Policy of the National Institute of Nursing Research for Data and Safety Monitoring of Extramural Clinical Trials

Purpose and Scope

This policy sets forth the National Institute of Nursing Research (NINR) requirements for data and safety monitoring (DSM) for all clinical trials funded in whole or in part by NINR extramural programs. For each NIH-supported clinical trial, NIH requires a data and safety monitoring plan that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. (NOT-OD-98-084). This policy is incorporated as part of the terms and conditions for all *awards* (training, career and research projects) involving clinical trials regardless of whether they are contracts, grants, supplements, or cooperative agreements.

Funding for clinical trial research activities is contingent upon compliance with this DSM policy.

This policy does not take the place of Institutional Review Board (IRB) guidelines, Food and Drug Administration (FDA) requirements, or special NIH guidelines.

This policy supersedes "Policy of the NINR for NINR Data and Safety Monitoring of Clinical Trials" issued in 2014. This revised policy is effective with competing projects issued in FY 2020 and is effective for all future years in the competitive project periods.

The NINR DSM policy and procedures can be subject to change. Notifications of changes will be posted on the NINR website.

Background

In June of 1998, NIH issued a policy stating that "each Institute or Center (IC) in NIH should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials." Data and safety monitoring is required for all types of clinical trials, including toxicity and dose-finding studies (Phase I); efficacy studies (Phase II); and effectiveness and comparative trials (Phase III). It includes all types of intervention studies (e.g., behavioral, prevention, diagnostic trials). Monitoring should be commensurate with the study risks. Each IC has flexibility to implement the requirement for data and safety monitoring as appropriate for its clinical research activities (http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Further guidance to this policy (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html), released in June of 2000, stated that beginning with the October 2000 receipt date, investigators must submit a detailed monitoring plan for Phase I and Phase II clinical trials to the IC before the trial begins. The detailed monitoring plan must also be approved by the local IRB before the trial begins. A general description of data and safety monitoring plans must be included as part of the competing grant application.

NINR Policy

All clinical trials supported by NINR should have some form of monitoring based on a DSM plan. The level of monitoring should be commensurate with the size and complexity of the trial, the level of risk to study participants, and phase of the trial. All mechanisms for data and safety monitoring are subject to IRB review and approval.

Data and safety monitoring is the responsibility of the Principal Investigator (PI) or designee. Monitoring by the PI or designee may be appropriate for protocols involving minimal risk or no more than a minor increase over minimal risk which are conducted at a single site. Data and safety monitoring may also be conducted by independent entities external to the study team such as an independent safety monitor (ISM), small committee (Safety Monitoring Committee (SMC)) or Data and Safety Monitoring Board (DSMB):

a. **Independent Safety Monitor (ISM)** – a physician, nurse or other appropriate expert who is independent of the study and available in real time to review and recommend appropriate action regarding adverse events and other safety issues.

b. **Safety Monitoring Committee (SMC)** – A group of two or more experts, who are independent of the protocol, which reviews data from a particular study. Generally, independent investigators and biostatisticians should be included.

c. **Data and Safety Monitoring Board (DSMB)**– an independent committee charged with reviewing safety and trial progress and providing advice with respect to study continuation, modification, and termination. A DSMB is generally required for Phase III clinical trials involving interventions that entail potential risk to participants. A DSMB may be required for phase I or phase II clinical trials that have multiple sites, or are blinded, or include high-risk interventions, high risk procedures (i.e., particularly invasive or is associated with other safety concerns), or vulnerable populations (e.g., children, pregnant women, elderly, terminally ill, or those of diminished mental capacity). For many phase I and phase II trials, a DSMB may not be necessary when the intervention is low risk. A DSMB may be established if the principal investigator, their institution or NINR deems it necessary.

The organization, responsibilities, and operation of the DSMB are mandated by NIH and NINR policy (See Appendix A: NINR Guidelines for Extramural Internal and External DSMBs).

The DSM Plan

Grant applicants must submit a general description of the DSM plan as part of the research grant application. The DSM plan describes oversight and monitoring to ensure the safety of participants and the integrity of the data. DSM plans should address the following essential elements.

a. Monitoring entity or who will monitor the study, (i.e.., PI, ISM, SMC or DSMB). The roles and responsibilities of everyone on the team involved in monitoring to include the entity responsible for submitting necessary reports to NINR.
b. Procedures for 1) monitoring study safety to include monitoring schedule, auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance; and 2) minimizing research-associated risk.
c. A data monitoring plan that includes the following elements related to data quality, management, confidentiality and security:
    - A description of data integrity procedures including identification of data sources (e.g., questionnaires, medical records, collections,

audio/video recordings), protocol adherence, and flow of essential data forms.

- A description of security measures in place to protect data sources, protect and back up databases, including how data will be labeled and stored. (NIH Grants Policy 2.3.12 Protecting Sensitive Data and Information Used in Research)
- A description of data handling practices that ensure data changes are documented and there is no deletion of entered data, security systems prevent unauthorized access to data, adequate backup of data, blinding is safeguarded. (ICH Harmonized Tripartite Guidelines for Good Clinical Practice ICH GCP 5.5.3, 21 CFR, Part 11, Subpart B)
- A description of quality assurance measures (and timeline) used to verify data integrity and validity, including reviewing data collection forms for completeness and accuracy of the data, verifying accuracy of data in electronic databases, as well as protocol compliance. (ICH GCP 5.1)
- A description of how participant data confidentiality will be protected. The plan should delineate steps that will be taken to monitor and maintain confidentiality of data (e.g., password protected encrypted electronic records, limited access) and any limits to confidentiality (e.g., abuse, suicidal ideation) (§46.111, CFR 21, Part 11, Subpart B, ICH GCP 2.11, NIH GPS 2.3.12). An additional level of protection for human subjects involved in clinical studies is a Certificate of Confidentiality, which is issued to a researcher to provide special privacy protection to subjects involved in clinical research. https://grants.nih.gov/policy/humansubjects/coc.htm

d. Procedures for identifying, reviewing, and reporting *adverse events* and *unanticipated problems* to the IRB, NINR, and FDA (if applicable). If applicable, the type and number of events that would halt accrual and would generate a review of eligibility, monitoring, assessments, intervention, and how the resumption of accrual would occur. For further information, see:

   - NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (http://grants1.nih.gov/grants/guide/notice-files/not99-107.html)
   - OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (http://www.hhs.gov/ohrp/policy/advevntguid.html)

e. For multi-site studies, procedures to ensure compliance with the monitoring plan and reporting requirements across study sites.

f. An assessment of external factors or relevant information (e.g., developments in the literature, results of related studies) that may have an impact on the safety of participants or on the ethics for the research study.

g. The advanced plans for interim and/or futility analysis as appropriate.

If monitoring plan information is found in institutional or consortium or network standard operating procedures and documents, then the DSM plan does not need to repeat the information. However, the DSM plan should have a brief summary of the essential elements as outlined above with a reference to the applicable standard operating procedures.

The Scientific Review Group (SRG) will review the general DSM plan in the research application. SRG comments or concerns with the general DSM plan will be included in the summary statement. The SRG focuses on the quality of the process that the investigator is planning to have in place to ensure the safety of the participants and obtain reliable results, (i.e., plan is appropriate with respect to risks of participants, complexity of study design).

NINR program staff will review and approve the general DSM plan included with the research application prior to commencement of the human subjects activities of the trial. If the general DSM plan is insufficient, (e.g., plan is not appropriate with respect to risks of participants; essential elements are not included), the PI will be requested by the NINR to submit a revised, detailed DSM plan for review and approval by the NINR program staff. The revised, detailed DSM plan must be submitted and approved by the NINR before human subjects clinical trial research activities begin.

The DSM plan approved by the NINR must be submitted to the local IRB. The IRB should consider the appropriateness of the DSM plan proposed by the PI based on the level of risk, the number of study participants to be enrolled, and the complexity of the study. Specifically, each of the criteria above (i.e., a-f) should be addressed as appropriate in the DSM plan.

The responsibility for compliance with the DSM plan rests with the PI. The oversight of the monitoring activity described in the DSM plan is the responsibility of NINR program staff to include ensuring that those responsible for monitoring have the appropriate expertise to accomplish its mission and responding to recommendations that emanate from monitoring activities. NINR must be notified within 7 days if the human subjects research or DSM plan is changed prior to or during implementation of the clinical trial. NINR program staff must approve the changes prior to implementation.

The PI must provide **timely reporting** to NINR of the following:

a. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol.
b. IRB-approved revisions to the study protocol that indicate a change in risk for participants.
c. A summary of recommendations made by the SMC/DSMB or other monitoring entity as appropriate and (if applicable) the action plan for response.
d. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

NOTE: All personal identifiers must be removed from any documents sent to NINR.

FAQs:

1) Does this policy apply to all award mechanisms used by NINR?

Yes, this policy applies to all NINR-sponsored training, career, and research projects regardless of whether they are *contracts*, *grants*, or *cooperative agreements*.

2) To what population of grants does this policy apply?

This policy is effective with competing grants issued in FY2020 and is effective for all future years in the competitive project periods.

3) My DSM plan is part of my research grant application. Is this sufficient or am I required to send something else?

If the general DSM plan in the application is insufficient (e.g., plan is not appropriate with respect to risks of participants; essential elements are not included), the NINR will request a revised plan if your application is being considered for funding.

4) The NINR did not request a revision of the DSM plan included in my research grant application. Does this indicate that the general DSM plan has been approved by NINR program staff?

Yes. If you are being considered for funding, and the NINR does not request a revised DSM plan, the DSM plan submitted with the research grant application has been approved by the NINR program staff.

5) Does my NINR approved DSM plan require IRB approval?

The current policy has removed the requirement for submission of the IRB approval of the NINR-approved DSM Plan. The determination for IRB review of a revised NINR-approved DSM plan is the responsibility of the institution and/or PI prior to commencement of human subjects clinical trial activities.

6) What if the human subjects aspect of my research begins after the first year of funding?

This policy only applies to *human subjects research*. For example, if the human subjects research portion of your study was outlined in your application and begins in year 3, then this policy must be followed prior to the commencement of human subjects research activities starting in year 3. If you are proposing a delayed onset study, please see below. Other research activities that do not involve human subjects may proceed. See the terms and conditions of the award for further information.

7) Where and when do I send the revised DSM plan if requested?

All official documentation must be sent electronically to the *Grants Management Specialist* —with a copy to the *Program Official* —listed in eRA Commons (https://commons.era.nih.gov/commons/). NINR also should be notified within 7 days if the human subjects research or approved DSM plan is changed prior to or during implementation. This documentation must be countersigned by the *Authorized Organization Representative* and must be approved before NINR changes are implemented.

8) If I have a Career Development (K) Award or a Training (T or F) Award do I need to comply with Data and Safety Monitoring of Clinical Trials?

NINR Career Development awards (K awards) may support either independent clinical trials or a mentored Clinical Trial Research Experience. If the career grant awardee is carrying out an independent clinical trial, s/he should consult with his/her mentors about DSM plans for the clinical trials. Because trainees will be in a mentored stage of their career and will in most cases lack the experience needed to provide appropriate oversight of the trial, if PI oversight is considered appropriate for the DSM plan, a senior individual responsible for monitoring the trial must be named and the role of the trainee in trial oversight should be outlined.

Career Development awards that do not include independent clinical trials, and NINR training fellowships (F) and institutional awards (T) may support studies that provide Clinical Trial Research Experience. The "Clinical Trial Research Experience" designation refers to studies where the clinical trial is led by a mentor or other investigator, with the goal of providing trainees with clinical trial experience relevant to their research interests and career goals. While the trainee can be part of the clinical trial team and can use the data generated during the clinical trial research experience in his/her proposed research project, the Principal Investigator of the clinical trial is expected to assume overall responsibility of the trial including registering and reporting in clinicaltrials.gov, ensuring data and safety monitoring and obtaining IRB approval. NIH supported fellowships and institutional training awards do not allow the trainee to propose an independent clinical trial.

1) *What information is needed if I am proposing a pilot (delayed onset study) that was not fully described in the original application?*

If human subject studies were not adequately described in the application because they were planned for a later time within the project period ("Delayed Onset studies"), provide the information per NOT-OD-15-129 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-129.html) including the DSM plan.

2) What are the requirements for DSM reporting in the annual progress report?

Any changes in the DSM Plan, any adverse events, or any violations of the DSM plan should be reported promptly to NINR, according to the specifications in the approved DSM Plan. Such reports should not wait until the annual progress report.

Human Subjects changes in studies with approved Data and Safety Monitoring Plans:
Changes from the approved involvement of human subjects that would result in an increased risk require NINR/NIH prior approval (NIH GPS 8.1.2.5).

If there is a change in scope from "no clinical trial" to "includes a clinical trial", a competitive revision application must be submitted to a clinical trial FOA (NIH GPS 8.1.2.5).

Appendix A

National Institute of Nursing Research (NINR) Guidelines for Extramural Internal and External Data and Safety Monitoring Board (DSMB)

The organization, responsibilities, and operation of DSMBs are mandated by NIH and NINR policy. A DSMB is generally required for phase III clinical trials involving interventions that entail potential risk to participants (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). DSMBs are either a) NINR-appointed and act as an independent advisory group to the NINR Director or designee (i.e., internal), or are institution-based and appointed by the local IRB of the awardee institution (i.e., external).

The NIH and NINR DSMB policy and procedures can be subject to change. Notifications of changes will be posted on the NINR website.

Assignment of an Internal or External Data Safety Monitoring Board

For NINR approved data and safety monitoring (DSM) plans that specify a DSMB as the monitoring entity, the assignment of an internal or external DSMB will be determined by NINR program staff and the NINR Director or designee as appropriate. The selection of an internal or external DSMB for oversight and monitoring is commensurate with risks, size, and complexity of the clinical trial.

a. An internal DSMB may be assigned for very large, phase III multi-center trials, research networks, and other large clinical trials that involve greater than minimal risk to participants and are performed under a contract or a cooperative agreement.

b. An external DSMB may be assigned for investigator–initiated clinical trials (phase I, II, or III) involving greater than minimal risk to participants and are performed under a grant.

Generally, both types of monitoring boards (i.e., internal and external) should function in accordance with criteria described below, and essential elements of the board must be included in the data and safety monitoring plan. For studies co-funded with other ICs, the lead IC will be responsible for oversight of a DSMB if necessary.

DATA AND SAFETY MONITORING BOARD

a) Role of the Data and Safety Monitoring Board

The ongoing review of data by an independent review body (i.e., DSMB) assures the investigator(s) that the trial can continue without jeopardizing patient safety. These monitoring activities are distinct from the requirement for study review and approval by an IRB. Specifically, DSMBs:

1. Protect participants in clinical protocols from exposure to unreasonable or unnecessary research risks by monitoring the trial data for effectiveness and safety.
2. Review interim data in the context of the most recent scientific literature and may access unmasked data.

3. Ensure that clinical studies do not continue beyond the point when the objectives have been met and a clinically meaningful answer of importance to the scientific community and the public has been obtained.
4. Monitor study progress and conduct.

b) Responsibilities and Functions of the Internal and External DSMB

The DSMB is responsible for oversight of the activities related to implementing the clinical trial to ensure patient safety, conformance to the clinical protocol, overall performance of the trial components such as the Coordinating Center and clinical sites, and integrity of the data being collected.

Since each clinical trial supported by the NINR has been approved previously by the institution's IRB, the role of the DSMB is not to serve as a peer review group to redesign any portion of the trial unless the DSMB feels that patient safety is compromised under the proposed design. In this case, the DSMB should communicate their concerns to the NINR staff and the appropriate IRB prior to the start of patient recruitment. Specific responsibilities and function of the DSMB include:

1. Have a charter that has been reviewed and approved by the board. The charter should state that DSMB members are made aware of their ability to access unmasked data and provide guidance for the timing and conditions of accessing unmasked data.
2. Approve study protocol, review plans for data and safety monitoring, including informed consent template, reporting templates for data to be presented to the board, and other items the board may wish to see before a study begins enrollment
3. Establish specific guidelines for monitoring for safety. This should include a listing of events that should be reported immediately to the DSMB and the format of reporting cumulative data at intervals.
4. Review, as appropriate, interim analyses of outcome data to include allowing the unmasking of blinded data for early evidence of efficacy, lack of efficacy, or evidence of study futility.
5. Review toxicity data, such as adverse events for safety and efficacy and make recommendations as appropriate to whether the trial should continue as originally designed, be changed, suspended or terminated based on the observed beneficial or adverse effects of any of the treatments under study.
6. Review trial performance information such as patient recruitment and retention, resource center performance, and proposals for ancillary studies follow-up information and listings of protocol violations.
7. Review published reports of related studies submitted by the study investigators, or DSMB members to determine whether the monitored study needs to be changed or terminated.
8. Review proposed modifications to the study prior to their implementation (e.g., increasing target sample size, dropping an arm based on other trial outcomes or toxicity results, modifying outcomes, monitoring plans etc.) and make recommendations.
9. Review the proposed stopping guidelines as specified in the protocol and, at its discretion, recommend modification to the proposed plan, or propose a plan, if none has been proposed.

10. Provide advice and feedback on data analysis to the study statistician or study monitor.
11. As soon as possible after the meeting, and following the schedule in the charter, a written summary recommendation along with justification related to continuing, changing, or terminating the trial. In addition, provide a statement, where appropriate, concerning the impact on the trial of individually observed or cumulative adverse events.

c) Membership of Internal and External DSMB

A duly constituted DSMB must have members with sufficient expertise to review the scientific design and conduct of a study, to evaluate safety and risks to participants, to interpret data statistically, and to make recommendations concerning continuation, modification, suspension, or termination of a study. Every DSMB must have an Executive Secretary who is not otherwise involved in the study or with the study team. The Executive Secretary is usually a non-voting, ex-officio member of the monitoring board with clinical trial expertise or a contractor with equivalent expertise

The DSMB must include a minimum of 5 voting members that includes a Chair. Voting member composition will include at least one clinical trials expert, a biostatistician, an expert(s) in the ethics of clinical research, an expert(s) in the clinical aspects of the disease/patient population being studied, and expert(s) in the work of DSMBs. It is important that the DSMB biostatistician as well as other members have expertise in clinical trials conduct and methodology, including the work of DSMBs. At the discretion of the Chair, ad hoc members may be invited to participate for a short period of time to review specific protocols if additional expertise is desired.

Voting and non-voting members of the DSMB should be independent of the trial(s) to be monitored. In exceptional circumstances, a voting member may be from an institution participating in the trial. In this situation, the member should view his/her role as representing the interest of the participants enrolled in the trial and not that of the institution.

d) Membership Appointment to an Internal and External DSMB

1. For internal DSMBs, NINR staff will nominate the DSMB voting and non-voting members including the DSMB chair. NINR staff may request from the PI a list of potential voting and non-voting members who have the requisite expertise for serving as a DSMB member. Proposed DSMB members must be reviewed and appointed by the NINR Director or designee prior to initiation of patient recruitment. Selection will be based on appropriate composition of members, participation on other DSMBs, and absence of apparent conflicts of interest including financial, propriety, or intellectual. In general, members will be appointed for a term that will coincide with the duration of the study or the award. For studies that continue beyond a single award period, board members' service will be evaluated at the time of the new award, and may be renewed, based on expertise, contributions and participation, and study needs. Ad hoc members invited by the Chair must also be reviewed and

appointed by the NINR Director or designee prior to participation in DSMB meetings.

2. For external DSMBs, the local IRB of the awardee institution is responsible for ensuring adequate and appropriate membership composition as specified by NINR policy (i.e., each monitoring board must have a Chair and Executive Secretary, consist of members who are independent of the study and have expertise in biostatistics, clinical trials methodology, ethics of clinical research, and key subject areas involved in the research). Experience of participation on other DSMBs and absence of apparent conflicts of interest including financial, propriety, or intellectual must also guide selection of members.

e) Conflict of Interest

It is essential that voting and non-voting DSMB members do not have close current or recent affiliations with the studies they are monitoring. DSMB members should not be directly involved in protocol development, nor supervise persons who are so involved. Each proposed member will be asked to disclose potential conflicts of interest, including for example current or expected financial ties to any commercial concerns likely to be affected by the outcome of any trial. Only those individuals who provide such disclosures may serve on the DSMB. Any member directly involved with the conceptual design or analysis of a specific trial must recuse himself from all related DSMB discussions and will not receive that portion of the unmasked DSMB report. In this instance, an ad hoc member may be added to the Board for that specific trial.

1. For internal boards, individuals invited to serve on the DSMB, will disclose any potential conflicts of interest, whether real or perceived, to the Executive Secretary and NINR Deputy Ethics Counselor in accordance with the HHS/NIH policies on an annual basis or when a significant change occurs in a member's status. Conflict of interest may include financial interest, professional interest (in the sense of the trial outcome benefiting the individual professionally), proprietary interest, and miscellaneous interest as described in the NIH Grants Policy and 45 CFR Part 94 and 21 CFR Part 21. Professional interest in this context is when the trial outcome would benefit the individual professionally.

2. For external boards, awardee institutions are expected to have a Conflict of Interest (COI) policy and/or plans for management and monitoring of COIs of DSMB members. This policy or plan must reflect the essentials as specified in this NINR policy (e.g., voting and non-voting DSMB members do not have close current or recent affiliations with the studies they are monitoring, DSMB members should not be directly involved in protocol development, nor supervise persons who are so involved). Disclosure of conflict of interest must include financial interest, professional interest (in the sense of the trial outcome benefiting the individual professionally), proprietary interest, and miscellaneous interest as described in the NIH Grants Policy and 45 CFR Part 94 and 21 CFR Part 21. Professional interest in this context is when the trial outcome would benefit the individual professionally.

RESPONSIBILITIES of SELECTED DSMB MEMBERS and PRINCIPAL INVESTIGATOR

a) Responsibilities of the DSMB Chair

For internal and external boards:

1. Develops agenda
2. Conducts meeting using Robert's Rules of Order
3. Chairs the open session
4. Chairs the closed session and executive session as outlined in "Meetings" section
5. Ensures DSMB charter is finalized at first meeting
6. Ensures that meeting summaries and final minutes are adequately prepared and approved as appropriate
7. Acts as the primary contact person for the DSMB
8. Sets the meeting dates
9. Contacts new members as needed to assess their content expertise and inform them of the DSMB process

b) Responsibilities of the NINR Staff

For internal boards:

1. Forward DSMB minutes, reports, and recommendations to the NINR Director or designee for approval

2. Attend specific sessions of the DSMB meetings at the discretion of the Chair. If invited to attend meeting by the Chair, act in the role of objective observer with no participation in deliberations or providing of additional information that may influence the recommendations of the DSMB.

For external boards:

1. Provide general advice to the PI and Executive Secretary related to DSMB operational issues according to NIH and NINR policy.
2. Attend specific sessions of the DSMB meetings at the discretion of the Chair If invited to attend meeting by the Chair, act in the role of objective observer with no participation in deliberations or providing of additional information that may influence the recommendations of the DSMB.

c) Responsibilities of the DSMB Executive Secretary

For internal and external boards:

1. Create a list of proposed board members for approval. Generate invitation letters for board members
2. Ensure invitees Conflict of Interest (COI) form and Human Subjects verification are completed
3. Ensure that invitees COI forms are approved
4. Finalize board membership
5. Establish meeting dates with Chair

6. Ensure that the Board Charter is drafted and approved by the board. Review with the DSMB Chair what information should be made available for review at each meeting to assist the DSMB in carrying out their primary charge related to patient protection oversight, study operation, and data integrity. This should be discussed at each meeting since different information or tables may be required from meeting to meeting.
7. Ensure meeting materials are distributed to each member prior to the meeting and in sufficient time to permit adequate review.
8. Take adequate notes during the open, closed, and executive sessions of each meeting or during each conference call so that final draft minutes and written meeting summary (i.e., DSMB recommendations related to study changes or continuation) can be prepared following the meeting for review by the DSMB chair (See section, Data and Safety Monitoring Reports).
9. Forward DSMB final draft minutes and written meeting summary for approval within specified time frames as appropriate.
10. Maintain all protocol documents, conflict of interest forms, data, final minutes and meeting summaries from each DSMB meeting.

d) Responsibilities of the Principal Investigator

For internal and external boards:

1. Provide written reports to the DSMB on current status of the trial, interim analyses, adverse events, and problems encountered. The report may contain recommendations for consideration by the DSMB concerning clinical site performance, whether to continue accrual and/or follow up, whether to close the trial, and whether the results should be reported.
2. Amend the protocol in accordance with DSMB recommendations and notifying the clinical site and IRBs as expeditiously as possible.
3. Provide to the DSMB for review modifications to the study prior to their implementation (e.g., increasing target sample size, dropping an arm based on other trial outcomes or toxicity results, modifying outcomes, monitoring plans etc.).

Forward DSMB recommendations and meeting minutes as appropriate to the NINR, IRB and/or other clinical research sites involved.

DATA AND SAFETY MONITORING BOARD MEETINGS

For internal and external boards:

The frequency of DSMB meetings will depend on the nature of the trial. However, a DSMB should meet at least annually. Interim meetings and/or conference calls may be held at the request of DSMB members, the study leadership, the NINR Director or designee, or local IRB or awardee institution.

All meeting materials should be considered privileged by DSMB members. This confidentiality should be maintained at all times to the extent permitted by law.

Each meeting may be divided into four parts:

1. Open Session

An open session at which members of the DSMB, voting and non-voting and Executive secretary, clinical trial team, and ad hoc members may be present, at the request of the DSMB Chair. The focus of the open session is on the general conduct and progress of the study. Specifically, the focus of the open session is: adverse events and toxicity issues, subject accrual, protocol compliance, demographic characteristics of enrollees, disease status of enrollees (if relevant), site performance, quality control, and timeliness and completeness of follow-up. During this time, no confidential data will be discussed and the blind, if present, will be maintained.

The PI and other appropriate study leadership and the protocol specific biostatistician should be in attendance in order to present results and respond to questions.

One NINR program staff may participate in the open session at the discretion of the Chair. The Chair may decide not to invite NINR program staff if their presence may inhibit free and open discussion, or compromise or appear to compromise the board's independence. If NINR program staff are invited to participate, they should be informed of upcoming board meetings at least 1-2 weeks in advance and receive the appropriate meeting materials at the same time as the board members. DSMB members must be informed prior to the meeting that NINR program staff are invited to the open session and, to contact the Chair if there is concern regarding NINR program staff attendance at the meeting.

NINR program staff, if invited to attend the open session, will act in the role of objective observer and will not provide additional information that may influence the recommendations of the DSMB.

For internal boards, one NINR staff (i.e., Executive Secretary) may be present in addition to the invited NINR program staff.

2. Closed Session

The second part of the meeting is a closed session involving the voting members, invited ex officio members at the discretion of the DSMB Chair, and the Executive Secretary. NINR program staff (i.e., limit is one) if invited to attend will act in the role of objective observer and will not participate in deliberations or provide additional information that may influence the recommendations of the DSMB. During this part of the meeting, grouped safety data and, if appropriate, efficacy data to include unmasking of blinded data are presented by the protocol specific statistician(s). NINR program staff that function as Project Officers for the study should not be privy to post-randomization data broken down by treatment group that may be discussed during closed session.

3. Executive Session

The third part of the meeting involves only voting DSMB members, and the Executive Secretary, to allow the members the opportunity to discuss the general

conduct of the trial, all outcome results, including toxicities and adverse events, and implications of data. The Chair may ask the Executive Secretary to not attend and the Chair will record minutes/recommendations of the session. The Chair, if applicable, may break the blind, if such action is required to make an informed decision. Recommendations will be made to continue the study as planned, to make adjustments to the study plan, suspend or to terminate the study. NINR staff participation is at the discretion of the DSMB Chair. NINR program staff (i.e., limit is one) if invited to attend will act in the role of objective observer and will not participate in deliberations or provide additional information that may influence the recommendations of the DSMB. NINR program staff that function as Project Officers for the study should not be privy to post-randomization data broken down by treatment group that may be discussed during this session.

At the end of the meeting, voting members discuss and vote on these recommendations. Votes may be done by voice/show of hands or by ballot. Every effort will be made to obtain a consensus. If consensus cannot be obtained, a majority vote is required to carry any recommendation. The Chair will participate in discussions and will vote. If there is a minority opinion, the recommendations will include a minority report. In case of a tie vote, both positions will be reported. Discussions and recommendations will be documented by the Executive Secretary or Chair as appropriate. The final recommendations must be summarized either as majority or minority positions or as actual vote tallies for the various divergent recommendations (i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc.). Specific positions will not be attributed to individual Board members.

DATA AND SAFETY MONITORING BOARD REPORTS

a) Written Meeting Summary of DSMB Recommendations

The DSMB will issue a written meeting summary signed by the Chair and Executive Secretary that identifies topics discussed by the DSMB that describes their individual findings, overall safety assessment and recommendations with justification related to continuing, changing, suspending, or terminating the trial and the impact on the trial of individually observed or cumulative adverse events. The summary will not, however, include safety or efficacy data identified by treatment group.

For internal boards:

1. The written meeting summary of DSMB recommendations submitted to the NINR Director or designee for approval

2. A written meeting summary with recommendations related to a study change for patient safety or efficacy reasons (e.g., suspension, termination), or that the study be closed early due to slow accrual or other reasons should be provided to the NINR Director or designee for approval as soon as possible after the meeting but no later than 48 hours following the meeting. The summary must be forwarded to the PI and IRB(s) no later than 24 hours after approval.

3. A written meeting summary with recommendations for continuation of the study should be provided to the NINR Director or designee for approval as soon as possible after the meeting but no longer than 7 business days following the meeting. The summary must be forwarded to the PI and IRB(s) no later than 7 business days after approval.

4. In the absence of disagreement, the PI must act to implement the recommendations as expeditiously as possible regarding amending the protocol or changing the award. In the unlikely situation that the PI does not concur with the DSMB, then the NINR Director or designee must be informed of the reason for disagreement. The PI, DSMB Chair, and the NINR Director or designee will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions.

For external boards:

1. Written meeting summaries must be submitted to NINR program staff and the local IRB within the timeline specified in the board charter. Meeting summaries need not be sent to the NINR Director or designee unless requested.

2. In the absence of disagreement, the PI must act to implement the recommendations as expeditiously as possible regarding amending the protocol or changing the award. If the recommendations result in a change of scope for the award, NINR approval is needed prior to implementation of the recommendations. In the unlikely situation that the PI does not concur with the DSMB, then the PI will be responsible for reaching a mutually acceptable decision about the study with the local IRB.

b) Minutes of Data Safety Monitoring Board Meetings

For internal and external boards:

Meeting minutes will be prepared, and a final draft version will be signed/approved by the Executive Secretary and DSMB chair. The minutes should include:

1. General highlights of the discussions
2. General recommendations
3. Action items
4. Suggested protocol/study changes and the rationale for each
5. The date for the next scheduled meeting of the DSMB should be specified at the end of the minutes.
6. Confidential data is **not** to be included in the minutes.

For internal boards:

1. A final draft version of the minutes will be provided to the NINR Director or designee within 20 business days following the meeting.
2. A final draft version of the minutes will be distributed to the DSMB Members. DSMB members may submit corrections via the Executive Secretary prior to the next DSMB meeting.
3. The final draft version of the meeting minutes will be approved by DSMB Members at the next meeting.
4. Final meeting minutes will be provided to the NINR Director or designee within 20

business days following the meeting.

For external boards:

1. Final meeting minutes must be submitted to NINR program staff and the local IRB within the timeline specified in the board charter. Final minutes need not be sent to the NINR Director or designee unless requested.

RELEASE OF OUTCOME DATA

Confidential outcome data should not be made available to individuals outside of the DSMB. Any release of outcome data to individuals outside of the DSMB must be reviewed and approved by the DSMB, and the study leadership.

1. For internal boards, any release of outcome data to individuals outside of the DSMB must also be approved by the NINR Director or designee.

2. For external boards, any release of outcome data to individuals outside of the DSMB must also be approved by the local IRB.

CONFIDENTIALITY PROCEDURES

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in these guidelines. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB.