

**National Institute of
Neurological Disorders and Stroke:
Developing a Manual of Procedures (MOP)**

June 28, 2005

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1.0 INTRODUCTION

The National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), 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. This template for a Manual of Procedures (MOP) is designed to help clinical investigators comply with NIH regulations and procedures and promote high quality research. The MOP transforms a protocol into an operational research project. It documents study flow so that the screening, initial evaluation, enrollment, randomization, treatment, and follow-up of all study participants are conducted in a structured and standardized manner. It details how the data are observed, collected, and recorded. It specifies quality control procedures, and it defines methods for ensuring confidentiality of participant information. The MOP is written in sufficient detail such that it could be used as a training manual for new study investigators.

The MOP is a dynamic document that is updated throughout the study to record amendments to the protocol or consent forms, and to document refinement of procedures. It is maintained in a format that allows it to be easily updated, typically in a three-ring binder. The version number and date should appear on each page of the MOP to track all changes and additions to the document. Revised pages replace the original pages as they are updated. All previous versions should be archived.

The MOP 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, composed of the Principal Investigators from each of the sites, is often appointed to finalize the protocol and elements of the MOP.

2.0 MOP CONTENTS AND ORGANIZATION

The MOP typically includes the following sections that delineate study implementation and operations:

- a. Protocol
- b. Staff Roster
- c. Study Organization and Responsibilities
- d. Training Plan
- e. Communications Plan
- f. Recruitment Plan
- g. Study Flow
- h. Screening and Eligibility Criteria
- i. Informed Consent and HIPAA
- j. Randomization
- k. Study Intervention
- l. Blinding and Unblinding
- m. Participant Evaluations and Follow-up
- n. Participant Retention
- o. Concomitant Medications
- p. Safety Reporting
- q. Data and Safety Monitoring Responsibilities
- r. Study Compliance
- s. Data Collection and Study Forms
- t. Data Management
- u. Quality Control Procedures
- v. Study Completion and Closeout Procedures
- w. Policies
- x. MOP Maintenance

The above sections apply not only to drug intervention studies, but also to surgery, behavioral, and device studies. In studies where a section does not apply (e.g., randomization in a study with no randomization), it does not need to be included. The MOP outline above, described in the following sections, is a guide rather than a prescription and must be adapted to each study's specific needs.

2.A PROTOCOL

The final version of the study protocol with the date of approval and version number is often included in the MOP. See http://www.ninds.nih.gov/funding/clinical_trials/protocol.htm for a detailed discussion of protocol development. If the protocol is modified, the MOP should be updated with the most current version and list of all changes by version.

2.B STAFF ROSTER

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

Information on whom to contact regarding specific study procedures as well as specific questions and situations should also be included, e.g.:

- randomizing a participant
- reporting a serious adverse event
- requesting additional supplies
- protocol questions
- eligibility questions

2.C STUDY ORGANIZATION AND RESPONSIBILITIES

The study's organizational structure is often depicted, especially for multi-site studies. Multi-center studies, especially Phase III and other large studies, may have a Clinical, Statistical, and/or Data, Coordinating Center that each has responsibilities in the development of materials and oversight of study operations. Each of the Centers' responsibilities should be described along with

central laboratories and study committees, as relevant. Organization charts help to clarify organizational responsibilities and roles.

Study organizational responsibilities include the contents of the MOP as well as the development of this document. Thus, the MOP outline can be used to assure that the scope of a study's requirements and responsibilities are assigned to an organization and individual. In single-site studies, study staff members have analogous responsibilities.

2.C.1 Responsibilities to NINDS

Figure 1.a provides guidance on the steps necessary prior to study initiation for a study requiring a Data and Safety Monitoring Board (DSMB). Figure 1.b outlines the steps for a study with a Safety Monitoring Committee (SMC) or an Independent Medical Monitor (IMM).

2.C.2 Clinical Sites

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

- maintaining the study binder
- participating in protocol finalization and preparing study materials
- assuring that the study is conducted according to the protocol
- participating in a Steering Committee and other study committees
- identifying, recruiting, screening and enrolling participants
- protecting participants' rights
- obtaining informed consent from each participant
- collecting study data and following participants through study completion
- controlling the distribution of the study intervention, as required
- 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

Figure 1.a

**Steps that Precede Clinical Study Initiation
(DSMB)**

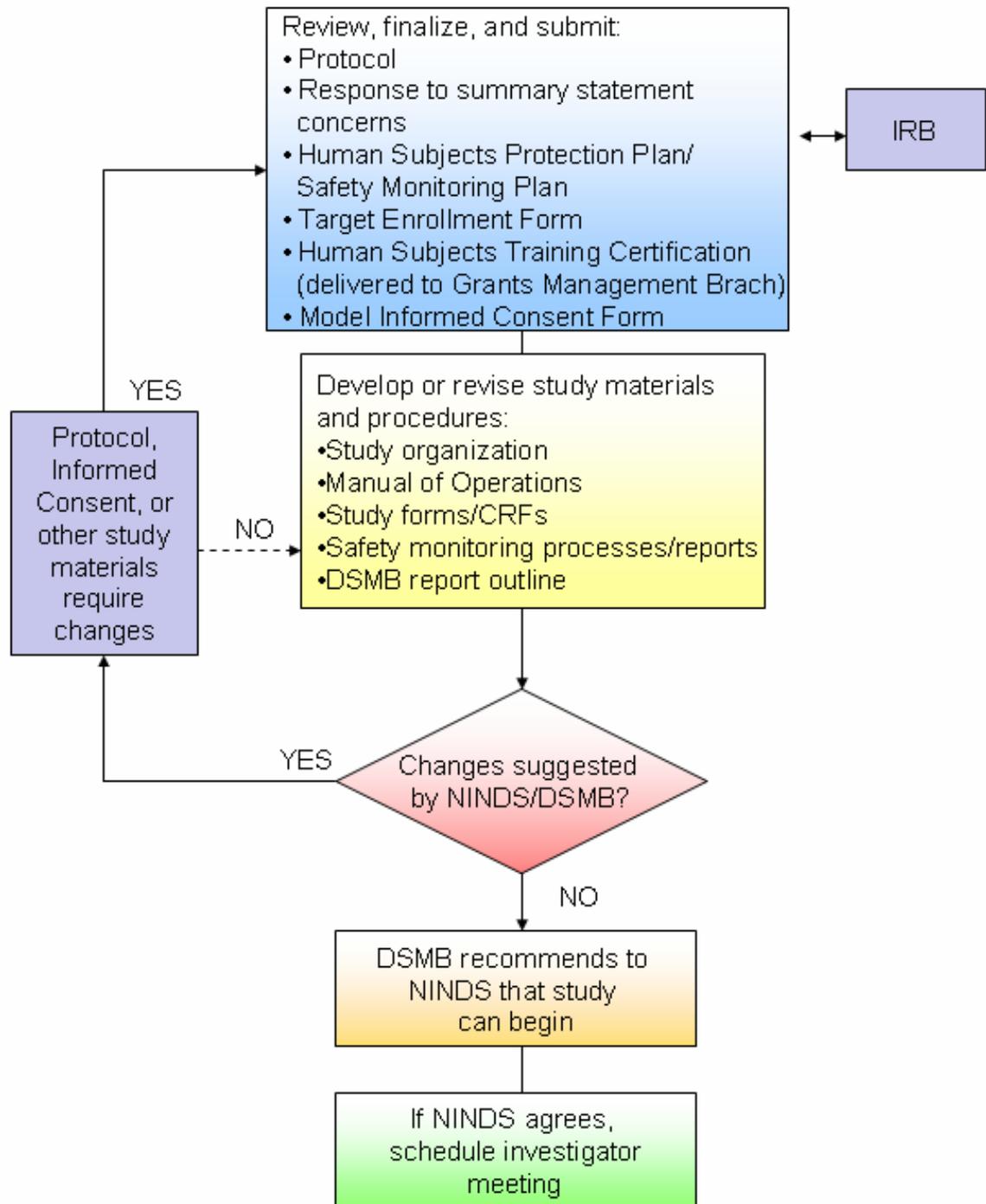
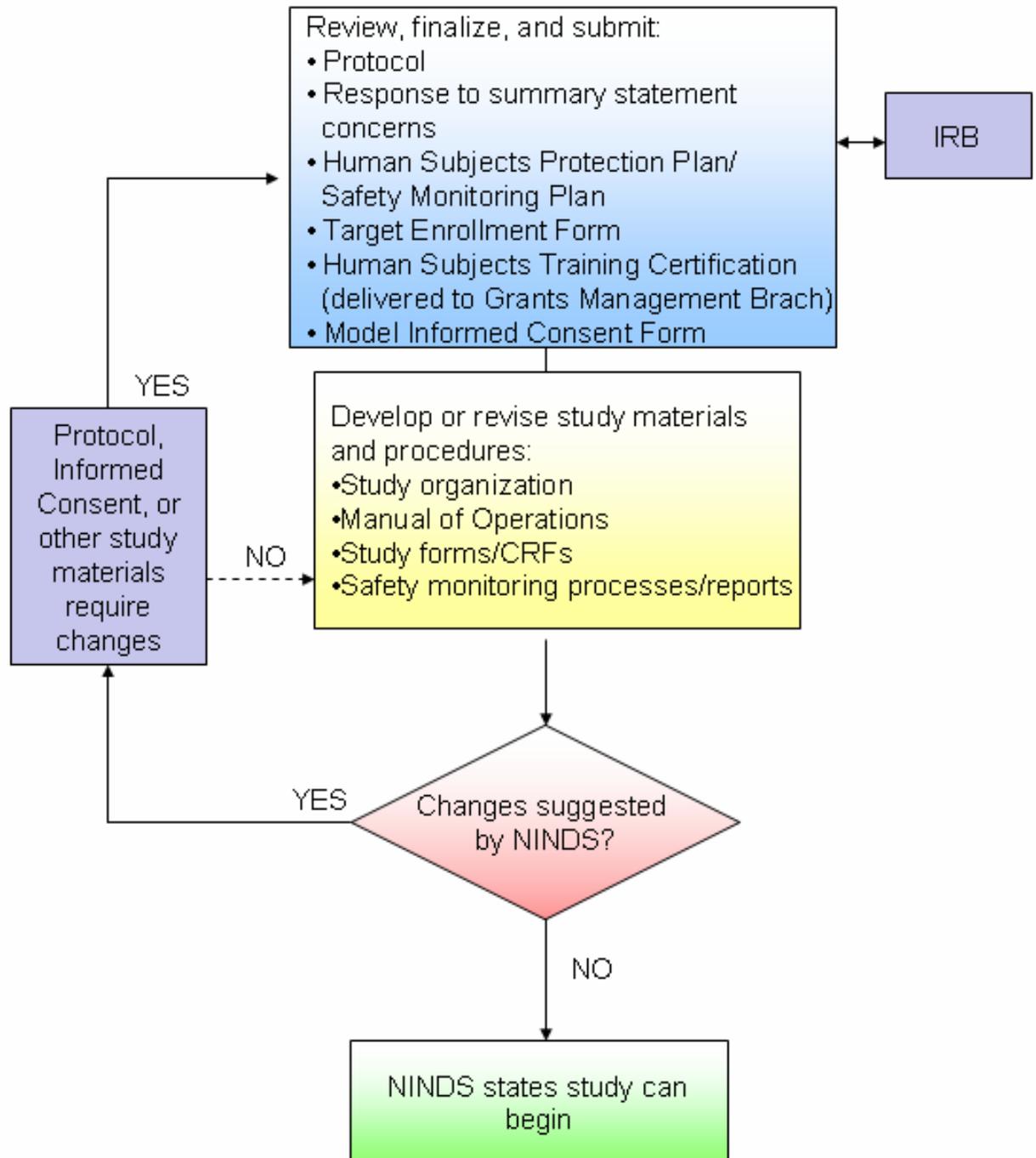


Figure 1.b

**Steps that Precede Clinical Study Initiation
(SMC/IMM)**



2.C.3 Pharmacy

“Pharmacy” refers to the unit responsible for the storage, dispensing and accountability for a study treatment intervention. An actual pharmacy may or may not be directly involved in a study. For example, in some studies the treatment intervention may be delivered in pre-labeled, sealed packages directly to the clinical centers.

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

2.C.4 Steering Committees

In some large multi-center studies, the Steering Committee is responsible for the overall direction of a study and is the main leadership committee. The Steering Committee is typically comprised of the Principal Investigator, Clinical Site and Coordinating Center Principal Investigators and NINDS staff.

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

- general design and conduct of the study
- protocol
- review of the essential study documents, including MOP and forms
- review of data collection practices and procedures
- changes in study procedures
- appointments to and disbanding of committees and subcommittees
- allocation of resources based on priorities
- review of study progress
- review and implementation of recommendations from the DSMB
- review and response to other general advice and/or recommendations (e.g., from the NINDS Program Director)

2.C.5 Executive Committees

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

2.D TRAINING PLAN

Training of study staff, including clinical site investigators, should be described in this section. The Investigators' meeting or other training format can be utilized to introduce the study protocol and procedures

2.E COMMUNICATIONS PLAN

In addition to routine administrative communications with clinical sites, such as scheduling meetings and training sessions there should be a plan to assure ongoing communication among site investigators, especially during protocol finalization and as part of the Steering Committee, Executive Committee, and/or subcommittees. Once a study is operational, routine telephone calls among the clinical site coordinators are useful to build an *esprit de corps*, share strategies, discuss issues, and share successful strategies. The communications should be documented by the designated coordinating center. The Steering Committee and Executive Committees will also participate in routine calls once the study is implemented to discuss progress, issues, and potential solutions.

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

2.F RECRUITMENT PLAN

To assist clinical sites in recruiting study participants, this section of the MOP describes the target population and suggests recruitment strategies such as identifying primary care referral practices, grand rounds, and publicity. It is suggested that each site develop a recruitment plan that documents approach and alternatives.

2.G STUDY FLOW

It is useful to provide an overview of the study in a flow diagram (see Figure 2) that describes each of the study's major steps. It is uniquely tailored to the study and is useful in describing the study to new staff members.

2.H SCREENING AND ELIGIBILITY CRITERIA

To help assure that clinical sites accrue participants with the same characteristics, this section provides a detailed discussion of the screening procedures utilized to identify and determine participant eligibility. Frequently, there is a *pre-screening* phase during which the study coordinator reviews the investigator's patient medical records or responds to initial telephone inquiries from physicians or potential study participants. Pre-screening may be performed prior to obtaining an individual's informed consent.

If the individual meets the pre-screening criteria (e.g. age, apparent diagnosis) then there is likely to be a physical exam, laboratory tests, medical history, and other **screening** procedures that can confirm individual eligibility. Prior to administering any of these procedures, the study staff must provide a detailed description of the study and must obtain the individual's informed consent (see Section 2.I)

2.H.1 Screening Log

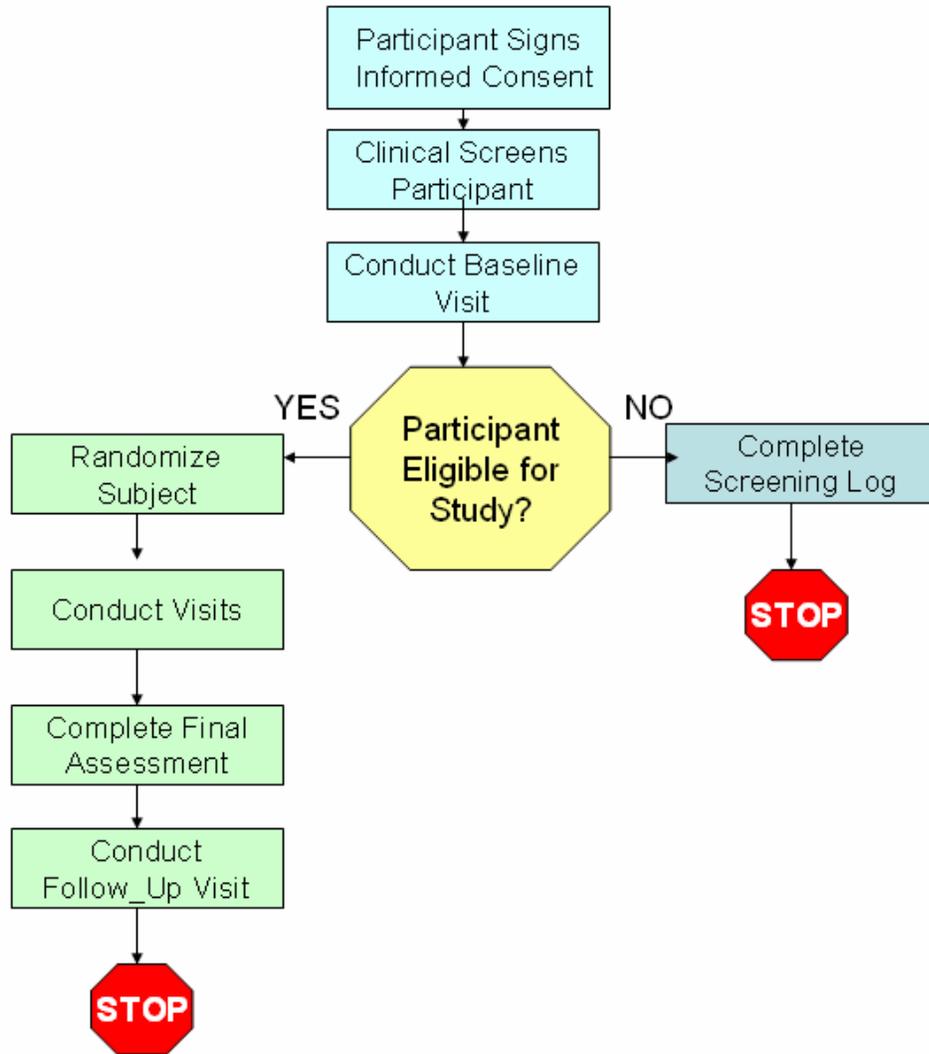
A Prescreening/Screening Log provides documentation of all potential study participants that are reviewed for study eligibility. It generally contains an identification number and individuals' initials, age, gender, race and ethnicity, screening date, and eligibility status:

- eligible for study participation and date enrolled
- ineligible for study participation and reason
- consent refused and why

It may also contain the randomization number. The MOP describes the contents of the Screening Log and maintenance procedures.

Figure 2

Study Flow



2.H.2 Eligibility Criteria

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

2.I INFORMED CONSENT AND HIPAA

Informed consent is a process that involves:

- providing participants with adequate information concerning the study procedures and scope
- providing adequate opportunity for an individual to consider all available options
- responding to individuals' questions and concerns
- ensuring that 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 document include:

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

The informed consent regulations are administered by the Office of Human Research Protections (OHRP), whose Web site (<http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm>) also provides a number of tips to guide investigators in developing informed consent documents.

2.1.1 Informed Consent Process

Once a clinical site coordinator, investigator, or other site staff member identifies an individual that appears to meet pre-screening criteria, the informed consent process is initiated and the individual must sign an informed consent form prior to undergoing a physical examination, medical history, laboratory procedures, or other eligibility assessments. This section describes the specific instructions regarding the process of obtaining informed consent. The study investigator or nurse coordinator typically provides a detailed explanation of the study and informed consent form to a prospective participant. Additionally, the study staff member must discuss the nature of the study, randomization and blinding, study procedures, visit obligations and importance of compliance, potential risks and benefits, and study duration. The process should provide for ample time for the prospective participant to read the informed consent form.

An individual 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 individuals do not participate or if they cease participation at any time. Adequate time should be allowed for the prospective participant to ask questions.

This section should delineate the necessary signatures based on the site's IRB requirements (i.e. the participant's signature/legal representative, the investigator or person actually obtaining the consent, and a witness).

The location of where the informed consent form should be maintained and to whom a copy of the form should be provided are also described.

2.1.2 Informed Consent Document

The written Informed Consent should be brief and written in plain language so that a participant who has not graduated from high school can understand the contents. Consent documents should be written with the assumption that prospective participants will not talk to a researcher (or research nurse) at all about the study, and that their information will come entirely from the consent document. If this approach is used, the document is more likely to be clear, complete, written for non-scientists, and able to “stand alone.”

The Principal Investigator, participant, and witness must each sign and date the Informed Consent Document. The Principal Investigator, study nurse and a

witness should be present when the participant signs the informed consent document.

The International Committee on Harmonization (ICH) Good Clinical Practice (GCP) guidelines requires that the participant or legal representative receive a copy of the signed and dated informed consent form. OHRP and the Food and Drug Administration (FDA) both require that the participant receive a copy, although it may not necessarily be a signed copy. Additionally, the investigator must maintain a signed copy of the informed consent document for each participant in the study. The source documents should indicate that the informed consent form was signed, along with the date of signing.

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

2.I.3 HIPAA Procedures

The Health Insurance Portability & Accountability Act (HIPAA) provides guidelines for investigators pertaining to protection of participant confidentiality. 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 source is *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*, NIH Publication 03-5388 at <http://privacyruleandresearch.nih.gov>. A HIPAA form is usually presented to a potential participant for signature in addition to the Informed Consent Form unless the necessary assurances are incorporated into the Informed Consent Form. The HIPAA form describes participant and data confidentiality associated with the study.

2.J RANDOMIZATION

Randomization is introduced into studies to reduce bias in treatment selection. The study statistician develops the randomization schema prior to study implementation. The participant is assigned to a study treatment group after

informed consent has been signed. This section of the MOP describes the randomization approach and procedures including:

- **Process Responsibilities:** The individual who maintains the master randomization list at the Coordinating Center must be identified. This person is responsible for assigning randomization codes, notifying appropriate study staff that a participant has been randomized, and securely storing all randomization files.
- **Procedure for Randomizing a Participant:** At each site, the individual responsible for initiating the randomization procedure must be identified. This individual must know whom to contact once an individual is determined eligible for a study and which forms must be completed prior to randomization (e.g., informed consent form and subject eligibility form).
- **Documentation of Randomization:** The person responsible for completing the randomization log at each site must be named.

In today's age of computerization, the randomization process may take place via the Web or an interactive voice recognition system (IVRS). If so, the process for using these systems must be described.

2.K STUDY INTERVENTION

A clinical trial has an intervention that is assessed for safety and/or efficacy. The study intervention includes drugs, surgery, devices, biobehavioral activities (e.g., coping mechanisms), and/or lifestyle changes (e.g., diet, exercise). The intervention must be thoroughly described so that all sites, investigators and participants have the same exposure. Clinical trial phases are described in (add location on Web site). Specific types of therapy considerations follow.

For **drug intervention** studies, the distribution, preparation and handling, labeling, and administration are detailed along with the duration of treatment and criteria for treatment discontinuation. A detailed description of the information that must be provided is documented in the ICH E6 Good Clinical Practice Guidelines. This document is available on the Internet at http://www.ich.org/MediaServer.jserv?@_ID=482&@_MODE=GLB

Device studies require a detailed description of the device and its intended use. Information on device studies is provided in the Code of Federal Regulations (CFR) Title 21, Parts 800-1299, revised as of April 1, 2000 (see http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfrv8_00.html).

Surgical studies require a detailed description of the procedure.

Biobehavioral and **lifestyle** studies describe how the intervention is to be carried out.

2.L BLINDING AND UNBLINDING

Ideally, study participants and the treating physician are "blinded" or "masked" to the treatment. That is, in a "double-blind" study, neither the participant nor the investigator knows whether the participant is receiving drug or placebo. The study statistician and/or a designated study staff member securely maintains the randomization codes so that the treatment assignments are not known.

In blinded studies, unblinding is a serious action and should be performed only if necessary to ensure the safety of a study participant. The DSMB or Medical Safety Monitor as well as the NINDS Program Director is typically involved in the decision to unblind a participant.

The procedure for unblinding should be described in this section along with the documentation of the event that includes:

- ID of unblinded participant
- reason for unblinding study staff
- person responsible for unblinding study staff
- list of person(s) who are unblinded (including the participant, if applicable).

2.M PARTICIPANT EVALUATIONS AND FOLLOW-UP

As you can see, a primary purpose of the MOP is to ensure that study procedures are administered in the same way for all participants and across all sites. Once a participant is enrolled, there is typically a baseline and follow-up evaluations and tests. All evaluations, and treatment interventions, as well as

schedules and 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), including timing, must be specifically defined (e.g., at 30 days from baseline).

2.M.1 Time line and visit schedule

A useful study tool included in the MOP is a schedule of visits and evaluations that specifies what is to be done at each study phase and at each contact with the study participant. An example of a schedule is provided in Figure 3.

2.M.2 Scope

Each visit by visit type should be explained in this section in enough detail so that a new or substitute team member can perform the visit.

2.M.3 Follow-up

Participants should be actively followed, especially in a lengthy study. This section can detail strategies sites can use to follow participants such as calling monthly, sending birthday cards, sending postcards, etc. Participants should be followed to the end of the study, even if they discontinue treatment.

FIGURE 3: Generic Time and Events for an NINDS Clinical Research Study

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

2.N PARTICIPANT RETENTION

Every effort should be made to retain study participants other than coercion. Thus, it is important that several contacts should be identified during the screening process (see Section H). In some cases, the coordinator or investigator may need to chat with the family or participant to find out if issues can be resolved. Suggestions for participant retention should be provided in this section.

2.O CONCOMITANT MEDICATIONS

The MOP provides a discussion of 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 should be described.

2.P SAFETY REPORTING

A proposed Safety Monitoring Plan should be included with the study grant application and will be reviewed with the NINDS Program Director to determine whether a Data and Safety Monitoring Board (DSMB) will be appointed by the Institute to monitor the study. Multi-center and high risk studies will have a DSMB. Single site studies that do not pose risk will generally have an Independent Safety Monitor.

This section of the MOP details the definitions of and procedures for reporting adverse events (AEs) and serious adverse events (SAEs).

Relevant 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. 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.

- **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).

2.P.1 Adverse Event Reporting

All AEs are collected, analyzed, and monitored using an Adverse Event Form, a sample of which is shown in Figure 4. AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety must be reported. All AEs experienced by participants during the study time frame specified in the protocol (e.g., from the time of study drug administration to 30 days following the last administration of study drug) are to be reported

2.P.2 SAE 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, Study Monitoring Committee(SMC), or independent medical monitor(IMM), and NINDS. All interventional studies, independent of phase or type, must report SAEs. The immediate reports should be followed promptly by detailed, written reports.

2.Q DATA AND SAFETY MONITORING RESPONSIBILITIES

The roles and responsibilities of the DSMB, SMC, or IMM are described in this section. These entities monitor study quality, safety of participants, and efficacy. Monitoring *performance* of the study usually includes reviewing:

- patient recruitment
- flow of forms
- quality control of the data
- adequacy of medical monitoring
- adverse effect reporting
- adherence to protocol
- appropriateness of protocol changes with regard to scientific integrity

2.Q.1 Definitions

Monitoring *safety* usually includes reviewing:

- risk of harm inherent in participating in the study
- adverse events (type, incidence, and severity)
- effect of protocol changes on risk

Monitoring *efficacy* usually includes reviewing:

- data (blinded or unblinded)
- planned and/or unplanned interim analyses
- stopping rules, their implementation, and resulting decisions
- results and conclusions

FIGURE 4: SAMPLE ADVERSE EVENT FORM

Severity	Study Drug Relationship	Action Taken Regarding Study Drug	Outcome of AE	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Not Related 2 = Possibly/Probably Related	1 = None 2 = Discontinued Perm. 3 = Discontinued Temp. 4 = Reduced Dose 5 = Increased Dose	1 = Resolved without effects 2 = Resolved with effects 3 = Ongoing 4 = Death 5 = Unknown	1 = Yes 2 = No (If yes, complete SAE form)

Adverse Event	Start Date	Stop Date (enter "C" if continued)	Severity	Relatedness	Action Taken W / Study Drug	Outcome	Serious?

2.Q.2 DSMB Membership

Members of a DSMB or SMC, and Independent Medical Monitors 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 participant safety and conduct a scientifically rigorous study. The DSMB members must also assure that they have no direct or indirect financial interest by signing a Conflict of Interest statement.

(http://www.ninds.nih.gov/funding/clinical_trials/dsm_guidelines.htm).

2.R 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. Comprehensive training, early review of the data, and routine communications with the sites help to minimize protocol deviations. However, there should be a mechanism to track protocol violations and procedures to notify appropriate parties that are described in this section. Protocol violations include but are not limited to the following:

- randomization of an ineligible participant
- failure to obtain informed consent
- entering a participant into another study
- failure to keep IRB approval up to date
- wrong treatment administered to participant

The MOP should describe relevant violations and the reporting process to appropriate parties including the Principal Investigator at the study site, NINDS, and the DSMB or Medical Safety Monitor. Study staff should report a violation within 24 hours of occurrence or as soon as it is discovered. In addition, if site monitors discover any of these violations during a monitoring visit, they should notify NINDS of the occurrence in writing.

The Coordinating Center or identified responsible person in a single site study should maintain a log of protocol deviations and/or violations and should report them routinely to the study monitoring body or individual. While there may be

rational clinical reasons for an occasional violation, a site with serious continual problems is at risk for losing its funding.

2.S DATA COLLECTION AND STUDY FORMS

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

2.S.1 Source Documentation

Patient medical data are collected on source documents, such as lab reports, ECG tracings, medical records, standardized test forms, and laboratory reports. A source document is any document on which study data are initially recorded.

To document study-specific data requirements, source data are transcribed to a paper case report form (CRF) or entered into an electronic case report form (eCRF).

All essential study documents must be retained by the study investigator as described in the glossary. The following are considered participant file documents:

- case report forms
- data correction forms
- workbooks
- source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- signed participant consent forms
- questionnaires completed by the participant

This section describes how study data are initially collected and maintained for the study.

2.S.2 Study Forms

Data must be collected consistently across patient and sites so that any variability is limited to the patients and responses to intervention. Study forms,

also called case report forms (CRFs), provide the vehicle for consistent data collection and thus, this section describes each study form and question.

The section also identifies the person responsible for producing and distributing forms, how the forms are packaged or placed in a binder for each participant, how they are to be maintained, and who should be contacted in the event that additional forms are needed. In addition, a list of all study forms and the collection schedule are included.

2.S.3 Data Flow

It is the site's responsibility to ensure that all forms are complete, intact, and are transmitted to the Coordinating Center, if appropriate. More recently, in some studies data are directly entered into an electronic CRF (eCRF). This section describes the disposition of study forms or entry of data into the computer system (see Section 2.T), schedule for completion and transmission, and which copies of forms are to be maintained at the site as well as which are to be submitted for data entry. In addition, the section describes the data flow, data entry, and data correction procedures.

2.S.4 Retention of Study Documentation

The length of time all study files are to be maintained is specified in this section. NIH policy requires that studies conducted under a grant retain participant forms for three years, while studies conducted under contract must retain participant forms for seven years. Researchers should pay special attention to studies involving children, as study documentation retention procedures are often longer in duration and more comprehensive. The FDA individual IRBs, institutions, sponsors, countries, and states may have differing requirements for record retention; investigators should adhere to whichever requirements are most rigorous.

Investigators should retain forms and all other study documents for the longest applicable period. This period should be stated in the MOP.

2.S.5 Administrative Forms

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

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

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

Screening Log is a record of *all* individuals who are screened for participation in the study. It should be arranged chronologically and be kept up to date (see Section 2.d.1).

Record of Request for Exemption to Entry Criteria is used to document a participant's exemption to an entry criterion, if relevant.

Participant Identification List records each participant's name, medical record number, study identification number and/or randomization number, and study entry and exit dates. Due to the confidential nature of the information, it should be maintained in a secured location apart from 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 NINDS, site institution, FDA, or other governing body.

Study Drug Accountability Record should be maintained, as relevant, in the Pharmacy by the research pharmacist and must not be shared with other members of the study team.

Record of Destruction of Clinical Product is a log used to document destruction of any unused study drug. The date and time of incineration as well as how many vials were incinerated must be recorded. This record should be attached to the Study Drug Accountability Record.

CRF Transmittal Sheet serves as a cover page for each packet of CRFs submitted for data entry. It provides an inventory of the forms that are included in each mailing for mailed forms.

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
- 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.

Some of these forms may have been superseded by automated logs. The message is that *study procedures must be documented*. Especially in multi-site studies, the more clearly the procedures are defined, the greater the likelihood that study documentation will be uniform across sites.

2.T DATA MANAGEMENT

This section describes the data management approach that will support the study and details how data are to be entered (if eCRF), edited and corrected. For studies that involve a large number of sites and/or participants, the investigators may wish to consider a computerized approach.

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

- **Data Tracking** - to provide the status of participant enrollment, number of forms completed at the sites, and number of forms transmitted to a Coordinating Center or lead site, as appropriate.
- **Data Entry** - that is easy to use and minimizes errors, such as using 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** - to correct data and maintain an audit trail of all data changes.
- **Reporting** - to describe and account for participants accrued, entered, completed, etc.
- **Statistical Analysis** - mechanism 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 database from edited or "clean" records. These areas should be discussed in this section.

As relevant, the MOP should include a description of the computer system used to support the study and a copy of the User's Guide.

Investigators should be aware that if they are conducting studies that will also be submitted to the FDA, the systems will need to be documented and validated. Guidance for electronic systems is found on the FDA Web site, *Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures* (http://www.fda.gov/ora/compliance_ref/part11/Default.htm).

2.T.1 External Data

External data refers to data such as laboratory samples, MRIs, and other study participant samples. This section of the MOP should describe how this information will be collected, labeled, handled, shipped, and tracked so that study data are not lost. As stated in the new Health Insurance Portability and Accountability Act (HIPAA) guidelines, personal identifiers such as name, geographic location, social security number, and fifteen other specific individual identifiers should not be used. Thus when transmitting participant materials it is important to specify how the material is to be identified (e.g. the participant identification number).

2.U 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 should continue 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.

2.U.1 Standard Operating Procedures

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

2.U.2 Data Form Checks

Data and form checks depend upon data flow and computer procedures. However, data quality control checks may specify the following types of review:

- All data received from participating clinical centers
- No missing forms or data
- Unique identification (ID) number for each study participant is consistent across all forms and visits
- Correct numbers in the site ID and participant's ID number
- Legible data
- Consistent and logical dates over time
- Data within acceptable ranges
- Data consistent across forms and visits
- All fields of a "completed form" actually completed or reason for no data noted
- All required forms completed or reason for no data noted.

2.U.3 Double Data Entry

In recent years, there have been several articles written on the value of double data entry. While conventional wisdom used to insist that double data entry was mandatory, it is now recognized that it may not be necessary, especially if the data entry system provides edits as data are entered. Double data entry is still

recommended for cases in which data entry staff enters data “heads down” or with no edits flagged as the data are entered.

2.U.4 Monitoring

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

The purposes of monitoring visits are to:

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

During the monitoring visits, the data recorded on the study forms are reviewed and verified against source documents and/or study data base to assure:

- informed consent has been obtained and documented
- adverse events have been identified and recorded
- the information recorded on the forms is complete and accurate
- there are no omissions in the reports of specific data elements
- missing examinations are indicated on the forms
- participant disposition at study exit is accurately recorded

Site investigators must allow the clinical monitor 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 any problems or issues that may have been uncovered during the visit. This format should be straightforward, stating what the problem is and then describing recommendations the visitor may have to deal with the problem. A time line should be agreed upon and included in the report to ensure that follow-up of the issues is completed and implemented into the study conduct procedures.

2.U.5 Reports

Once a study begins, routine reports prepared for the Principal Investigator or by the Coordinating Center, are an important quality control tool. Monthly reports may describe participants enrolled by site and in aggregate. Enrollment reports can describe participants screened, enrolled, refused participation, completed, discontinued treatment, and lost to follow-up. Monthly reports can also describe adverse events and serious adverse events. Administrative reports can enumerate the forms completed, entered, and missing and/or erroneous data and forms.

Reports are also provided to the DSMB. While DSMBs can specify the format and content of the reports they wish to receive, the reports are generally similar to the above.

2.V STUDY COMPLETION AND CLOSEOUT PROCEDURES

Study closeout activities are performed to confirm that the site investigator's study obligations have been met and post study obligations are understood. Closeout activities include, but are not limited to, the following:

- Verification that study procedures have been completed, data collected, and study drug and supplies are returned to the responsible party or prepared for destruction.
- Review of investigator's correspondence and study files against the coordinating center's records for completeness
- Assurance that all data queries have been completed.
- Assurance that correspondence and study files are accessible for external audit.

- Reminder to investigators of the ongoing responsibility to maintain study records and to report any relevant study information to NINDS.
- Meeting with the site investigators to ensure that they are aware of regulatory obligations and requirements for record retention.
- Assurance that the investigator will notify the IRB of study completion and obtaining a copy of the notification.
- Preparation of a report summarizing study conduct.

2.V.1 Participant Notification

In addition, the Principal Investigator and Coordinating Center should work with the site investigators to 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 reference to the article.

2.V.2 Site Procedures

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

2.W POLICIES

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

2.W.1 Confidentiality Procedure

It is the responsibility of the study leadership to outline and enforce participant 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 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 or record number, or other unique identifiers, such as Social Security number, should not be included in any published data listing.
- **Data distribution** - internally utilized data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- **Data disposal** - computer listings that contain participant identifying information should be disposed of in an appropriate manner.
- **Access** - participant records stored in the data center should not be accessible to persons outside the center without the express written consent of the participant.
- **Storage** - study forms and related documents retained both during and after study completion should be stored in a secure, fireproof location.

If computers are used to store and/or analyze clinical data, the Coordinating Center or investigator 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 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 if it is modified, the system should be tested to verify that it performs as expected. Testing should verify that the password

approach to system access 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.

2.W.2 Publications

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

2.X MOP MAINTENANCE

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

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

3.0 SUMMARY

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

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RELEVANT WEB SITES

NINDS, NIH:

www.ninds.nih.gov/funding/clinical_trials/protocol.htm

(NINDS protocol template)

www.ninds.nih.gov/funding/clinical_trials/dsm_guidelines.htm

NINDS data and safety monitoring board guidelines

www.ninds.nih.gov/funding/clinical_trials/toolkit.htm

(NINDS' "tool kit" for investigators interested in performing NINDS-sponsored clinical research, including the above and links to other sites)

NIH:

<http://ohrp.osophs.dhhs.gov/polasur.htm>

(Office of Human Research Protections' Regulations on conducting research with human subjects)

<http://www.nih.gov/sigs/bioethics/IRB.html>

(Bioethics Resources on the Web)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-040.html>

(Guidance on financial conflicts of interest and research objectivity for IRBs and investigators)

<http://www.ccc.nih.gov/ccc/protomechanics/index.html>

(Guide to preparing a research protocol from the Warren G. Magnuson Clinical Center at NIH)

http://ohsr.od.nih.gov/info/finfo_6.php3

(Guidance for writing informed consent documents from the NIH Office of Human Subjects Research, which supports NIH intramural studies)

DHHS Office for Civil Rights - HIPAA Information:

<http://www.hhs.gov/ocr/>

<http://privacyruleandresearch.nih.gov>

(*Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*)

Food and Drug Administration (FDA):

<http://www.fda.gov/oc/gcp/regulations.html>

(FDA Good Clinical Practice regulations)

<http://www.fda.gov/cder/>

(FDA Center for Drug Evaluation and Research)

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

(FDA Center for Biologicals Evaluation and Research)

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

(FDA regulations on electronic records and electronic signatures)

http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr312_00.html

(FDA application for an Investigational New Drug)

<http://www.fda.gov/oc/ohrt/irbs/default.htm>

(FDA Guidelines for protection of human subjects)

The following notices are guidance provided periodically to investigators by NIH on specific topics:

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>