Policy of the National Institute of Nursing Research for Data and Safety Monitoring of 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. This policy is incorporated as part of the terms and conditions for all *awards* involving clinical trials. 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, e.g., NIH Guidelines for Research Involving Recombinant DNA Molecules. Specifically, Phase I and II gene transfer trials must comply with additional requirements imposed by NIH Guidelines, e.g., reporting of adverse events to the Office of Biotechnology Activities.

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 monitoring plan for Phase I and Phase II clinical trials to the IC before the trial begins. Also, a general description of data and safety monitoring plans must be included as part of the competing grant application.

Policy

All clinical trials supported by NINR should have some form of monitoring based on a data and safety monitoring (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 or designee. Monitoring by the Principal Investigator or designee may be appropriate for protocols involving 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 committees (safety monitoring committee; SMC) or Data and Safety Monitoring Boards (DSMBs):

1. **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.
2. **Safety Monitoring Committee (SMC)** – a small group of experts with at least 2 members who are independent of the protocol who review data from a particular study. Generally, independent investigators and biostatisticians should be included.
3. **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. In general, all phase III clinical trials that pose more than minimal risk must be reviewed by a DSMB; other trials may require DSMB oversight as well.

The DSM Plan

Grant applicants must submit a general description of the DSM plan as part of the research grant application. The Scientific Review Group will review the DSM plan and any comments or concerns will be included in the summary statement. The review focuses on 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...). A detailed DSM plan must be submitted to NINR before clinical trial research activities begin. NINR staff will review and approve the detailed DSM plan prior to starting the trial.

The detailed 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—e.g., PI, independent safety monitor, data and safety monitoring board (DSMB) or study monitoring committee (SMC). The roles and responsibilities of everyone on the team involved in monitoring to include 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; 2) minimizing research-associated risk, and 3) protecting the confidentiality of participant data.
c. 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)

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

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

f. The advanced plans for interim and/or futility analysis.

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 IRB should consider the appropriateness of the DSM plan proposed by the Principal Investigator based on the level of risk, the number of study participants to be enrolled, and the complexity of the study. Specifically, the criteria above (a-f) should be reviewed as appropriate in the DSM.

The responsibility for compliance with the DSM plan rests with the Principal Investigator. The oversight of the monitoring activity described in the DSM plan is the responsibility of NINR 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.

The Principal Investigator 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 DSMB/SMC or other monitoring entity 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.

The DSMB

A DSMB is generally required for multi-site *phase III clinical trials* involving interventions that entail potential risk to participants. The organization, responsibilities, and operation of the DSMB are mandated by NIH policy (Appendix A). 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 (particularly invasive or is associated with other safety concerns), or vulnerable populations (children, pregnant women, elderly, terminally ill, or those of diminished mental capacity).

FAQs :

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

Yes, this policy applies to all NINR-sponsored 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 FY2012, and is effective for all future years in the competitive project periods.

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

If the DSM plan in the application is insufficient, the NINR JIT letter will request a detailed plan if your application is being considered for funding.

4) 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 begins in year 3, then this policy must be followed prior to the commencement of human subjects research activities starting in year 3. Other research activities that do not involve human subjects may proceed. See the terms and conditions of the award for further information.

5) Where and when do I send the 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/). Please send the documentation anytime BEFORE any human subjects research commences. NINR also should be notified if the human subjects research or DSM plan is changed prior to or during implementation. This documentation must be countersigned by the *Authorized Organizational Representative* and must be approved by NINR before changes are implemented.

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

The following information must be submitted as part of the annual progress report:

Human Subjects:

If the protocols planned for the coming year are different from those proposed in the previous submission, or if a new applicable clinical trial is proposed, include an explanation of how they differ and provide a new or revised Protection of Human Subjects section as described in Part II.3 of the competing application instructions. Include designated headings, as appropriate, for Exempt Human Subjects Research, Non Exempt Human Subjects Research, Clinical Trial, or NIH Defined Phase III Clinical Trial, Data and Safety Monitoring, Inclusion of Women and Minorities, and Inclusion of Children. New protocols or

protocol changes will require IRB approval, in accord with the DHHS regulations for protection of human subjects. Provide a protocol only upon request.

If human subject studies planned for the coming year were identified in the Research Plan of the competing application, but were not adequately described because they were planned for a later time within the project period, provide a Protection of the Human Subjects section as instructed in Part II of the competing application instructions.

If studies involving human subjects are planned, and they were not part of the originally proposed research design, provide a Protection of Human Subjects section as instructed in Part II of the competing application instructions, and also provide the following information: whether all of the research is exempt under 45 CFR Part 46, and if so, the exemption number, the Federalwide Assurance number, whether the research is a Clinical Trial and whether the research is an NIH defined Clinical Trial (see definitions in Part III of the competing application instructions).

Appendix A

National Institute of Nursing Research Guidelines for Extramural Data and Safety Monitoring Board

DATA AND SAFETY MONITORING BOARD

a) Role of the Data and Safety Monitoring Board

The ongoing review of data by an independent review body (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:

- Protect participants in clinical protocols from exposure to unreasonable or unnecessary research risks by monitoring the trial data for effectiveness and safety;
- Review interim data in the context of the most recent scientific literature;
- 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; and
- Monitor study progress and conduct

For studies co-funded with other ICs, the lead IC will be responsible for monitoring the study and oversight of a DSMB if necessary.

b) Responsibilities and Functions of the DSMB

The DSMB serves as an independent advisory body to both the PI and to the NINR Director. 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 Director and appropriate IRB prior to the start of patient recruitment. Specific responsibilities and function of the DSMB include:

1. Review plans for data and safety monitoring.
2. 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 interval.
3. Review, as appropriate, interim analyses of outcome data for early evidence of efficacy, lack of efficacy, or evidence of study futility.
4. Review toxicity data, such as adverse events for safety and efficacy and make recommendations to the PI, IRB, and NINR Director or designee as 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.

5. Review, as appropriate, interim outcome data.
6. Reviews 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 to the NINR Director or designee, PI, and IRB.
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 but within 20 business days following each DSMB meeting, provide the PI with a copy to provide to the NINR Director or designee a written recommendations along with justification related to continuing, changing, or terminating the trial.
12. As soon as possible after the meeting but within 20 business days following each DSMB meeting, provide the PI and the NINR with a statement, where appropriate, concerning the impact on the trial of individually observed or cumulative adverse events. The PI will provide this information to each clinical center director to be shared with their IRBs.

c) DSMB Membership

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.

The committee will include at least one clinical trials expert, a biostatistician, and an expert(s) in the clinical aspects of the disease/patient population being studied. Some trials, depending on the population and nature of the intervention, may require a bioethicist to participate in the DSMB review. At the discretion of the Chair, ad hoc members may be invited to participate at any time to review specific protocols if additional expertise is desired. It is important that the DSMB statistician as well as other members have expertise in clinical trials conduct and methodology, including the work of DSMBs.

The PI will appoint the DSMB voting members including the DSMB chair. Proposed DSMB members must be reviewed and approved by the NINR Director or designee prior to their appointment. The DSMB shall consist of a minimum of 5 voting members with expertise in biostatistics, clinical trial methodology, ethics, and specialty areas related to the research study content as appropriate. Selection will be based on experience, knowledge of clinical trial methodology, participation on other DSMBs, and absence of apparent conflicts of interest including financial, propriety, or intellectual. An Executive Secretary appointed by the PI shall serve as

non-voting ex officio members. An NINR program staff appointed by NINR will also serve as non-voting ex officio member.

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) Conflict of Interest

It is essential that 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 and whom the NINR Director or designee deems to have no significant conflicts may serve on the DSMB.

Individuals invited to serve on the DSMB, as either a voting or non-voting member, will disclose any potential conflicts of interest, whether real or perceived, to the PI and appropriate institutional officials in accordance with the institution's 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.

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 unblinded DSMB report. In this instance, an *ad hoc* member may be added to the Board for that specific trial.

RESPONSIBILITIES of SELECTED DSMB MEMBERS and PRINCIPAL INVESTIGATOR

a) Responsibilities of the DSMB Chair

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 that meeting summaries and final minutes are adequately prepared
6. Acts as the primary contact person for the DSMB
7. Sets the meeting dates
8. Contacts new members as needed to assess their content expertise and inform them of the DSMB process

b) Responsibilities of the NINR program Staff

1. Forward DSMB minutes, reports, and recommendations to the NINR Director or designee
2. Provide general advice to the PI and DSMB related to operational issues
3. Attend DSMB meetings depending on issues to be discussed and the nature and stage of the study
4. Apprise DSMB of any programmatic concerns related to the trial
5. Keep the NINR Director or designee apprised of the status of the trial.

c) Responsibilities of the DSMB Executive Secretary

1. 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.
2. Ensure meeting materials are distributed to each member prior to the meeting and in sufficient time to permit adequate review.
3. Take adequate notes during the open, closed, and executive sessions of each meeting or during each conference call so that draft minutes from each meeting or conference call can be prepared within 20 business days following the meeting for review by the DSMB chair.
4. Maintain all protocol documents, conflict of interest forms, data, final minutes and meeting summaries from each DSMB meeting.

d) Responsibilities of the Principal Investigator

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 center 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 centers 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.)
4. Forward the recommendations and meeting minutes to the IRBs, other clinical centers involved, and NINR program staff.

DATA AND SAFETY MONITORING BOARD MEETINGS

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, or the NINR Director or designee.

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, The focus of the open session is on the general conduct and progress of the study. Specifically, 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.

2. **Closed Session.**
   A second, closed session involving the voting members invited ex officio members, NIH program staff and the Executive Secretary. During this part of the meeting, grouped safety data and, if appropriate, efficacy data are presented by the protocol specific statistician(s).

3. **Executive Session.**
   The third part of the meeting involves only voting DSMB members, NIH program staff and the Executive Secretary to allow them the opportunity to discuss the general conduct of the trial , all outcome results, including toxicities and adverse events, and implications of data. 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.

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. 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

The DSMB will issue written meeting summary 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. The DSMB written meeting summary of recommendations will be provided to the PI to , to include a copy to provide to the NINR Director or designee as soon as possible after the meeting, but no longer than 20 business days following the DSMB meeting .

DSMB recommendations related to a study change for patient safety or efficacy reasons, or that the study be closed early due to slow accrual or other reasons should be communicated to the PI no later than 48 hours following the meeting.

In the absence of disagreement, the trial PI must act to implement the recommendations as expeditiously as possible in regards to 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. However, in some cases, relevant data may be shared with other selected trial investigators and NINR staff to seek advice to assist in reaching a mutually acceptable decision.

Meeting minutes will be prepared and a final draft version (signed/approved by the ES and DSMB chair) and provided to the NINR Director or designee within 20 days following the meeting. 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.

Final draft minutes will be distributed to the DSMB Members. DSMB members may submit corrections to the minutes via the Executive Secretary prior to the next DSMB meeting. Final minutes will be approved by DSMB Members at the next meeting.

The PI is responsible for forwarding the meeting minutes to the other IRBs involved in the oversight of the study.

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, the NINR Director or designee, and the study leadership.

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.