

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

**October 2014**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>3</b>
<b>II.</b>	<b>MOP CONTENTS AND ORGANIZATION.....</b>	<b>4</b>
<b>III.</b>	<b>PROTOCOL SYNOPSIS.....</b>	<b>5</b>
<b>IV.</b>	<b>STAFF ROSTER.....</b>	<b>5</b>
<b>V.</b>	<b>STUDY ORGANIZATION AND RESPONSIBILITIES .....</b>	<b>6</b>
	A. Clinical Coordinating Center.....	6
	B. Data Coordinating Center.....	6
	C. Central Units .....	7
	D. Clinical Sites .....	7
	E. Study Leadership Committees.....	8
<b>VI.</b>	<b>TRAINING PLAN.....</b>	<b>9</b>
<b>VII.</b>	<b>TEAM COMMUNICATIONS PLAN .....</b>	<b>9</b>
<b>VIII.</b>	<b>RECRUITMENT PLAN.....</b>	<b>9</b>
<b>IX.</b>	<b>RETENTION PLAN .....</b>	<b>10</b>
<b>X.</b>	<b>STUDY FLOW .....</b>	<b>10</b>
<b>XI.</b>	<b>SCREENING AND ELIGIBILITY CRITERIA .....</b>	<b>11</b>
	A. Screening Log .....	12
	B. Eligibility Criteria .....	12
<b>XII.</b>	<b>INFORMED CONSENT AND HIPAA .....</b>	<b>12</b>
	A. Informed Consent Document and Process.....	13
<b>XIII.</b>	<b>RANDOMIZATION .....</b>	<b>13</b>
<b>XIV.</b>	<b>STUDY INTERVENTION .....</b>	<b>13</b>
<b>XV.</b>	<b>BLINDING AND UNBLINDING .....</b>	<b>14</b>
<b>XVI.</b>	<b>PARTICIPANT EVALUATIONS AND FOLLOW-UP .....</b>	<b>14</b>
	A. Time line and visit schedule.....	14
	B. Scope .....	15
	C. Visit Procedures .....	15
<b>XVII.</b>	<b>PARTICIPANT RETENTION .....</b>	<b>16</b>
	A. Follow-up .....	16
<b>XVIII.</b>	<b>CONCOMITANT MEDICATIONS.....</b>	<b>16</b>
<b>XIX.</b>	<b>SAFETY REPORTING .....</b>	<b>16</b>
	A. Adverse Event Reporting .....	16
	B. SAE Reporting .....	16
<b>XX.</b>	<b>DATA AND SAFETY MONITORING RESPONSIBILITIES.....</b>	<b>17</b>
<b>XXI.</b>	<b>PROTOCOL VIOLATIONS.....</b>	<b>17</b>
<b>XXII.</b>	<b>DATA COLLECTION AND STUDY FORMS .....</b>	<b>17</b>
	A. Source Documentation .....	17
	B. Study Forms .....	17

C.	Data Flow .....	18
D.	Reports .....	18
E.	Retention of Study Documentation .....	18
F.	Administrative Forms.....	19
<b>XXIII.</b>	<b>DATA MANAGEMENT.....</b>	<b>20</b>
A.	External Data.....	20
<b>XXIV.</b>	<b>QUALITY ASSURANCE/CONTROL PROCEDURES.....</b>	<b>20</b>
A.	Standard Operating Procedures .....	21
<b>XXV.</b>	<b>SITE MONITORING .....</b>	<b>21</b>
<b>XXVI.</b>	<b>STUDY COMPLETION AND CLOSEOUT PROCEDURES .....</b>	<b>21</b>
A.	Participant Notification .....	22
B.	Site Procedures.....	22
<b>XXVII.</b>	<b>POLICIES.....</b>	<b>22</b>
A.	Confidentiality Procedure.....	22
B.	Publications .....	23
C.	Ancillary Studies .....	23
<b>XXVIII.</b>	<b>MOP MAINTENANCE .....</b>	<b>24</b>
<b>XXIX.</b>	<b>SUMMARY.....</b>	<b>24</b>
<b>XXX.</b>	<b>APPENDICIES.....</b>	<b>24</b>
A.	Appendix I: Central Pharmacy Manual of Operations .....	24
B.	Appendix II: Imaging or Other Reading Centers Manual of Procedures .....	24
C.	Appendix III: Central Laboratory Manual of Procedures.....	24
D.	Appendix IV: Biorepository Manual of Procedures.....	24
E.	Appendix V: Other .....	24
<b>XXXI.</b>	<b>REFERENCES .....</b>	<b>25</b>
<b>XXXII.</b>	<b>RELEVANT WEBSITE LINKS:.....</b>	<b>26</b>
A.	National Institute of Neurological Disorders and Stroke (NINDS):.....	26
B.	National Institutes of Health (NIH):.....	27
C.	Food and Drug Administration (FDA): .....	27
D.	Department of Health and Human Services (DHHS):.....	27
E.	NIH Guide Notices:.....	27

<b>TABLES &amp; FIGURES</b>
-----------------------------

<b>Table 1:</b>	<b>Staff Roster.....</b>	<b>6</b>
<b>Figure 1:</b>	<b>Study Flow .....</b>	<b>11</b>
<b>Table 2:</b>	<b>Generic Time and Events for an NINDS Clinical Research Study.....</b>	<b>15</b>

## **I. 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.

The purpose of this document is to provide a Manual of Operating Procedures (MOP) template for principal investigators (PIs) of multisite clinical trials. The role of the MOP is to facilitate consistency in protocol implementation and data collection across participants and study sites. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored. This MOP template is designed to help clinical investigators comply with NIH regulations and procedures and promote high quality research.

In preparing the MOP, the PI (study chair) must be aware of the terms of award with respect to required reporting, data and safety monitoring, and Institutional Review Board (IRB) approval.

The goal of the MOP is to describe the procedures with sufficient clarity to ensure that all clinical centers use the same examination procedures, participant management, intervention schedules, definitions, and, as far as possible, the same equipment. The Clinical Coordinating Center is usually responsible for minor revisions of the MOP. The MOP should:

- Transform a protocol into an operational research project.
- Document 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.
- Detail how the data are observed, collected, and recorded.
- Specify quality control procedures, and
- Define methods for ensuring confidentiality of participant information

The MOP should be written in sufficient detail such that it could be used as a training manual for new study investigators and coordinators.

Changes to the MOP and relevant forms should be made as soon as practical and, unless otherwise noted, become effective on receipt of the revised procedures at the clinical centers. Once accepted, the policies in the Protocol and the procedures

described in the MOP must be followed by each clinical center. The Coordinating Center monitors adherence to the protocol and prepares regular reports for the study leadership summarizing adherence to protocol and deviations from these documents. The MOP is a dynamic document that should be updated throughout the study to record amendments to the protocol or consent forms, and to document procedure changes, refinements or clarifications. It should be maintained in a format that allows it to be easily updated, typically in a three-ring binder, although electronic versions are now easily updated with computer applications such as MS Word and Adobe. The version number and date should appear in the header or footer of 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 by the study management team and each participating site, either electronically or on paper (e.g. three-ring binder).

## **II. MOP CONTENTS AND ORGANIZATION**

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

- A. Protocol Synopsis
- B. Staff Roster
- C. Study Organization and Responsibilities
- D. Training Plan
- E. Communications Plan
- F. Recruitment Plan
- G. Retention Plan
- H. Study Flow
- I. Screening and Eligibility Criteria
- J. Informed Consent and HIPAA
- K. Randomization
- L. Study Intervention
- M. Blinding and Unblinding
- N. Participant Evaluations and Follow-up
- O. Participant Retention
- P. Concomitant Medications
- Q. Safety Reporting
- R. Data and Safety Monitoring Responsibilities
- S. Protocol Violations
- T. Data Collection and Study Forms
- U. Data Management
- V. Quality Assurance and Quality Control Procedures

- W. Site Monitoring
- X. Study Completion and Closeout Procedures
- Y. Policies
- Z. MOP Maintenance

The above sections apply to all intervention research, including drug, 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 template outlined above, and described in the following sections, is a guide rather than a prescription and should be adapted to each study's specific needs.

### **III. PROTOCOL SYNOPSIS**

A brief synopsis of the final protocol with the date of approval and version number should be included in the MOP and should be updated with each amendment or change to the protocol as applicable. The full protocol may be included as an appendix to the MOP. See the [NINDS Protocol Template](#). If the protocol is modified, the MOP and Synopsis should be updated with the most current version and list of all changes by version.

### **IV. STAFF ROSTER**

The roster includes the names, roles, addresses, phone numbers, fax numbers, pager and/or mobile numbers, and e-mail addresses of study staff, committee 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
- reporting protocol deviations and violations
- invoicing/financial issues

*(See table below for a template format)*

**Table 1: Staff Roster**

Role	Name	Contact Info	Responsibility	When To Contact
Principal Investigator		Institution Address Phone(s) Email		
Co-Investigator		Institution Address Phone(s) Email		
Data Manager		Institution Address Phone(s) Email		
Monitor		Institution Address Phone(s) Email		
Etc...		Institution Address Phone(s) Email		

**V. STUDY ORGANIZATION AND RESPONSIBILITIES**

A study’s organizational structure should be described, especially for multi-site studies. Multi-site studies, especially Phase III and other large studies, may have several central units, including a Clinical Coordinating Center, Statistical Center or Data Management Center, reading centers, central laboratories, etc., each of which has responsibilities in the development of materials and oversight of study operations. Each of the Centers’ responsibilities should be described along with those of study committees, as relevant. Organization charts help to clarify organizational responsibilities and roles. An appendix is provided at the end of the MOP to describe each of the Central Unit’s specific procedures.

**A. Clinical Coordinating Center**

The role and responsibilities of the Clinical Coordinating Center should be detailed in this section.

**B. Data Coordinating Center**

The role and responsibilities of the Data Coordinating Center should be detailed in this section.

## C. Central Units

- **Pharmacy**  
“Pharmacy” refers to the unit responsible for the storage, dispensing and accountability for a study treatment intervention. See [Appendix I](#) for a detailed explanation of the Central Pharmacy Unit’s roles, responsibilities and processes.
- **Imaging or Other Reading Centers**  
See [Appendix II](#) for a detailed explanation of the Imaging or Other Reading Center Unit’s roles, responsibilities and processes
- **Central Laboratory**  
See [Appendix III](#) for a detailed explanation of the Central Laboratory Unit’s roles, responsibilities and processes
- **Biorepository**  
The Biorepository is the unit responsible for the collection and storage of biobanked specimens collected in the study. See [Appendix IV](#) for a detailed explanation of the Biorepository unit’s roles, responsibilities and processes.
- **Other**  
If any other central units will be used, please briefly describe them here. See [Appendix V](#) for a detailed explanation of the XXXXX unit’s roles, responsibilities and processes.

## D. Clinical Sites

Detail here the roles and responsibilities of the Investigators and Clinical Sites, which may include:

- Achieving efficient site activation (include expected timelines)
- Maintaining the study binder (paper or electronic per institutional guidelines)
- Compliance with protocol, MOP, IRB, Federal and State Regulations
- Obtaining and maintaining IRB approval; notifying IRB of any protocol changes; communicating IRB concerns to study leadership
- Ensuring that all study staff meet regulatory and training requirements
- 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 in a timely and efficient manner (include expected screening and enrollment rates if appropriate)
- Obtaining informed consent and protecting participants rights
- Collecting study data and following participants through study completion

(include expected retention rates if appropriate)

- Controlling the distribution of the study intervention, as required
- Retaining specific records (e.g., laboratory drug distribution records, screening log)
- Preparing and sending required data, samples and reports to Coordinating or Data 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

## **E. Study Leadership Committees**

Most large multi-center studies are directed by one or more study leadership committees, with the principal leadership committee typically referred to as the Steering Committee. The Steering Committee is responsible for the overall direction of a study and typically comprises the Clinical and Statistical Principal Investigators as well as central unit Principal Investigators, one or more Clinical Site investigators, and NINDS program staff.

In large multi-center studies with multiple central units (e.g. clinical, data, statistical, reading, etc.), a subcommittee of the Steering Committee may be convened to guide the implementation and operation the study. Often referred to as the Executive Committee, this subcommittee includes the Clinical and Statistical Principal Investigators, the NINDS Program Director, and other key individuals.

This section should detail each of the Study Leadership Committees, their membership, roles and responsibilities, expected meeting frequency, communication mechanisms, etc.

The following areas typically fall under the purview of the Study Leadership Committees:

- General design and conduct of the study
- Protocol
- Review of the essential study documents, including MOP and case report 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 (e.g., site activation, recruitment, retention)

- Review of adverse events and protocol violations/deviations
- 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)

## **VI. TRAINING PLAN**

Training of study staff, including clinical site investigators, should be described in this section. Investigators' meetings or other training formats can be utilized to introduce the study protocol and procedures and should be repeated as necessary given the complexity of the protocol, staff turnover, changes to study procedures, protocol amendments, etc. Other training formats include webinars, web-ex conferences, teleconferences and in-person meetings at other largely attended meetings (e.g. professional society conferences, etc.). It is the responsibility of the grantee to ensure that training is adequate and frequent enough to ensure that all participating sites are complying with study procedures, good clinical practice and the code of federal regulations governing the conduct of research involving human subjects. Documentation of such training is mandatory.

## **VII. TEAM 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, provide an open forum for the discussion of issues relevant to recruitment, retention, data collection, etc., as well as to share successful strategies and processes.

The communications plan should be described in the MOP by the designated coordinating center and records of all relevant communications stored (e.g. dates/times of meetings, attendance, minutes, etc.) should be maintained. Once the study is implemented, the Steering Committee and Executive Committees should also participate in routine calls to discuss progress, issues, and potential solutions. Routine reports required by NINDS should also be described in this section.

## **VIII. RECRUITMENT PLAN**

To assist clinical sites in recruiting study participants, this section of the MOP should describe the target population and audiences and the recruitment strategies to be implemented by the Study Leadership (e.g. marketing, interaction/involvement with

advocacy organizations, etc.) as well as suggested local strategies such as identifying primary care referral practices, grand rounds, and publicity. Detail whether a structured recruitment plan will be required from each site and what should be included in such a plan. Explain how recruitment will be monitored and by whom and how site productivity will be shared (if planned). Consider including site recruitment expectations (if appropriate) and when a corrective action plan may be required in order to maintain participation in the study.

## **IX. RETENTION PLAN**

Avoidance of losses to follow-up or withdrawal of consent is a high priority in clinical trials, where intent-to-treat analysis requires study endpoints for all enrolled participants. Every effort should be made to retain study participants without being coercive. Thus, it is important that several contacts should be identified during the screening process, including collection of alternative contact information (home, work, mobile numbers, email and mailing addresses), as well as contact information for friends and family members who may be able to assist in locating participants. Any new technologies for following/finding subjects that will be employed (e.g. SMS text messaging, email, etc.) should be described in this section.

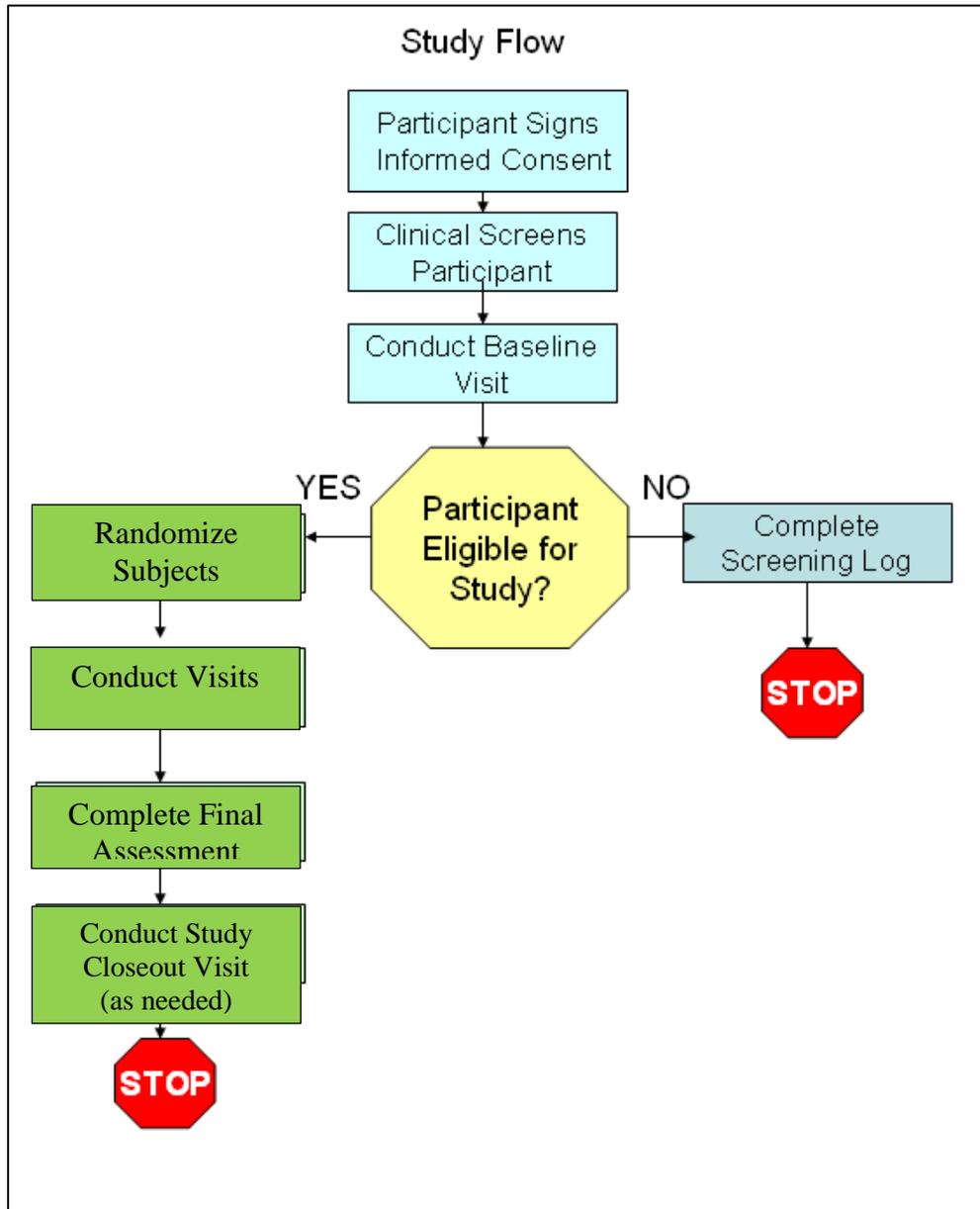
This section should also detail strategies sites can use to follow participants such as calling monthly, sending birthday cards, sending postcards, electronic messaging mechanisms (SMS, text messaging, etc.), etc.

Any methods to minimize withdrawals or losses to follow-up should be described in this section. Expectations for minimum retention rates should be detailed as well as when corrective action plans may be required in order to maintain active participation in the study.

## **X. 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.

**Figure 1: Study Flow**



## **XI. SCREENING AND ELIGIBILITY CRITERIA**

To help assure that clinical sites accrue participants with appropriate characteristics, this section should provide a detailed discussion of the screening procedures utilized to identify and determine participant eligibility. Frequently, the study coordinator reviews the patient’s medical records or responds to initial telephone inquiries from physicians or potential study participants during a pre-screening phase. 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 X)

### **A. 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
- Source of subject (e.g. referral, advertising, advocacy, etc.)

It may also contain the randomization number. The MOP describes the contents of the Screening Log and maintenance procedures. Although typically not incorporated into the study database, the information in the screening log may be reviewed during site visits and may provide useful insights into enrollment patterns at individual clinical centers. **It is strongly suggested that the screening log include a mechanism for collecting detailed information regarding why eligible subjects decline participation as this can be informative to future iterations of the protocol.**

### **B. 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).**

## **XII. INFORMED CONSENT AND HIPAA**

This section should describe procedures and responsibilities for discussing the informed consent and HIPAA privacy rules with the participant. The necessary assurances may be incorporated into the Informed Consent form or may be documented separately; if separate, procedures for obtaining the participant's

signature, maintenance of the form, and distribution of copies should be included in this section.

Informed consent regulations are administered by the Office of Human Research Protections (OHRP), whose [website](#) also provides a number of tips to guide investigators in developing informed consent documents. You may also refer to the NINDS guidelines [here](#) and [here](#) for developing an informed consent document.

### **A. Informed Consent Document and Process**

This section should describe specific instructions regarding the process of obtaining informed consent, including individual staff responsibilities, timing, acceptable levels of consent, and any other relevant information.

Please refer to the [Informed Consent section](#) on the NINDS website for more information on what should be included in the informed consent document and the informed consent process.

## **XIII. RANDOMIZATION**

Describe the randomization procedures including:

- When is a participant deemed ready to be randomized?
- What is the timeframe for randomization (e.g., within 8 hours of symptom onset)?
- Where must the participant be when randomized (e.g., present at the study site, in ambulance on the way to the emergency room)?
- Who is authorized to randomize the participant?
- What procedures are followed to randomize the participant (e.g., open a randomization assignment envelope, log on to web site)?
- What backup procedures are followed if the usual randomization procedures cannot be followed?
- How is the randomization documented?

## **XIV. STUDY INTERVENTION**

A clinical trial has at least one intervention that is assessed for safety and/or efficacy. The study intervention may include drugs, surgery, radiotherapy, devices, biobehavioral activities, and/or lifestyle changes. The intervention must be thoroughly described so that all sites and investigators can apply them in a standard manner. Specific types of therapy considerations follow.

- For **drug intervention** studies, the distribution, preparation and handling, labeling, and administration of the experimental intervention and placebo 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](#).

- **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](#).
- **Surgical or radiotherapy** interventions require a detailed description of the procedure.
- **Biobehavioral** and **lifestyle** studies describe how the intervention is to be carried out.

## **XV. BLINDING AND UNBLINDING**

When relevant, the MOP should describe procedures for blinding study investigators and participants. Specify which individuals are to remain blinded, who maintains the code, and how blinding is maintained.

The procedures for emergency unblinding should be described in this section, including whom to notify and what forms must be completed. Documentation of decisions to unblind typically 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)

## **XVI. PARTICIPANT EVALUATIONS AND FOLLOW-UP**

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, typically a baseline evaluation and a series of follow-up assessments and tests are conducted at specified intervals. All evaluations and treatment interventions, as well as schedules and procedures for obtaining data, must be clearly described in this section. Specific requirements, such as training and certification for study procedures, should also be described.

### **A. 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. The visit schedule should stipulate the permissible visit window (e.g., 3 month follow-up visit must be scheduled within 2 weeks before or after the 3-month date).

## B. 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. For each visit, list specific procedures that must be completed as well as relevant instructions (e.g., order in which procedures must be done, required forms, etc.).

## C. Visit Procedures

This section should describe in detail what variables will be considered the primary and secondary outcomes for evaluating efficacy and/or safety. 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). Procedures for collecting, reviewing, and adjudicating outcomes should be developed and described.

Include a copy of the schedule of evaluations below. See example:

**Table 2: 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

## **XVII. PARTICIPANT RETENTION**

Plans for retention of participants should be outlined:

- Who will contact participants
- At what frequency will participants be contacted
- How will participants be contacted

### **A. Follow-up**

This section should provide explicit definitions of “lost-to-follow-up”, “withdrawal of consent”, “discontinued”, etc. Procedures to minimize losses should be delineated, including instructions on how to track participants and methods to encourage continued compliance.

## **XVIII. CONCOMITANT MEDICATIONS**

While the protocol will list concomitant medications which may be allowed/disallowed, this section should expand upon the information contained in the protocol:

- Individual medications should be listed if the protocol refers to classes of medications
- The form used to document concomitant medication information should be described
- The period of time for which this information will be collected should be described

## **XIX. SAFETY REPORTING**

The safety monitoring plans and AEs and SAEs should be defined in the protocol. The process for identifying, reporting and reviewing adverse events (AEs) and serious adverse events (SAEs) should be outline:

### **A. Adverse Event Reporting**

- Who will report AEs and in what timeframe
- To whom will AEs be reported
- How will AEs be documented
- Who will review AEs and in what timeframe
- How will AEs be followed
- What information will be collected on the AE form

### **B. SAE Reporting**

- Who will report SAEs and in what timeframe
- To whom will SAEs be reported
- How will SAEs be documented (immediate and follow-up reporting)
- Who will review SAEs and in what timeframe
- How will SAEs be followed
- What information will be collected on the SAE form

## **XX. DATA AND SAFETY MONITORING RESPONSIBILITIES**

The roles and responsibilities of the DSMB, SMC, or IMM are described in this section. In addition to monitoring participant safety and adverse events, these entities may also monitor study progress and quality, and efficacy/futility of the intervention. Detailed information on [NINDS Monitoring Guidelines](#) and [NINDS Guidelines for Data and Safety Monitoring in Clinical Trials](#) are available.

## **XXI. PROTOCOL VIOLATIONS**

Protocol violations include but are not limited to the following:

- randomization of an ineligible participant
- failure to obtain informed consent
- failure to keep IRB approval up to date
- wrong treatment administered to participant

Describe the processes for identifying protocol violations. This should include how violations might be discovered either by the site or by a coordination center. Also describe how, when and to whom violations are to be reported, and what steps will be taken to ensure they are not repeated. 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.

## **XXII. DATA COLLECTION AND STUDY FORMS**

Use the following sections to describe the study data collection and data management procedures. It may be useful to include copies of all forms as an appendix.

### **A. Source Documentation**

A source document is any document on which study data are initially recorded/collected such as:

- case report forms (when data are originally collected directly on them)
- data correction forms
- workbooks
- Lab reports, ECG tracings, x-rays, radiology reports, etc.
- signed participant consent forms
- Questionnaires completed by the participant.

Describe what constitutes source documents for this study and how and where these documents should be organized and maintained at the study site.

### **B. Study Forms**

Describe each study form (case report form, CRF) to be used in the study. If not clear from the instructions found on the form, describe who is responsible for completing the form. Also describe how the data are to be collected, such as

directly onto the form or transcribed onto the form from a source document. Mention that the data should be collected in black or blue ink and that corrections must be made by striking out the original entry and writing the corrected value next to it, along with the initials of the person making the correction and the date the data were corrected.

Describe the person (or center) 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 how to obtain additional forms as needed.

### **C. Data Flow**

Describe the flow of data from initial collection to transmittal to person (or Data Coordinating Center) responsible for central data management. This might include, for example, the recording of data into a participant's hospital chart, then transcription of these data onto a paper study form, followed by entry into a web-based system. Clarify who at the site is responsible for each step and how data are to be checked for accuracy and completeness. Describe procedures for ensuring data confidentiality such as storage of completed data forms in locked file drawers. If data are collected or transferred to electronic records by the site staff, describe who can access these data, how they do so, and who they should contact for assistance if the electronic system is not working. Also describe how the site staff will be notified of potential errors in the data and how they should correct previously submitted data.

### **D. Reports**

Once a study begins, routine reports prepared for the Principal Investigator (or Steering Committee) or by the Coordinating Center (or Study Statistician) 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 those above but include safety and efficacy data broken down by (coded) treatment group assignment. This section describes what reports are prepared, the frequency of the reports, and to whom they are provided. Alternatively, this information may be provided in a separate document called the Statistical Analysis Plan (SAP).

### **E. Retention of Study Documentation**

Specify the length of time all study files are to be maintained, 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. In some cases it may be prudent for the sponsor to make arrangements for the central storage of study files from all sites after a study has completed all participant follow-up, if the data will be used to support the licensing of the investigational agent/device. Describe the procedures for transferring study files from the study sites to this central storage facility.

## **F. Administrative Forms**

List and describe the administrative forms to be used in the study, that is, forms that do not collect individual participant study data but are used to facilitate administrative aspects of the study. These may include the following:

- **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. The screening log provides important data that may be used to document the site's recruitment efforts and help determine how representative the study sample is of the underlying population. It may include codes to represent which eligibility criteria the screenee failed to meet.
- **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 or Device 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 electronic logs. The important thing is that study procedures be documented.

### **XXIII. DATA MANAGEMENT**

Describe the data management approach that will support the study and detail how data are to be entered (if eCRF), edited and corrected. Data management activities typically 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 Data Editing and Querying** - 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).
- **Data Updating** - to correct data and maintain an audit trail of all data changes.

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.

#### **A. External Data**

External data refers to data such as laboratory samples, MRIs, and other data or samples obtained outside of the study protocol. This section of the MOP should describe how this information will be collected, labeled, handled, shipped, and tracked. Procedures for protecting patient confidentiality of the external data should be described (i.e. use of the participant identification number on all materials to be transmitted rather than any other personal identifiers). If there need to be detailed instructions (e.g., how blood samples will be collected, labeled with accession numbers, centrifuged, stored on dry ice, sent overnight to a central lab, etc.), it may be best to create separate MOP chapters for each type of external data.

### **XXIV. QUALITY ASSURANCE/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, see the [NINDS Quality Assurance Guidelines](#) for more information.

## **A. 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.

## **XXV. SITE MONITORING**

Site monitoring is often conducted as an important component of the QA/QC program in multicenter clinical trials. Monitoring can be accomplished through periodic site visits conducted on a routine or for cause basis. The frequency of visits depends upon funding, site 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

NINDS has developed a process checklist for NINDS clinical studies and in preparation for site visit, the link can be found on the “Things You Need to Know Now That You Are Funded” [Tool Kit](#)

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.

## **XXVI. 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. Detailed closeout activities at the sites and the central units should be described in this section. Closeout activities may 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.

### **A. Participant Notification**

Procedures for developing and implementing plans 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 should be provided here.

### **B. Site Procedures**

Plans for closing out site activities should be described.

## **XXVII. POLICIES**

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

### **A. 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. Study participant confidentiality safeguards that should be described in the MOP:

- Data flow procedures
- Electronic files
- Forms
- Data listings
- Data distribution
- Data disposal
- Access
- Storage

The Coordinating Center or investigator should address computer security to ensure that the data remain confidential:

- Passwords

- User Training
- System Testing
- System Backups

## **B. 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

- By law (Title VIII, Section 801 of Public Law 110-85), the “responsible party” must register Phase II-IV “applicable clinical trials” on the [Clinicaltrials.gov](http://Clinicaltrials.gov) website. Applicable clinical trials must be registered no later than 21 days after the first participant is enrolled. ["Basic results" information for applicable clinical trials is to be submitted within one year](#) after the “[Primary Completion Date](#)” of the trial.
- NIH now requires that published articles resulting from NIH-funded research be submitted to PubMed Central. [These articles will be made publicly available on PubMed Central within 12 months of the publication date.](#)
- If applicable, the NINDS and the DSMB will review the primary publication prior to submission for any large Phase III trial or cooperative agreement.

## **C. Ancillary Studies**

It is generally recognized that large clinical trials and epidemiological studies offer opportunities to investigate many questions and hypotheses that are related to the scope and intent of the study but are not part of the study objectives. These "ancillary studies" or sub-studies may include studies that simply require new analyses of existing data; studies requiring new analyses of existing specimens; or studies requiring collection and analysis of new data or new specimens. Because ancillary studies may have an impact on the progress and scientific integrity of the parent study, it is essential that no such ancillary study is initiated without appropriate evaluation of its merit, relevance to the goals of the parent study, and impact on the parent study protocol and progress. Ancillary study proposals should be formally reviewed and approved by the leadership of the parent study and the NINDS. The review and approval of the Data and Safety Monitoring Board (DSMB), Safety Monitoring Committee (SMC) or Observational Study Monitoring Board (OSMB) is also required.

This section of the MOP should describe procedures for proposing ancillary studies, internal review criteria, and any other relevant matters, such as data and safety monitoring, internal reports, etc. Refer to the following [guidelines](#).

## **XXVIII. MOP MAINTENANCE**

The MOP must be maintained and updated throughout a study. This section describes the procedures for updating and distributing updated MOP versions and identifies staff members responsible for this activity. The MOP should be available to site staff in loose-leaf or electronic 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.

## **XXIX. 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.

## **XXX. APPENDICIES**

### **A. Appendix I: Central Pharmacy Manual of Operations**

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.

### **B. Appendix II: Imaging or Other Reading Centers Manual of Procedures**

This section of the MOP describes how imaging and other reading centers will be used and provides instructions for submission of materials (i.e. imaging, EKGs, etc.) to the central reading center.

### **C. Appendix III: Central Laboratory Manual of Procedures**

This section of the MOP describes how laboratory specimens will be used and will be submitted to central labs.

### **D. Appendix IV: Biorepository Manual of Procedures**

### **E. Appendix V: Other**

## XXXI. REFERENCES

- Blumenstein BA, James KE, Lind BK, Mitchell HE. Functions and Organization of Coordinating Centers for Multicenter Studies. *Controlled Clinical Trials* 1995;16:4S-29S.
- Bohaychuk W, Ball G, Lawrence G, Sotirov K. Good Clinical Practice: Data Integrity Needs Upgrading. *Applied Clinical Trials* 1999(January):54-61.
- Bucher HC, Guyatt GH, Cook, DJ, Holbrook A, McAlister FA. Users Guide to the Medical Literature. *JAMA* 1999;282(8):771-778.
- Code of Federal Regulations & ICH Guidelines*, Revised April 1, 1998.
- Collins JF, Williford WO, Weiss DG, Bingham SF, Klett CJ. Planning Patient Recruitment: Fantasy and Reality. *Statistics in Medicine* 1984;3:435-443.
- Data Safety Monitoring Boards Offer Credible Clinical Data Review, Says Expert Panel. *Good Clinical Practice Monthly Bulletin* 1999;6(6):1.
- Ellenberg SS, Myers MW, Blackwelder WC, Hoth DF. The Use of External Monitoring Committees in Clinical Trials of the National Institute of Allergy and Infectious Diseases. *Statistics in Medicine* 1993;12:461-467.
- Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. Mosby, Baltimore: 1996.
- Gassman JJ, Owen WW, Kuntz TE, Martin JP, Amoroso WP. Data Quality Assurance, Monitoring, and Reporting. *Controlled Clinical Trials* 1995;16:104S-136S.
- Gibson D, Harvey AJ, Everett V, Parmar MKB. Is Double Data Entry Necessary? *Cont Clin Tri* 1994;15:482-488.
- Greenwald et. al. *Human Subjects Research, A Handbook for IRBs* at 81, 1982.
- Guidelines for Quality Assurance and Data Integrity in NIAMS Clinical Trials*, October 1997.
- Hawkins BS. Data Monitoring Committees for Multicenter Clinical Trials Sponsored by the National Institutes of Health. *Controlled Clinical Trials* 1991;12:424-437.
- Huster W, Shah A, Kaiser G, Dere W, DiMarchi R. Statistical and Operational Issues Arising in an Interim Analysis When the Study Will Continue. *Drug Information Journal* 1999;33:869-875.
- Hyde AW. The Changing Face of Electronic Data Capture: From Remote Data Entry to Direct Data Capture. *Drug Info Jour* 1998;32:1089-1092.

Knatterud GL, Rockhold FW, George SL, Barton FB, Davis CE, Fairweather WR, Honohan T, Mowery R, O'Neill R. Guidelines for Quality Assurance in Multicenter Trials: A Position Paper. *Controlled Clinical Trials* 1998;19:477-493.

Meinert CL. *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York: 1986.

*Protection of Human Subjects*, Title 45 Code of Federal Regulations, Part 46. PRR Reports, Revised June 18, 1991, Reprinted April 2, 1996.

Psaty BM, Weiss NS, Furberg CD, Koepsell TD, Siscovick DS, Rosendaal FR, Smith NL, Heckbert SR, Kaplan RC, Lin D, Fleming TR, Wagner EH. Surrogate End Points, Health Outcomes, and the Drug-Approval Process for the Treatment of Risk Factors for Cardiovascular Disease. *JAMA* 1999;282(8):786-795.

Senturia YD, Mortimer KM, Baker D, Gergen P, Mithchell H, Joseph C, Wedner J. Successful Techniques for Retention of Study Participants in an Inner-City Population. *Controlled Clinical Trials* 1998;19:544-554.

Van der Putten E, van der Velden JW, Siers A, Hamersma EAM, for the Cooperative Study Group of Dutch Datamanagers. A pilot Study on the Quality of Data Management in a Cancer Clinical Trial. *Controlled Clinical Trials* 1987;8:96-100.

Weiss NS. *Clinical Epidemiology, The Study of the Outcome of Illness, Second Edition*. Oxford University Press, New York: 1996.

Witkin KB. *Clinical Evaluation of Medical Devices* Humana Press, Totawa, New Jersey: 1998.

Wittes J. Behind Closed Doors: The Data Monitoring Board in Randomized Clinical Trials. *Statistics in Medicine* 1993;12:419-424.

## **XXXII. RELEVANT WEBSITE LINKS:**

### **A. National Institute of Neurological Disorders and Stroke (NINDS):**

- [NINDS protocol template](#)
- [Data and safety monitoring board guidelines](#)
- [NINDS "tool kit" for investigators interested in performing NINDS-sponsored clinical research](#)

## **B. National Institutes of Health (NIH):**

- [Guidance on financial conflicts of interest and research objectivity for IRBs and investigators](#)
- [Bioethics Resources on the Web](#)

## **C. Food and Drug Administration (FDA):**

- [FDA Good Clinical Practice regulations](#)
- [FDA Center for Drug Evaluation and Research](#)
- [FDA Center for Biologicals Evaluation and Research:](#)
- [FDA regulations on electronic records and electronic signatures](#)
- [FDA application for an Investigational New Drug](#)
- [FDA Guidelines for protection of human subjects](#)

## **D. Department of Health and Human Services (DHHS):**

- [Office of Human Research Protections' Regulations on conducting research with human subjects](#)
- [FDA Ethical Principles and Guidelines for the Protection of Human](#)
- [Subjects of Research \("The Belmont Report"\)](#)
- [Guidance for writing informed consent documents from the HHS Office of Human Subjects Research Protections](#)
- [DHHS Office for Civil Rights - HIPAA Information](#)
- [Protecting Personal Health Information in Research - Understanding the HIPAA Privacy Rule](#)

## **E. NIH Guide Notices:**

- **Gene Therapy, Stem Cells and Fetal Tissue:**  
[http://grants.nih.gov/grants/policy/gene\\_therapy\\_20000307.htm](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>