible to persons outside the site 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 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.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 subjected to rigorous review before they are submitted for publication.

Investigators/Institutions are responsible for adhering to any NIH requirements for reporting and publishing study results.

Any plans to publish study results prior to study completion should be vetted through the NIAMS and data and safety monitoring body to ensure study integrity is upheld.

3.t 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 study staff to consider the details of a study and to develop procedures that are understood and can be followed by multiple clinical centers should one of the teams need to expand.

BIBLIOGRAPHY

Avorn J. Medication Use in Older Patients – Better Policy Could Encourage Better Practice. *JAMA*. 2010 Oct 13;304(14):1606-1607.

Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials*. 2008;5(1):49-55.

Bains S, Bhandari M, Hanson B. Standard operating procedures: the devil is in the details. *J Long Term Eff Med Implants*. 2009;19(3):195-9.

Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, Heels-Ansdell D, Walter SD, Guyatt GH; STOPIT-2 Study Group. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA*. 2010 Mar 24;303(12):1180-7.

Campbell EG, Zinner DE. Disclosing Industry Relationships – Toward an Improved Federal Research Policy. *NEMJ*. 2010 Aug 12; 363;7: 604-606.

Cohen SB, Strand V, Aguilar D, Ofman JJ. Patient- versus physician-reported outcomes in rheumatoid arthritis patients treated with recombinant interleukin-1 receptor antagonist (anakinra) therapy. *Rheumatology (Oxford)*. 2004 Jun;43(6):704-11. Epub 2004 Mar 2.

DAMOCLES Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005 Feb 19-25;365(9460):711-22.

DeMets DL. Futility approaches to interim monitoring by data monitoring committees. *Clin Trials*. 2006;3(6):522-9.

DeMets D, Califf R, Dixon D, Ellenberg S, Fleming T, Held P, Julian D, Kaplan R, Levine R, Neaton J, Packer M, Pocock S, Rockhold F, Seto B, Siegel J, Snapinn S, Stump D, Temple R, Whitley R. Issues in regulatory guidelines for data monitoring committees. *Clin Trials*. 2004;1(2):162-9.

DeMets DL, Fleming TR. The independent statistician for data monitoring committees. *Stat Med*. 2004 May 30;23(10):1513-7.

DeMets DL, Fleming TR, Rockhold F, Massie B, Merchant T, Meisel A, Mishkin B, Wittes J, Stump D, Califf R. Liability issues for data monitoring committee members. *Clin Trials*. 2004;1(6):525-31.

Downs M, Tucker K, Christ-Schmidt H, Wittes J. Some Practical Problems in Implementing Randomization. *Clin Trials*. 2010; 7:235-245.

Englev E, Petersen KP. ICH-GCP Guideline: quality assurance of clinical trials. Status and perspectives. *Ugeskr Laeger*. 2003 Apr 14;165(16):1659-62.

George SL, Freidlin B, Korn EL. Strength of accumulating evidence and data monitoring committee decision making. *Stat Med*. 2004 Sep 15;23(17):2659-72.
Horigian VE, Robbins MS, Dominguez R, Ucha J, Rosa CL. Principles for defining adverse events in behavioral intervention research: lessons from a family-focused adolescent drug abuse trial. *Clin Trials*. 2010 Feb;7(1):58-68.

Knottnerus JA, Spigt MG. When should an interim analysis be unblinded to the data monitoring committee? *J Clin Epidemiol*. 2010 Apr;63(4):350-2. Epub 2009 Sep 17.

Menikoff J. Making Research Consent Transparent. *JAMA*. 2010 Oct; 304(15): 1713-1714.

Menikoff J. The Paradoxical Problem with Multiple-IRB Review. *NEMJ*. 2010 Oct; 363(17): 1591 -1592.

Otte A, Maier-Lenz H, Dierckx RA. Good clinical practice: historical background and key aspects. *Nucl Med Commun*. 2005 Jul;26(7):563-74.

Ottevanger PB, Therasse P, van de Velde C, Bernier J, van Krieken H, Grol R, De Mulder P. Quality assurance in clinical trials. *Crit Rev Oncol Hematol*. 2003 Sep;47(3):213-35.

Rosa C, Campbell A, Kleppinger C, Sampson R, Tyson C, Mamay-Gentilin S. Quality assurance of research protocols conducted in the community: the National Institute on Drug Abuse Clinical Trials Network experience. *Clin Trials*. 2009 Apr;6(2):151-61.

Rosen DH, Johnson S, Kebaabetswe P, Thigpen M, Smith DK. Process maps in clinical trial quality assurance. *Clin Trials*. 2009 Aug;6(4):373-7. Epub 2009 Jul 22.

Sather MR, Raisch DW, Haakenson CM, Buckelew JM, Feussner JR; Department of Veterans Affairs Cooperative Studies Program. Promoting good clinical practices in the conduct of clinical trials: experiences in the Department of Veterans Affairs Cooperative Studies Program. *Control Clin Trials*. 2003 Oct;24(5):570-84.

Shaughnessy M, Beidler SM, Gibbs K, Michael K. Confidentiality challenges and good clinical practices in human subjects research: striking a balance. *Top Stroke Rehabil*. 2007 Mar-Apr;14(2):1-4.

Steinman M, Hanlon J. Managing Medications in Clinically Complex Elders – There Got to Be a Happy Medium. *JAMA*. 2010 Oct; 304(14): 1592-1601.

Sydes MR, Altman DG, Babiker AB, Parmar MK, Spiegelhalter DJ; DAMOCLES Group. Reported use of data monitoring committees in the main published reports of randomized controlled trials: a cross-sectional study. *Clin Trials*. 2004 Feb;1(1):48-59.

Sydes MR, Spiegelhalter DJ, Altman DG, Babiker AB, Parmar MK; DAMOCLES Group. Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. *Clin Trials*. 2004 Feb;1(1):60-79.

Williams GW. The other side of clinical trial monitoring; assuring data quality and procedural adherence. *Clin Trials*. 2006;3(6):530-7.