

1 PURPOSE

This guidance describes the requirements, recommendations and procedures of the National Institute of Neurological Disorders and Stroke (NINDS) Division of Intramural Research (DIR) for the inclusion and implementation of data and safety monitoring plans (DSMPs) in research protocols conducted within the NINDS DIR. The purpose of a DSMP is to ensure, to the extent possible, the safety of research subjects and the integrity of research data consistent with regulatory and NIH requirements. This guidance is an effort to operationalize applicable NIH and HHS policies and regulations for the NINDS DIR.

2 POLICIES AND REGULATIONS

The Deputy Director of Intramural Research, NIH Quality Officer, Institutes and Centers, Office of Human Subjects Research Protections (OHSRP), IRBs, and investigators work together to carry out the NIH Human Research Protection Program (HRPP). In accordance with regulatory requirements (45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6) (Criteria for IRB approval of research), and 21 CFR 50.24(a)(7)(iv) (Exception from informed consent requirements for emergency research)), the NIH HRPP requires the inclusion of DSMPs in all research protocols submitted to NIH IRBs (OHSRP SOP 17). Each IC is responsible for ensuring that each study's DSMP provides adequate protection of research subjects and safeguards scientific integrity. Data and safety monitoring must be performed on a regular basis throughout the participant accrual, treatment, and follow-up periods.

3 DEFINITIONS

Listed in Appendix H.

4 PROCEDURE

Data and safety monitoring activities should be appropriate to the trial phase, participant population, research environment, and degree of risk involved.

4.1 Data and Safety Monitoring Plan (DSMP)

The DSMP is part of the research protocol. The DSMP should be present for all studies, no matter which DSM entity is selected. The study principal investigator (PI) will develop a DSMP, which should be established prior to IRB approval of the study. The final determination on the elements of monitoring required for each study is made by the NINDS Clinical Director (CD) and the IRB during the initial review of the study. The NINDS CD and/or IRB may require a different type of monitoring than is specified in the PI's proposed DSMP. In addition, the DSM entity (i.e., Independent Medical Monitor (IMM), the Safety Monitoring Committee (SMC), or the Data and Safety Monitoring Board (DSMB)) must approve the plan,

or recommend changes, before the study starts enrollment. The DSM entity may also make recommendations for changes at any time during the study.

The DSMP should include the following elements:

- Type of DSM entity (PI/Investigator only, IMM, SMC, or DSMB)
- Name(s) and credentials of the DSM entity member(s)
- Review frequency
- Nature of review (e.g., access to blinded/unblinded and/or interim data)
- Method and timing of reports
- If SMC, DSMB: meeting details (e.g., in-person meetings/teleconferences)
- As applicable:
 - Interim analysis, if planned
 - Reporting schedule for notifying the sponsor and, as applicable, the DSM entity about AEs and UPs
 - Stopping rules
 - Procedures for communication between all involved parties (e.g., PI, research team, DSM-entity, sponsor, regulatory bodies, etc.)

The DSM entity should meet with the PI to approve or make recommendations to change the DSMP prior to the enrollment of the first study subject. If the DSM makes recommendations that change the plan approved by the IRB, the protocol must be amended to incorporate those changes and approved by the IRB before the study can proceed.

4.2 Types of Data and Safety Monitoring

OHSRP SOP 17.4.A. provides examples of DSM mechanisms (referred to in this guidance as “entities”). The example provided in SOP 17.4.A.3 (“Monitoring by a group of experts, which may be a DSMB”) has been expanded below to list both a Data and Safety Monitoring Board (DSMB) and a Safety Monitoring Committee (SMC) as potential “groups of experts” who may be specified as the DSM entity.

- Data and Safety Monitoring Board (DSMB)
- Safety Monitoring Committee (SMC)
- Independent Medical Monitor (IMM)
- Principal Investigator (or PI-designated investigator or individual)

A study may have more than one type of DSM entity.

At the NINDS IRP, the role of the ‘data’ monitor per OHSRP SOP 17 is being addressed in accordance with the NINDS Quality Assurance SOP.

4.2.1 Determining the type of DSM entity for clinical research studies conducted at the NINDS DIR

Below are examples of determinants for each type of DSM entity.

DSMB

A DSMB must be established for studies that fall into any of the following categories:

- Phase III Clinical Trials
- Multi-site Clinical Trials in which there is a need for investigators to submit reports of adverse events to a central reporting entity
- FDA regulated trials for emergency research with an exception from informed consent (21 CFR

50.24(a)(7)(iv)) required

Safety Monitoring Committee (SMC)

A DSMB may be appropriate for the following types of studies. At a minimum, a SMC is recommended for:

- Trials with more than one intervention (e.g., controlled trial) where study endpoints that are highly favorable/unfavorable would ethically mandate early termination
- Trials with high possibility of severe study-related adverse events (AEs) based on prior knowledge
- Greater than minimal risk trials that include vulnerable populations
- Blinded treatment groups in which the validity and integrity of the trial may be adversely affected by having an individual (or group) associated with the design and conduct of the trial break the blind
- High risk interventions (e.g. gene transfer or gene therapy, a drug with significant toxicities) where death or severe disability is a major risk of research participation, or testing a new intervention where limited safety data is available
- A controlled trial in which mortality or major morbidity is a primary or secondary endpoint

Independent Medical Monitoring (IMM)

An IMM is recommended for studies that fall into any of the following categories that do not otherwise require an SMC or DSMB:

- Greater than minimal risk studies
- Multi-site clinical research studies or clinical trials, other than determined above
- FDA regulated trials, other than determined above
- Trials with more than one intervention (e.g., controlled trial) and the investigator(s) are blinded to intervention
- Endpoints that are not serious irreversible events
- Intervention that is not high risk and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness
- Short term intervention where effects are evaluated over periods of a few days to a few months
- Small number of research subjects, a short period of time and risk that can be adequately assessed through simple comparisons
- Trials in which the PI or Medically Advisory Investigator (MAI) have a conflict of interest

PI/Investigator Monitoring

The PI should monitor data and safety for all studies, regardless of the type of DSM entity listed in the DSMP. If a different DSM type is not otherwise required or recommended, it may be appropriate for the PI or a qualified study investigator to be the sole DSM entity for studies that fall into both the following categories:

- No more than minimal risk studies or a minor increase over minimal risk
- Single-site studies

In such cases, continuous monitoring of events by the PI/designated AI, and prompt reporting of toxicities/SAEs/UPs to the sponsor, FDA, IRB, and/or other regulatory bodies as applicable, may be adequate. The details of the PI/designated AI DSMP should be included in the protocol DSMP section. If not covered under requirements for expedited reporting, a report on the monitoring activities and

findings by the PI / designated AI will be submitted to IRB as part of the annual continuing review.

4.3 General DSM procedures

The following procedures apply to all DSM entities.

4.3.1 Data and Information to be Monitored

The DSM entity is responsible for evaluating the progress of the study, including periodic assessments of aggregate data, participant recruitment, accrual and retention, overall risk versus benefit, performance of study sites, and other factors that can affect study outcome. The DSM entity should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may impact the safety of the participants or the ethics of the study. If an interim analysis is desired, this should be pre-specified in the protocol.

Interim Reports

The frequency and method of interim reports will be specified in the DSMP. The content of the interim report should be pre-specified. An interim report template can be found in Appendix G.

Interim Analysis, Stopping/Pausing Criteria, and Futility Analysis

If an interim analysis is planned, the following parameters should be pre-specified in the protocol:

- Timing of the interim analysis relative to study milestones
- A statistical analysis plan (and the effect of the analysis on alpha).
- Any pre-specified plans to modify key aspects of the study design (e.g., sample size, randomization)
- Any decision rules (e.g., for stopping or pre-planned modifications)
- Procedures for recommending early termination.

If the DSM entity determines that a trial: (a) has answered the primary study question; (b) is futile; (c) will not be able to reach a firm conclusion; (d) cannot recruit participants within a reasonable timeframe; (e) is not being conducted according to scientific or ethical standards; or (f) poses an unreasonable or unnecessary risk to study participants, the DSM entity will recommend to the PI (and the NINDS Clinical Director for NINDS sponsored trials) that the study protocol be amended, temporarily suspended, or terminated, as appropriate. See section 4.3.4 below for reporting guidelines.

Access to Unblinded Data

The DSM entity must have access to the unblinded treatment assignments and data. This can be accomplished in several ways:

1. DSM entity can be blinded, with access to unblinded treatment information upon request.
2. For DSMB/SMC, the majority of the Committee can be blinded, with one member (ideally a clinician) unblinded to treatment assignment; that member will unblind remaining members if warranted.
3. DSM entity is fully unblinded. For DSMB/SMC, the study statistician(s) performing analysis to present to the DSM entity may also be unblinded. In this case, the study statistician can be present in closed session.

It is recommended that safety and/or efficacy data is reported by coded study group or unblinded. These reports should be prepared by an unblinded member of the study team (e.g., designated investigator, statistician, pharmacist, etc.) and available only to the unblinded DSM entity, and be

withheld from the sponsor and the blinded investigators until the study is complete or the blind is broken.

4.3.2 Conflict of Interest (COI)

Each IMM or DSMB/SMC member must review the *Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH* (referred to here forward as “the Guide”), and adhere to the rules set forth in the Guide. Specific examples of COI can be found in section III and IV of the Guide. Each DSM entity member must sign the “*Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH*” Acknowledgement Form (Appendix B) prior to beginning review activities, and at least annually thereafter. DSM entity members are required to report any change in COI. The Acknowledgement Form should be kept in the study file. Additional instruction for DSMBs can be found in the DSMB Charter: Template, section 4.

4.3.3 DSM Entity Compliance

Suspected DSM non-compliance (e.g., breach of confidentiality, non-reported conflicts of interest, non-compliance with DSMP) should be reported to the study sponsor and the NINDS CD, and to the IRB as required. The NINDS OCD will conduct periodic compliance reviews of DSM operations. In addition, Quality assurance (QA) audits/monitoring will include a review of DSMP adherence.

4.3.4 DSM Entity Minutes, Reports, and Recommendations

DSM entities (IMM, SMC, DSMB) decisions and recommendations should be documented. The DSM entity submits recommendations to the PI concerning continuation, modification, suspension or termination of the study based on the DSM entity's assessment. DSM entity meeting minutes and/or recommendations should include the date of review, what information was reviewed, an assessment of the information reviewed, and recommendation based on the review. In addition, DSMB and SMC meeting minutes should be divided into open and closed section minutes. Closed session minutes should not be circulated until the trial is terminated. DSM entity minutes, recommendations, and other materials provided to Board members are subject to possible release in redacted form within the Freedom of Information Act (FOIA) (Freedom of Information Act, 5 U.S.C. 552(a)). Minutes/reports must not include any confidential outcome data or any information about trends from blinded or multicenter studies, unless that information is essential to substantiate a finding by the DSM entity (e.g., consideration of stopping a study if recommended by the NINDS CD). All recommendations by the DSM entity will be communicated to the PI in writing. Safety/serious concerns should be communicated immediately.

The PI must promptly submit all DSM entity reports and recommendations to the IRB and NINDS OCD (in cases where the DSM entity does not directly report to the NINDS OCD, e.g., for studies with an outside sponsor). “Promptly” should be defined in the protocol with a specific timeframe for reporting. The PI must report recommendations to suspend or terminate the protocol, or that require taking other immediate actions to ensure the safety of human subjects, to the IRB and NINDS OCD (when not already directly reported to the NINDS OCD) as soon as possible and in writing not more than 7 days after the PI receives the recommendations.

The IRB Chair reviews the reports as they are received, and may recommend review by the convened IRB at any time. The convened IRB should review all monitoring reports since the date of the last IRB review and approval at the time of continuing review. The PI may further circulate the communications to the FDA, study sponsor, collaborators, and/or other required partners (e.g. CRADA partner), if applicable and within required timeframes.

After receipt of the DSM entity recommendations (if any), the PI is responsible for implementing agreed upon recommendations.

If the PI does not agree with the recommendations, a justification for why recommendations will not be followed must be provided. This communication to the DSM entity should be in writing. The DSM entity may submit further comments back to the PI. If there is a disagreement requiring resolution, the NINDS CD has the authority to override the recommendations of the DSM entity. If the NINDS CD does not approve a DSM entity recommendation, the DSM entity will be provided with a justification from the NINDS CD through the PI. All involved parties will be notified of the outcome in writing. The PI will forward the minutes, including correspondence as necessary to document the disagreement if not included in the minutes, to the IRB based on the reporting guidelines documented in the DSM plan.

All written communications between the DSM entity and the PI need to be maintained in the regulatory file.

Any changes to the protocol or trial documents as a result of the DSM entity recommendations must first have IRB approval (via an amendment to the protocol) prior to implementation except as needed to prevent imminent harm. As stated above, these instances should be reported to the IRB as soon as possible and in writing not more than 7 days after the PI receives the recommendations.

Amendments to FDA-regulated protocols must also be submitted to the FDA. If the DSM entity recommends substantial changes to the protocol, it may be advised to consult with the FDA prior to submitting the amendment.

If the PI (or PI-designated investigator or individual) is the monitor, they need to assure data and safety are monitored in accordance with the protocol DSM plan. Data and safety monitoring concerns (e.g. AEs, SAEs, UPs, Deviations, Non-compliance) should be reported to the IRB, sponsor, and other applicable regulatory bodies promptly (as defined in the protocol).

4.3.5 DSM Entity Administration

The NINDS OCD is responsible for providing administrative resources for DSM entity operations. The PI will estimate potential DSM entity expenses at the time of initial review of the protocol. Unless otherwise covered, for DSMBs, the PI may submit a DSMB expense request to the NINDS OCD (support request form: Appendix F). Upon review and approval, the NINDS OCD will cover DSMB expenses.

4.4 Data and Safety Monitoring Board (DSMB)

4.4.1 DSMB formation

If it has been determined that a DSMB will monitor the study, the DSMB members should be selected. Boards may be as few as three members, and should consider having an odd number of members to avoid tied votes. The precise number of DSMB members and their areas of expertise will be dictated by the complexity of the study. One member is designated by the PI as the Chair. Membership should consider the following:

- Appropriate scientific expertise pertinent to interpret study data
- Experience for the trial (e.g., clinician, biostatistician, ethicist, toxicologist, epidemiologist,

- clinical pharmacologist, or other experts)
- No COI
- Prior DSMB experience for at least one member of the DSMB

The DSMB members should be nominated by the PI and approved by the IRB and NINDS CD. Any changes of DSMB members should be reflected in an amendment to the DSMP, and communicated to the IRB accordingly.

4.4.2 DSMB Member Training

Prospective DSMB members without prior DSMB experience should undergo DSMB member training (see Appendix A for a URL for DSMB member training).

4.4.3 DSMB Meetings

DSMB initiation meeting

Prior to enrollment of first study subject, the DSMB will convene an initial implementation meeting to:

- Approve the DSMP or submit requests for modifications
- Approve the DSMB charter document.

The DSMB charter document should include:

- Definition of the roles and responsibilities of the DSMB
- Delineation of qualifications of the membership
- Meeting frequency, schedule, location, and format.
- Details of the monitoring plan including the nature of review (e.g., access to blinded/unblinded and/or interim data)
- Outline and content of DSMB reports.
- COI assessment of each member and management plan (if needed)

The DSMB charter should be proposed by the PI and modified/confirmed by the DSMB.

Convened DSMB meetings:

Meetings should convene in real time, either face-to-face or via passcode-protected tele- and/or web-conference. Precautions should be taken to ensure confidentiality. A quorum of greater than 50% of the voting members should be present for the meeting to proceed. DSMBs should meet at least annually or more often depending on the nature of the trial.

Below are the types of sessions that may constitute a DSMB meeting:

- Open Session: may include PI, study statistician, study staff, DSMB members, DSMB/NINDS administrative staff, other parties at the discretion of the DSMB chair
- Closed Session: restricted to DSMB members, DSMB/NINDS administrative staff, and additional invited unblinded attendees (e.g., unblinded pharmacist, unblinded statistician)
- Closed Executive Session: restricted to voting DSMB members and DSMB/NINDS administrative staff

In urgent matters, DSMB members might conduct reviews electronically without convening a formal meeting (e.g., SAE determination). In these instances, the communication must be retained in writing.

4.5 Safety Monitoring Committee (SMC)

A SMC will follow the same procedures as listed for DSMBs (see section 4.4, above) with the following exceptions.

- A SMC may consist of 2 or more members
 - If a SMC only has 2 members, both must be present at the time of scheduled meetings; otherwise, a quorum of greater than 50% must be present
- Members of an SMC may be NINDS employees, but must be independent and free of COI
- A SMC does not require a charter. If a SMC has no charter, the DSMP must include the following:
 - Frequency of meetings
 - Meeting format (in person, tele-conference, web-meeting)
 - Nature of review (e.g., access to blinded/unblinded and/or interim data)
 - Member list and qualifications
 - Method and timing of interim reports, if applicable

4.6 Independent Medical Monitor (IMM)

The DSMP may delineate an IMM as a DSM entity. The IMM may be a NINDS employee, but must be independent and free of COI. Procedures described in section 4.3 (General DSM procedures) should be followed. The IMM will review any reports submitted by the PI. All recommendations by the IMM will be communicated to the PI in writing. Safety/serious concerns should be communicated immediately. The PI may further circulate the communications to the IRB and FDA, if applicable.

4.7 Responsibilities of a study sponsor

Sponsor responsibilities (including reporting to the FDA) are delineated in 21CFR312 Subpart D, and ICH E6 Section 5. The DSM entity will submit all communications to the PI and copied to the NINDS OCD for PI or NINDS sponsored studies. If the PI or NINDS are not the study sponsor, it will be the PI's responsibility to submit the DSM communications to the sponsor, unless the study sponsor has made other arrangements with the DSM entity. The study sponsor is responsible for reporting to the FDA. The PI is responsible for reporting to the IRB and NINDS OCD for outside sponsored studies.

If the PI or NINDS is the study sponsor, NINDS OCD office is responsible for ensuring that conflict of interest requirements are addressed for the DSMB members, as applicable (see OHSRP SOP 21).

4.7.1 Study sponsor external to NINDS

Clinical trials conducted by the NINDS Intramural Research Program may involve an external sponsor. In this case, the monitoring plan is expected to meet the requirements of this guideline. The NINDS will work with the PI and the sponsor to amend the documents to meet the requirements of this guideline. The PI should forward DSMB reports to the NINDS OCD.

APPENDIX

A. LINKS

NIH Policy for Data and Safety Monitoring; June 10; 1998

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

Further Guidance on A Data And Safety Monitoring For Phase I And Phase II Trials;

June 5, 2000

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

Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees (FDA-March 2006):

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

21 CFR 50.24(a)(7)(iv)) Exception from informed consent requirements for emergency research

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24>

NIH HRPP SOP 17: Data and Safety Monitoring

https://federation.nih.gov/ohsr/nih/ohrdocs/SOP_17_v2_3-8-2016_508.pdf

NIH HRPP SOP 21: Conflict of Interest Requirements for Researchers and Research Staff and “A Guide to avoiding Financial and Non-financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH” (Appendix A)

https://federation.nih.gov/ohsr/nih/ohrdocs/SOP_21_v4_10-20-15_AppD4-16-16.pdf

NIH HRPP SOP 23: Quality Management system for the NIH HRPP

https://federation.nih.gov/ohsr/nih/ohrdocs/SOP_23_v3_2-24-2016_508.pdf

Human Research Protection Regulations (45 CFR 46):

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance, But Facing Some Issues (OIG Report June 2013)

<https://oig.hhs.gov/oei/reports/oei-12-11-00070.asp>

DSMB Member training:

<https://dsmblearningcenter.niaid.nih.gov>

NINDS (Extramural) Guidelines for Data and Safety Monitoring in Clinical Trials

http://www.ninds.nih.gov/research/clinical_research/policies/data_safety_monitoring.htm

NIAID Policy on the Intramural Research Program Data and Safety Monitoring Board; Effective December 21, 2010

<http://www.niaid.nih.gov/researchfunding/sop/pages/dsmb.aspx>

B. DSMB Charter: Template

[INSERT NAME OF TRIAL]

[Insert name of PI]

Data and Safety Monitoring Board Charter – Version; [DATE]

1. PURPOSE

The Charter defines the primary responsibilities of the Data and Safety Monitoring Board (DSMB) for the study [INSERT TITLE], which is conducted by the National Institute of Neurological Disorders and Stroke (NINDS). The DSMB will act in an advisory capacity to the study Principal Investigator (PI) and the NINDS Clinical Director (CD) to monitor participant safety, data quality and evaluate the progress of the study. The NINDS establishes DSMBs to provide independent, expert advice to the Institute regarding the safety and credibility of Institute-supported clinical trials. This charter will define the roles and responsibilities of the DSMB, delineate qualification of the members, describe the processes for conducting the DSMB meetings, and communication with the PI and NINDS Office of the Clinical Director (OCD). This charter will serve as the Standard Operating Procedure (SOP) for the DSMB. The DSMB will be independent of the sponsor, regulatory agencies, IRBs, and investigators. The DSMB will serve in accordance with the guidelines set forth in this charter.

2. DSMB RESPONSIBILITIES AND FUNCTIONS

The DSMB has the general charge of ensuring that the trial is conducted safely and ethically and that the trial meets its primary objectives. This includes the interests of currently enrolled participants and future participants, but also includes the interests of society. The DSMB is charged with making recommendations to the PI and CD with regards to the conduct of the trial. To these ends the DSMB has the following responsibilities and functions:

- review and acknowledge the protocol, including the data and safety monitoring plan (DSMP) and data analysis plan, before enrollment of the first subject; and provide opinion/advice on any substantial amendments to the protocol at any time, per the discretion of the PI or CD
- establish and confirm a DSMB Charter at the first DSMB meeting
- evaluate cumulative safety data; determine specific safety concerns that may arise during the conduct of the trial; and provide recommendations based on the DSMBs review
- perform periodic assessments of the following, as applicable: data quality, completeness and timeliness; performance of the study site(s), including participant recruitment, accrual and retention, compared to accrual targets; status of enrolled participants, overall and by treatment group (on/off study, on/off treatment, withdrawals/lost-to-follow-up, etc.); participants off-treatment, including the reason for discontinuation; participant baseline characteristics, overall and by treatment group; protocol deviations and Unanticipated Problems (UPs), including review of participant eligibility criteria and non-adherence to other protocol requirements; participant adherence to treatment regimen (e.g., based on pill counts or diaries); overall risk versus benefit; and other factors that can affect study outcome
- consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may impact the safety of the participants or the ethics of the study
- evaluate data per a pre-specified interim analysis plan, if included in the protocol

- make recommendations to the investigators concerning continuation, termination, or other modification of the study based 1) on the observed benefits or adverse effects of any of the investigations under study (overall risk versus benefit); and 2) the unlikelihood that a meaningful assessment of treatment effect could be established by the planned end of the trial
- review the general progress of the study and to assist in resolving any problems which may arise

3. MEMBERSHIP

The DSMB members and Chairperson were appointed by the study PI and approved by the CD and IRB. The members reflect the disciplines and medical specialties necessary to interpret the data from the study and ensure participant safety. The voting member of the DSMB consists of **[LIST ALL MEMBERS (N ≥ 3) BELOW, ADD/DELETE LINES AS NEEDED]**:

Chair Name & Discipline/Specialty area:
Voting member? Yes No

Name & Discipline/Specialty area:
Voting member? Yes No

Name & Discipline/Specialty area:
Voting member? Yes No

Name & Discipline/Specialty area:
Voting member? Yes No

Name & Discipline/Specialty area:
Voting member? Yes No

[INCLUDE THIS SECTION IF THE STUDY HAS AN INDEPENDENT MEDICAL MONITOR (IMM)] At times the expertise of the IMM may also be required, at which point an invitation will be extended to review study data and/or attend DSMB meetings.

The IMM is: **[NAME]**.

The DSMB Chair, in addition to **his/her** responsibilities as a DSMB member, is responsible for chairing and overseeing all meetings, reviewing and approving meeting minutes and reports, and acting as the primary contact within the DSMB for the immediate reporting of Serious and Unexpected Adverse Events.

[CONSIDER IDENTIFYING AN ALTERNATE CHAIR IN THE EVENT THE DSMB CHAIR IS UNAVAILABLE. IF YES, INCLUDE THE FOLLOWING] In the event the DSMB Chair is unavailable, **[INSERT NAME OF ALTERNATE HERE]** will serve as the Acting DSMB Chair until the DSMB Chair is available to resume **his/her** duties. A quorum (based on the number of members including the DSMB Chair) will still be required for meetings to proceed.

DSMB members are appointed for the duration of the trial.

- DSMB members in agreeing to serve, understand the responsibilities include making time for preparing and attending scheduled DSMB meetings, as well as to devote time and attention to other matters deemed necessary, such as Serious Adverse Event (SAE) reviews.
- While attendance of all DSMB members is preferable, in order to conduct a DSMB meeting, a quorum of greater than 50% of the voting members should be present to proceed. If the DSMB Chair is unable to attend, he/she may appoint another DSMB member to Chair the meeting.
- If any member leaves the Board or is dismissed during the course of the study, the reason(s) for their departure will be recorded and filed. If a member leaves the Board, the PI will propose a replacement to be approved by the CD and IRB.

4. INSERT ADMINISTRATIVE COORDINATOR/CONTRACTOR HERE IF APPLICABLE

The [SPECIFY CONTRATOR HERE] is the administrative Coordinating Center for the DSMB, under contract with NINDS. The Coordinating Center responsibilities include:

- Acting as the liaison between the DSMB members, study investigators and NINDS CD
- Providing a secure website for transfer of confidential reports and materials
- Organizing the DSMB meetings
- Providing a DSMB Secretary to write the meeting minutes and obtaining approval of the minutes from, at minimum, the DSMB Chair and the NINDS CD
- Obtaining and reviewing Conflict of Interest (COI) forms for all DSMB member; Any interest perceived as a conflict will be reviewed with the NINDS CD

5. CONFLICT OF INTEREST (COI)

Each DSMB member must review the *Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH* (referred to as “the Guide”), and adhere to the rules set forth in the Guide. Specific examples of COI for DSMB members can be found in section III and IV of the Guide. Each DSMB member must sign the “*Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH*” Acknowledgement Form prior to beginning review activities, and at least annually thereafter. The Acknowledgement Form should be kept in the study file.

Individuals invited to serve on the DSMB will disclose verbally and in writing any real or apparent COI at the initial DSMB meeting. Real and apparent COIs must be discussed by the DSMB to determine if/how the COI can be resolved. Those with COI are excluded from serving on NINDS DSMBs. Individuals with a COI may be present to provide information requested by the DSMB, but they cannot serve as voting members. The minutes will reflect the COI discussion, which individual(s) has a real or apparent COI, as well as the resolution.

At the beginning of every meeting, the [SPECIFY DSMB Chair, coordinating site, DSMB Secretary, or person responsible coordinating meetings/taking minutes] will ask members to disclose any changes to their COI. The COI discussion will be documented in the minutes.

6. HALTING/STOPPING CRITERIA

The halting/stopping criteria (as determined by the study PI) include:

- INSERT HALTING/STOPPING CRITERIA FROM THE STUDY DSMP HERE

The PI, IRB, CD, the Sponsor [IF NOT NINDS], or the FDA may halt the study at any time following review of any safety concerns. The DSMB [ADD "or the IMM" IF APPLICABLE] may recommend a study halt.

Specific events that would lead to the halting of the study and potential termination will include:

- [LIST EXAMPLES HERE, IF NEEDED, BASED ON THE STUDY DSMP]

Reporting a Study Halt: The PI must inform the OCD, IRB and the DSMB that a halting rule has been met, including a description of the event(s) or safety issue(s). [EDIT AS NEEDED IF THE DSMB IS TO DETERMINE IF A HALTING/STOPPING CRITERIA HAS BEEN MET]

Resumption of a Halted Study: The PI, CD, DSMB, IMM and the IRB will determine if it is safe to resume the study. The conditions for resumption of the study [DEFINED HERE].

7. MEETINGS

The Board will meet at intervals specified by the needs of the trial, via [SPECIFY MEETING TYPE HERE: Face-to-Face meeting, conference call, web-meeting; IF NOT FACE-TO-FACE, STATE WHICHEVER APPLIES: a password protected phone line/secured webmeeting will be used], which include:

- [LIST MEETING TIMEPOINTS HERE; the DSMB should meet at least annually while the study is open to enrollment or has participants in active follow-up, and more frequently if needed.]

Additional meetings may be scheduled when necessary for adequate monitoring. Any member of the DSMB may request a meeting if they believe data provided within interim reports warrant an additional meeting.

7.1. Initial DSMB review

The DSMB will review and acknowledge the protocol, including the DSMP and data analysis plan, with recommendations as appropriate, as well as establish and confirm the DSMB Charter, as stated above in section 2. COI of each member will be reviewed, and the Conflict of Interest and Confidentiality Statements will be collected and retained (see section 4). The DSMB may provide expectations for the reports provided by the study investigator; however, these standards may evolve over the course of a study.

7.2. Subsequent DSMB review

Subsequent DSMB review will be convened as specified above. Prior to each DSMB review, the study investigators will submit [ADD OR DELETE THE BELOW AS APPROPRIATE FOR EACH STUDY]:

- Summary of accrual, overall and by study site, compared to accrual targets.
- Summary of baseline characteristics, overall and by treatment group.
- Summary of the data completeness (e.g., percentage of missing data).

- Summary and status of study participants, overall and by treatment group (e.g., proportion of subjects on- and off-study, on- and off-treatment, including screening failures, withdrawals and drop-outs).
- Assessment of participant adherence to the treatment regimen, overall and by treatment group (e.g., drug accountability report).
- List of individual SAEs, including PI's determination of relatedness.
- List of AEs by treatment group and body system including summary of cumulative rates, overall and by treatment group.
- If an interim analysis is scheduled, summary of outcome data by treatment group.
- List of protocol deviations, unanticipated problems (UPs), and non-compliance, if any.
- Summary of protocol amendments since the last DSMB review

[RECOMMENDED; INCLUDE AS APPLICABLE] Interim reports, which include safety data and/or comparative effectiveness data, should be reported by study group and be [coded by group/completely unblinded]. These reports should be available only to DSMB members (i.e. presented during closed session), and be withheld from the sponsor and investigators until the study is complete or the blind is broken. [ADD THE FOLLOWING IF THE RANDOMIZATION IS STRATIFIED (E.G., BY AGE)] These tables and figures [may/will] be presented by strata.

In addition to the above, the DSMB may request additional information to aid in their determination. This may include recommendations to include additional content or to change the format of the data provided.

7.3. DSMB meeting format

DSMB meetings will be divided into the below types of sessions [LIST ALL AS APPROPRIATE], with the expected attendees as listed:

- Open Session: may include PI, study statistician, study staff, DSMB members, DSMB/NINDS administrative staff, other parties at the discretion of the DSMB chair
 - Trial progress such as patient accrual, baseline characteristics, safety data, statistics and outcome data may be presented and discussed
- Closed Session: restricted to DSMB members, DSMB/NINDS administrative staff, and additional invited unblinded attendees ([ADD/DELETE AS APPROPRIATE:] unblinded pharmacist, unblinded statistician, IMM, or other may be requested to attend by DSMB)
 - Study progress is discussed, and the DSMB will vote/make recommendations
- Closed Executive Session: Only voting DSMB members and DSMB/NINDS administrative staff
 - Used only if non-DSMB members or non-voting DSMB members are present at the closed session; to allow the DSMB to reach an independent decision

7.4. DSMB Vote

The DSMB will vote and make recommendations and decisions to continue, modify or terminate the study during the closed session as described above. If there is a tie, the Chair will be the deciding vote. In the case of a 3 member board, if only 2 members are present for a meeting and there is a tie, they should attempt to get the opinion of the 3rd member if at all possible. If there is not unanimous support for a decision, the recommendations will include a minority report.

8. DSMB ACCESS TO UNBLINDED DATA

For all blinded studies, DSMB members will have access to unblinded treatment assignments and data. [SPECIFY WHICH OF THE FOLLOWING WAYS THIS WILL BE ACCOMPLISHED]

1. DSMB members will be blinded, with access to unblinded treatment information upon request.
2. The majority of the DSMB will be blinded, with one member [SPECIFY; ideally a clinician] unblinded to treatment assignment. [SPECIFY NAME] will unblind the remaining members if warranted.
3. DSMB is fully unblinded. The study statistician(s) performing analysis to present to the DSMB may also be unblinded. In this case, the study statistician can be present in the closed session, followed by a separate executive closed session with DSMB members only.

9. DSMB RECOMMENDATIONS

Following the meeting, formal minutes will be prepared by [SPECIFY: coordinating site, DSMB Secretary, or DSMB member] to record the proceedings of the meeting. [INCLUDE THE FOLLOWING 2 SENTENCES IF OPEN SESSIONS WILL BE CONDUCTED] Meeting minutes will be divided into open and closed sessions. Closed session minutes should not be circulated until the trial is terminated. The minutes will include the DSMB's recommendations concerning continuing, modifying, suspending or terminating the study. [SPECIFY NAME] will provide the minutes to the DSMB Chair, at minimum, for approval. Once the minutes are approved, closed session minutes will be distributed to study investigators and the OCD.

The PI should respond to the DSMB recommendations in writing prior to the next scheduled DSMB meeting, unless the DSMB requests an earlier response. Safety/serious concerns should be communicated immediately.

If the PI does not agree with the recommendations, a justification for why recommendations will not be followed must be provided. This communication to the DSMB should be in writing. The DSMB may submit further comments back to the PI. If there is a disagreement requiring resolution, the NINDS CD or designee has the authority to override the recommendations of the DSMB. If the NINDS CD or designee does not approve a DSMB recommendation, the DSMB will be provided with a justification from the NINDS CD or designee through the PI. All involved parties will be notified of the outcome in writing.

The PI must promptly submit all DSMB reports and recommendations to the IRB. "Promptly" should be defined in the protocol with a specific timeframe for reporting. The PI must report recommendations to suspend or terminate the protocol, or that require taking other immediate action to ensure the safety of human subjects, to the IRB as soon as possible and in writing not more than 7 days after the PI receives the recommendations.

10. Confidentiality Procedures for DSMB Members

Materials/information made available to the DSMB that are not in the public domain, as well as discussions that take place during the meetings, are strictly confidential. Each member of the DSMB, including non-voting members, will be required to sign a confidentiality agreement.

C. DSM Entity Signature Forms

CONFIDENTIALITY AGREEMENT
for participation on a NINDS-supported
Data Safety Monitoring Board/Safety Monitoring Committee/Independent Medical Monitor
[change as needed for NIH-external DSM entity members]

This agreement is made by and between the National Institute of Neurological Disorders and Stroke (“NINDS”), part of the National Institutes of Health (“NIH”), an agency of the United States Government and _____, a person residing at _____ (“Participant”).

WHEREAS, NINDS is either fully or partially supporting a clinical trial to be conducted within its intramural program [*insert protocol number(s) and title(s) here*] (the “Study”) and has established a **Data Safety Monitoring Board (“DSMB”)/Safety Monitoring Committee (“SMC”)/Independent Medical Monitor (“IMM”)** to oversee the conduct, safety, and integrity of the Study; and

WHEREAS, NINDS is either overseeing the **DSMB/SMC/IMM** directly or indirectly through its contractor, **The EMMES Corporation**; and

WHEREAS, the Study involves the support of [*the company _____*] (“Entity”); and [*this is optional*]

WHEREAS, the Participant has the background and expertise necessary to be an active member on the DSMB; and

WHEREAS, the Participant agrees to fulfill his/her duties in accordance with the DSMB Charter, a copy of which is attached as Appendix A; and [*this is optional*]

WHEREAS, a major duty of the Participant is to maintain all confidential information as confidential and NINDS would like to memorialize these obligations below.

NOW, the parties hereto agree as follows:

1. NINDS will disclose and transmit Confidential Information to Participant as necessary to fulfill the functions of the **DSMB/SMC/IMM**. “Confidential Information” may include but not be limited to: business, technical, financial, personal and clinical information; intellectual property; reports, drawings, videos; data (raw and/or aggregate); information from the Entity regarding the Study treatment or marketing/strategy of such treatment [*edit this as needed*]; and any other information provided as part of Participant’s duties on the **DSMB/SMC/IMM**. Confidential Information may or may not be marked confidential and Participant should maintain information as confidential even if not marked when the confidential nature of such information would be reasonably apparent from the subject matter.
2. Participant agrees to accept the Confidential Information and employ all reasonable efforts to maintain the Confidential Information as secret and confidential, such efforts to be no less than the degree of care employed by Participant to preserve and safeguard his/her own confidential information. Participant will not disclose to, discuss or share Confidential Information with any person or third party *except as permitted under the DSMB Charter [use the italics only if this is discussed under the charter]*.
3. NINDS acknowledges that Participant will not incur any liability merely for examining and considering the Confidential Information; however, Participant agrees that it will not use the

Confidential Information for any purpose except as set forth herein and will not use it for his/her personal benefit.

4. Participant's obligations above will not extend to any part of the Confidential Information:
 - (a) that can be demonstrated to have been in the public domain or publicly known at the time of disclosure; or
 - (b) that can be demonstrated to have been in Participant's possession or that can be demonstrated to have been readily available to Participant from another source prior to the disclosure; or
 - (c) that becomes part of the public domain or publicly known by publication or otherwise, not due to any unauthorized act by Participant; or
 - (d) that can be demonstrated as independently developed or acquired by Participant without reference to or reliance upon such Confidential Information; or
 - (e) that is required to be disclosed by law or court order.

5. Participant's obligations hereunder will begin on the date of last signature below (the "Effective Date"). Participant understands that this obligation of non-disclosure extends beyond his/her participation as a member of the **DSMB/SMC/IMM** as long as the material associated with the review and the substance of any confidential discussions are not within the public domain. If Participant becomes aware that a breach of confidentiality has occurred due to his/her or others' actions, Participant will immediately notify NINDS [*and Entity, if appropriate*] and will assist as requested in mitigating the extent or damage of such disclosure. At the expiration of this agreement, or at the termination of Participant's role on the **DSMB/SMC/IMM**, Participant agree to either return or destroy all Confidential Information, as directed by NINDS.

6. All identifiable private information concerning the Study's subjects will be kept confidential indefinitely.

8. It is understood that nothing herein shall be deemed to constitute, by implication or otherwise, the grant to Participant of any license or other rights under any patent, patent application or other intellectual property right or interest belonging to NINDS [*or the Entity*].

9. The illegality or invalidity of any provision of this agreement shall not impair, affect or invalidate the other provisions of this agreement. This agreement constitutes the entire agreement between the parties with respect to the subject matter and supersedes any prior agreements and understandings (whether written or oral). No modification of this agreement will be effective unless made in writing and signed by both parties.

10. The construction, validity, performance and effect of this agreement shall be governed by Federal law, as applied by the Federal Courts in the District of Columbia.

11. [*reserved for additional terms*]

ACCEPTED AND AGREED

National Institute for Neurological Disorders and Stroke

Avindra Nath, M.D.
Clinical Director, NINDS

Date

Notices to:

Dietrich Haubenberger, M.D.
Staff Scientist – Director, Clinical Trials Unit
NINDS, NIH
9000 Rockville Pike, Building 10, Room 6C-5700
Bethesda, MD 20892
dietch.haubenberger@nih.gov

Participant

[Printed Name]

Date

Address:

“Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH” Acknowledgement Form

NAME: _____

Primary employer: _____

I have read the “**Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH**”.

- I do not have a conflict of interest (COI)

OR

- I have a real or apparent COI, which has been discussed and will be resolved
 - List COI(s)
 - List resolution

I acknowledge I cannot participate as a member of a NINDS DSM entity for which I have a COI and agree to immediately disclose any change that creates a real or apparent COI. I will provide information as needed to support an assessment of the potential COI.

By my signature below, I agree that the above statements are accurate and I will comply with the rules set forth in the guide.

Signature: _____ Date: _____

D. DSMB Meeting/Review Summary: Template

NAME OF STUDY

Data and Safety Monitoring Board (DSMB) Meeting

MEETING LOCATION (If in person):

Date:

Meeting Summary

Attendees:

DSMB voting members:

Name, degree (*DSMB Chair*)

Name, degree

DSMB non-voting members (if applicable):

Name, degree

Name, degree

NINDS Staff:

Name, degree, (role)

Name, degree, (role)

Name, degree, (role)

Investigators:

Name, degree (*PI*)

Name, degree (Medical Monitor)

Name, degree

Name, degree

Name, degree

Other attendees (if applicable):

Name, degree, reason for attendance

Name, degree, reason for attendance

Meeting held (DATE) by (telecon/webcon/in-person)

OPEN SESSION: Content to include

- Who participated in session (e.g., investigators and medical monitor, NINDS staff)
- Brief summary of key topics discussed. If protocol amendment discussed, reference protocol date or version number
- Include information on current N

CLOSED SESSION: Content to include

- First Meeting Only: confirm that NINDS DSMB guidelines were reviewed; indicate DSMB decision to be blinded/unblinded; clarify SAE reporting
- COI review/confirmation of lack of COI
- Confirm that confidentiality policy was reviewed

- Safety review discussion
- General issues discussed
- Indicate if non-DSMB members participated in part of the session

CLOSED EXECUTIVE SESSION (IF APPLICABLE): Content to include

- Brief summary of issues discussed
- Documentation of any votes

RECOMMENDATIONS:

Check the box below and include a statement whether the Board is unanimous in its decision, or the numbers for and against; for example- "The DSMB unanimously agrees on the following recommendations:"

- Continuation
- Modification (specify):
- Suspension (include rationale and criteria to lift the suspension):
- Termination (include rationale):

Future Reports to DSMB (content and date(s) due)

Next meeting – general time next meeting anticipated, format (telecon/webcon/in-person).

Indicate here who copies of the report are sent to (i.e., the PI and NINDS Office of the Clinical Director (OCD))

Respectfully submitted,

Signature
NAME
DSMB Chair

DATE:

NINDS: ___ Concurrence ___ Does Not Concur (explanation below)

Signature: _____ Date:

Name
Title
NINDS Clinical Director's Designee

E. SMC Meeting/Review Summary: Template

NAME OF STUDY

Safety Monitoring Committee (SMC) Meeting

MEETING LOCATION (If in person; or state "electronic" or "teleconference"):

Date:

Meeting Summary

Attendees:

SMC voting members:

Name, degree (*SMC Chair, if applicable*)

Name, degree

Medical Monitor (if applicable)

Name, degree

NINDS Staff:

Name, degree, (role)

Name, degree, (role)

Name, degree, (role)

Investigators:

Name, degree (*PI*)

Name, degree

Name, degree

Name, degree

Other attendees (if applicable):

Name, degree, reason for attendance

Name, degree, reason for attendance

Meeting held (DATE) by (telecon/webcon/in-person)

OPEN SESSION: Content to include

- Who participated in session (e.g., investigators and medical monitor, NINDS staff)
- Brief summary of key topics discussed. If protocol amendment discussed, reference protocol date or version number
- Include information on current N

CLOSED SESSION: Content to include

- First Meeting Only: confirm that NINDS DSM guidelines were reviewed; indicate SMC decision to be blinded/unblinded; clarify SAE reporting
- COI review/confirmation of lack of COI
- Confirm that confidentiality policy was reviewed
- Safety review discussion
- General issues discussed

- Indicate if non-SMC members participated in part of the session

CLOSED EXECUTIVE SESSION (IF APPLICABLE): Content to include

- Brief summary of issues discussed
- Documentation of any votes

RECOMMENDATIONS:

Check the box below and include a statement whether the Committee is unanimous in its decision, or the numbers for and against; for example- "The Committee unanimously agrees on the following recommendations:"

- Continuation
- Modification (specify):
- Suspension (include rationale and criteria to lift the suspension):
- Termination (include rationale):

Future Reports to SMC (content and date(s) due)

Next meeting – general time next meeting anticipated, format (telecon/webcon/in-person).

Indicate that copies of this summary should be distributed to the PI and NINDS Office of the Clinical Director (OCD).

Respectfully submitted,

Signature
NAME
SMC Chair

DATE:

F. NINDS –Data and Safety Monitoring Board Meeting Support Request Form

Title of the study this DSMB is monitoring:	
PI contact for details (name/phone):	
Expected number of DSMB meetings per year:	
Meeting dates and locations (if already established):	
Are lodging and travel arrangements required:	
Confirm honorarium amount (not to exceed \$400 per meeting day):	
Is assistance with locating meeting rooms required and if so please note any audiovisual requirements:	
Expected number of DSMB conference calls per year:	
Will these meetings need a science writer to prepare minutes and a summaries:	
Please note any other pertinent details:	

- Please attach a list with contact information for the supported DSMB members as well as any other meeting participants who are not supported. Be sure to identify those who will be supported.
- Please also attach a copy of the protocol.
- Submit this form to the NINDS Office of the Clinical Director.

G. Interim Report Template

[NAME] DSM meeting [Date]

Pre-meeting summary report

General overview

Brief overview of the highlights from the reporting period.

Description of Study Progress

Include a detailed description of the study progress in the last year. Suggestions of things to include are:

- If an interim analysis is scheduled, summary of outcome data by treatment group.
- Summary of publications/finding since the last DSM meeting/review.
- Any major scientific, protocol related, or safety updates since the last DSM meeting/review.
- Summary of the data completeness (e.g., percentage of missing data).
- Assessment of participant adherence to the treatment regimen, overall and by treatment group (e.g., drug accountability report).
- Study milestones reached.
- Any concerning SAE/AE trend here, especially if the DSM brought it up as a concern previously.

Adverse events

Include summary of cumulative rates of AEs, overall and by treatment group (if known).

List of AEs by treatment group and/or body system should be attached (coded AE log).

Serious Adverse Events

XX SAEs have been reported to the IRB since the beginning of enrollment, **XX** in the last year.

SAEs in the last year:

List of individual SAEs, including PI's determination of relatedness.

State if changes/no changes were made to the protocol and consent in response to adverse events.

Problem Reporting: Protocol deviations, unanticipated problems (UPs), and/or non-compliance

XX protocol deviations have been reported to the IRB since the beginning of enrollment, **XX** in the last year. (Specify how many UPs and non-compliances, if any)

Problems in the last year:

List of protocol deviations, unanticipated problems (UPs), and non-compliance.

Amendments

XX protocol amendments have been approved by the IRB for this study (Amendments X-XXX). XX new amendments have occurred in the last year.

Amendments in the last year:

Summary of protocol amendments since the last DSM review

Recruitment, Enrollment, and Study Adherence

Things to include in this section

- Summary of accrual, overall and by study site, compared to accrual targets.
- Summary of baseline characteristics, overall and by treatment group.
- Summary and status of study participants, overall and by treatment group (e.g., proportion of subjects on- and off-study, on- and off-treatment, including screening failures, withdrawals and drop-outs).

Accrual progress

XX participants have been enrolled into the X and XX cohorts. X were enrolled in cohort X. XX were enrolled into cohort XX.

Gender breakdown: XX females, XX males.

Racial/Ethnic breakdown: X American Indian/ Alaska Native, X Asian, X Native Hawaiian or Other Pacific Islander, X Black or African American, X White, X more than one race, X Unknown or Not Reported (also state number of Hispanic/Latino).

Address any racial/ethnic disparities. Address accrual issues, if any.

Withdrawals

XX patients have withdrawn from the study; XX treated, X in baseline, etc. XX were withdrawn by the PI. Of the XX withdrawals, X are from Cohort X, XX are from Cohort XX. X withdrawals occurred in the last year. Discuss any trends in withdrawals here (for example, if 5/10 withdrawals withdrew due to AE post-treatment).

Previously:

Summary of withdrawals by each group and stage of the study, including reason for withdraw.

New in the last year:

Summary of withdrawals by each group and stage of the study, including reason for withdraw.

Summary of data completeness and participant adherence to the study schedule

Insert the percentage of missing data (group as needed, by individual/cohort/etc), and provide reasons (or state none). State whether or not missing data will affect study outcomes and/or patient safety.

H. Definitions

Adverse Event (AE): Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug or device in humans, whether or not considered drug or device related (OHSRP SOP 16; 16.3.A).

Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIH Office of Scientific Policy:

https://auth.osp.od.nih.gov/sites/default/files/NIH%20Definition%20of%20Clinical%20Trial%2010-23-2014-UPDATED_0.pdf).

Conflict of Interest: A conflict of interest (COI) occurs when a government matter, including clinical research, will have a direct and predictable effect on the financial interests of an individual or the individual's spouse, minor children, general partner(s), or certain other organizations the individual serves as officer, director, trustee, general partner or employee, and entities with which the individual is negotiating for or has an agreement regarding prospective employment (18 USC § 208, 5 CFR Part 2640)(OHSRP SOP 21; 21.3.B).

Apparent Conflict of Interest: An apparent COI occurs when an individual's impartiality in clinical research, particularly clinical research involving commercial interests, might reasonably be questioned because the interests of a member of the individual's household would be affected by the matter, or because certain persons or entities are involved in or will be affected by the research, including close relatives or household members of the individual or others with whom the individual has or recently had (within the past year) certain personal or business relationships, or with whom the individual's spouse, parent or dependent child has certain personal or business relationships (5 CFR § 2635.502)(Same as the OHSRP SOP 21 definition of "Appearance of Conflict of Interest"; 21.3.A).

Data and Safety Monitoring- a formalized process for reviewing accumulated outcome data from an ongoing research study to ensure the continuing safety and welfare of current research subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the study

Data and Safety Monitoring Board (DSMB) (also known as a Data and Safety Monitoring Committee {DSMC} or Data Monitoring Committee {DMC}): A formal committee made up of experts, i.e. not the trial organizers or investigators, which reviews accumulating data and critical efficacy endpoints from one or more ongoing clinical trials (or multisite research). The DSMB reviews the data on a pre-set schedule throughout the life of the study. A DSMB is the only trial oversight group that has on-going access to un-blinded safety and efficacy data. Its role is to make recommendations to continue, modify, or stop the research based on an assessment of risks and benefits. At NIH, the recommendations are sent to the PI and IC leadership and/or

other IC contacts based on the DSMB Charter and IC policy. It has the authority to request additional analyses and may schedule ad hoc meetings to review data. (OHSRP SOP 17; 17.3.D).

Data and Safety Monitoring entity (DSM entity): The individual or group designated as responsible for data and safety monitoring in the study's Data and Safety Monitoring Plan.

Data and Safety Monitoring Plan (DSMP): A written description of the procedures for reviewing outcome data, reportable event data (including adverse reactions and unanticipated problems) and overall compliance with the protocol. It is intended to ensure the safety and welfare of research participants during the course of the study (OHSRP SOP 17; 17.3.B). The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. The DSMP should establish guidelines for the assessment and progress of a clinical trial, at established intervals, to review safety data and the critical efficacy endpoints, and to recommend whether to continue, modify, or stop a trial. The mechanism for data and safety monitoring ranges from monitoring by the PI to monitoring by an Independent Medical Monitor (IMM), Safety Monitoring Committee (SMC), or a Data and Safety Monitoring Board (DSMB).

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (OHSRP SOP 23; 23.3 B).

Independence: For the purpose of this guideline, independence refers to individual(s) not engaged in the monitored research, not in supervisory or subordinate position, and unrelated to the investigators and sponsor. The individual(s) must not have a real or apparent conflict of interest (OHSRP SOP 17v1; 17.3.C).

Independent Medical Monitor (IMM): A person (e.g. physician or other expert in an appropriate scientific discipline needed to interpret the data and ensure safety (AHRQ Data and Safety Monitoring Policy, NOT-HS-11-015)) who is charged with the monitoring of a protocol, especially issues of individual subject management and safety. The IMM may be internal to NINDS, but must be independent of the investigative team and free of conflicts-of-interest. The IMM is proposed by the PI and approved by the IRB and CD.

Investigator: An "investigator" is any individual who is involved in conducting human subjects research studies. An investigator may perform a variety of tasks related to the conduct of human subjects research studies. Such involvement includes: (1) obtaining information about living individuals by intervening or interacting with them for research purposes; (2) obtaining identifiable private information about living individuals for research purposes; (3) obtaining voluntary informed consent of individuals to be subjects in research, or (4) studying, interpreting, or analyzing identifiable private information or data for research purposes. (OHSRP SOP 19.3.1). The Principal Investigator and key personnel (associate investigator(s), study coordinator) are responsible for fully cooperating with all QA audits. The Investigator is responsible for maintaining a record of audit reports and corrective action plans, and for implementing corrective actions for any objectionable or otherwise non-compliant audit observations. The Investigator will maintain all audit reports in a confidential file.

Monitoring: The act of overseeing the progress of a specific research study and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, NIH HRPP policies, standard operating procedures (SOPs), FDA GCP guidelines (when applicable), and the applicable regulatory requirement(s). This is a continuous process throughout the life of a research protocol (OHSRP SOP 23; 23.3.I). According to the International Conference on Harmonization Regulations (ICH E6), the intent of protocol monitoring is to provide objective appraisal of trials to verify that: 1) the rights and well-being of human subjects are protected; 2) the reported trial data are accurate, complete, and verifiable from source documents, and 3) the conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements. Protocol monitoring is an important component in ensuring human subject protection and the quality of clinical trial data.

Non-compliance: According to OHSRP SOP 16A, non-compliance is defined as the failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

This may include, but is not limited to, the following:

1. Failure to obtain IRB approval for research involving human subjects.
2. Inadequate or non-existent procedures for informed consent.
3. Inadequate supervision of research involving experimental drugs, devices, or procedures.
4. Failure to follow an IRB-approved protocol.
5. Failure to obtain prospective IRB approval for changes to a protocol.
6. Failure to report unanticipated problems and protocol deviations.
7. Failure to obtain continuing IRB review and approval.
8. Failure to ensure appropriate training of study personnel.

Non-compliance may be further characterized as:

2. Serious non-compliance that:
 1. Increases risks, or causes harm, to participants,
 2. Decreases potential benefits to participants, or
 3. Compromises the integrity of the NIH HRPP
 4. Invalidates the study data.
3. Continuing non-compliance: Non-compliance that is recurring, regardless of whether it is serious or minor. An example may be a pattern of non-compliance that suggests a likelihood that, absent an intervention, non-compliance will continue. Continuing non-compliance could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance.

Minor (non-serious) non-compliance: Non-compliance that is neither serious nor continuing.

Office of Human Subject Research Protection (OHSRP): OHSRP is an office within the NIH Intramural Research Program (IRP). The staff assists IRP investigators, research staff, IRBs and others to understand and comply with the ethical guidelines, regulatory requirements, and NIH policies and procedures for research involving human subjects.

Protocol Deviation: Any change, divergence, or departure from the IRB-approved research protocol (OHSRP SOP 16.3 D).

Safety Monitoring Committee (SMC): A committee of at least 2 members (e.g., physician, statistician, or other expert in an appropriate scientific discipline needed to interpret the data and ensure safety (AHRQ Data and Safety Monitoring Policy, NOT-HS-11-015)) who are charged with monitoring a protocol. Members of an SMC may be internal to NINDS, but must be independent and free of COIs. Members are proposed by the PI and approved by the IRB and CD.

Serious Adverse Event* (SAE): is any Adverse Event that:

1. Results in death
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect, OR
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*In FDA-regulated research, this term is used synonymously with "serious suspected adverse reaction" and "Unanticipated Adverse Device Effects"(See 21 CFR 312.32(a), 21 CFR 312.64(b) and 812.150(a)(1) (OHSRP SOP 15B; Appendix A;OHSRP SOP 16, 16.3.B)

Sponsor: An individual who take responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator (21 CFR 312.3 (b), 21 CFR 50.3(e), and 21 CFR 56.102(j)) (OHSRP SOP 16; 16.3.G).

Sponsor-Investigator: An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug, device or biologic is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor (21 CFR 56.102 (k), 21 CFR 312.3, 21 CFR 50.3 (f)) (OHSRP SOP 16; 16.3.H).

Stopping rules: identify specific triggers (i.e. events) that require some action. These are predetermined guidelines as to when enrollment, administration of study products or intervention or one or more study arms should be altered or stopped.

Quality Assurance (QA): A systematic evaluation of program functions to maximize the probability that quality standards are being attained. In the context of clinical research this means auditing NIH organizational systems to determine whether they are effectively meeting established NIH HRPP policies and regulatory requirements. QA includes a systematic and independent examination of study related activities and documents, including IRB operations. Audits are used to implement QA work (OHSRP SOP 23; 23.3.J).

Vulnerable Populations: 45 CFR 46.111(b) states the following regarding criteria for IRB

approval of research “when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.”