

Data and Safety Monitoring Guidelines

Last Revised 07/19/2007

Last Reviewed 10/17/2011

- 1...[Introduction](#)
 - 2...[NIH Policies for Data and Safety Monitoring](#)
 - 3...[Data and Safety Monitoring Activities](#)
 - 4...[Data and Safety Monitoring Board](#)
 - 5...[Board Process](#)
-

1. Introduction

The goals of these guidelines are to provide members of the scientific community, current and potential Principal Investigators, and members of the data and safety monitoring committees with the information necessary to protect subjects involved in clinical trials, to ensure the high quality, validity and scientific integrity of the study results and appropriate termination of studies for which significant benefits or risks have been found that impact the conduct of the trial.

Further, these guidelines summarize activities that are required by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), for data and safety monitoring (DSM) in addition to Institutional Review Board (IRB), Office for Human research Protections (OHRP) and Food and Drug Administration (FDA) requirements.

[Top](#)

2. NIH Policies for Data and Safety Monitoring

It is the policy of the NIH that all NIH-sponsored or -conducted clinical trial monitoring activities be commensurate with the risks, nature, size, and complexity of the trial. The NIH requires that NIAMS be responsible for oversight of data and safety monitoring to ensure that a monitoring system is in place, is appropriate for a study, and the Institute is informed of recommendations emanating from monitoring activities. The following documents NIH Policy for Data and Safety Monitoring <http://grants.nih.gov/grants/guide/notice-files/not98-084.html> (released on June 10, 1998) and Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html> (released on June 5, 2000) provide the detailed description of these policies.

Investigators must submit a monitoring plan for all clinical trials as part of the research application. The plan should include a description of the following elements:

- Who monitors the trial?
- How often are the data examined?
- What do monitors look for?
- What are the feedback mechanisms for protecting patient safety?

- What is the oversight by institutional committees?
- What procedures are in place for coordinating multicenter activities?
- Has the appropriate investigational new drug application (IND) or investigational drug exemption (IDE) been obtained prior to study initiation, if applicable?

“A Guide for Developing a Monitoring Plan for Studies Sponsored by NIAMS” can be located at http://niams.nih.gov/Funding/Clinical_Research/guidelines_monitoring_plan.doc.

This plan will be reviewed by a scientific review group as part of the application, and any comments and concerns will be included in an administrative note in the summary statement of the application review. The data and safety monitoring plan may name a Safety Officer or a committee, also known as a Data and Safety Monitoring Board (DSMB). Observational studies with large (i.e. greater than 1000 participants) or vulnerable populations or risks associated with tests or standard of care are likely to require monitoring oversight either through the Observational Study Monitoring Board (OSMB) or Safety Officer¹. (Note that for the remainder of this document, reference to a DSMB or monitoring body may also include an OSMB.) The ongoing review of the data by an independent individual or committee assures the investigators that the trial can continue without jeopardizing patient safety.

The Safety Officer will be appointed by the grantee institution and approved by NIAMS. For DSMBs, the grantee institution may have input into the selection of members, but the members will be appointed by NIAMS. The DSMB will consist of individuals who are independent of the institution(s) and investigator(s) participating in the trial. DSMB members must have no financial ties to the outcome of the trial to avoid any conflict of interest.

In small, single-site studies, safety monitoring is often performed by a statistician in conjunction with a Safety Officer. All Phase III studies and blinded and/or high risk Phase I or II therapeutic studies must be supported by a DSMB. NIAMS requires that all multi-site clinical trials involving interventions that entail risk to participants have a DSMB.

[Top](#)

3. Data and Safety Monitoring Activities

All studies funded by the NIH must have a Data and Safety Monitoring (DSM) plan. This plan should be developed by the Principal Investigator and submitted to NIAMS for approval. Monitoring activities should be appropriate to the study, study phase, population, research environment, and degree of risk involved. Study phases are summarized in the following link:

http://grants2.nih.gov/grants/funding/phs398/instructions2/p2_human_subjects_definitions.htm.

3.a Frequency of Meetings and Types of Document Review

The following discusses the types of documents reviewed by monitoring body, as well as the timeline for reviews. The documents reviewed by the monitoring body include, but are not limited to:

- The Manual of Operating Procedures (MOOP), including the research protocol and monitoring plan
- Routine reports (i.e., performance, safety and laboratory data)
- Serious Adverse Event (SAE) reports sent in “real time”

¹ Note that reference to a DSMB may also include an Observational Study Monitoring Board (OSMB).

MOOP - The monitoring body must review and approve the **Manual of Operating Procedures (MOOP)** prior to the start of the study. Guidelines to assist Investigators with drafting the MOOP can be located at http://niams.nih.gov/Funding/Clinical_Research/MOOP_guidelines_2007.doc,

Routine Reports - The Investigator will **routinely report ongoing study activities** with emphasis on data integrity and patient safety issues. Report templates can be located at http://niams.nih.gov/Funding/Clinical_Research/NIAMS_sample_documents.asp and are described further in section 5.a. The reports must be customized to each study, and the DSMB or Safety Officer may also request additional reports, as necessary. **DSMBs** will typically review biannual reports at set intervals either by teleconferences or in-person meetings. Additional meetings may be necessary, depending on the nature and complexity of the trial as well as any special circumstances (i.e., problems encountered). An initial meeting with the **Safety Officer** is held by teleconference prior to the study start, and subsequent review of reports can be conducted by email or fax on a biannual basis. The monitoring body will review ongoing study activities with emphasis on data integrity and patient safety issues, including:

- Reporting adverse events to NIAMS.
- Plans for and implementation of dose escalation.
- Recommendations to NIAMS concerning continuation or termination of the trial(s).
- Protection of the confidentiality of the trial data and the results of monitoring.
- Ensuring adequate protection of human subjects and addressing ethical concerns based on Federal Guidelines.
- Data and study quality

Serious Adverse Events (SAEs) - SAEs are sent to the DSMB and Safety Officer in “real time” (within 48 hours). An action plan proposed by the monitoring body is sent to NIAMS and the Principal Investigator, through the Executive Secretary. ,

[Top](#)

4. Data and Safety Monitoring Board

The remainder of this document addresses DSMB activities. The establishment of a NIAMS-initiated DSMB and the DSMB's responsibilities and operating procedures are guided by a charter. NIAMS has developed a template for the charter as shown in DSMB Charter: http://niams.nih.gov/Funding/Clinical_Research/dsmb_charter.asp.

The independent DSMB plays a crucial role in ensuring the safety and welfare of patients enrolled in clinical trials.

[Top](#)

4.a Responsibilities

The DSMB is responsible for assuring NIAMS that subjects are not exposed to unnecessary or unreasonable risks and that the investigator conducts the clinical trial according to the highest scientific and ethical standards.

Initially, for studies that are in the planning and development phase, DSMB responsibilities are to review and make recommendations regarding the research protocol, informed consent documents, quality control plans, and plans for data and safety monitoring prior to the study initiation.

Once a study is implemented, ongoing responsibilities of the DSMB are to:

- Evaluate the progress of intervention trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit ratio, performance of the trial site(s), and other factors that can affect study outcome;
- Consider the impact of factors external to the study when new information, such as scientific or therapeutic developments become available and may affect the safety of participants, their willingness to participate in the study, or the conduct of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety and privacy of study participants;
- Report on the safety and scientific progress of the trial;
- Make recommendations to NIAMS concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Review data after completion of each cohort to approve dose escalation;
- If in the statistical plan, request and review interim analyses in accordance with stopping rules, which may be defined in advance of data analysis and have approval of the DSMB.
- Ensure data integrity;
- Ensure confidentiality of the trial data and the results of monitoring;
- Assist NIAMS by commenting on any problems with study conduct, enrollment, sample size, statistics, and/or data collection; and
- Review and evaluate requests for protocol modifications after the trial begins and advise NIAMS as to whether a study should continue as approved or undergo a protocol modification.

[Top](#)

4.b Membership

Appointment of the members of the DSMB is the responsibility of NIAMS and is independent of the Principal Investigator. However, the study investigators may have input into the selection of members. The voting members should have appropriate expertise in the relevant scientific and methodological areas and may include physicians, laboratory scientists, statisticians, ethicists and patient advocates. Membership should consist of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Current or past collaborators or associates of the Principal Investigator (i.e., same institution) are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

A DSMB member is obligated to bring an issue of any potential conflict of interest to the attention of the full DSMB for open discussion and resolution. The DSMB members are required to complete a conflict of interest disclosure form and a statement of confidentiality on a yearly basis.

A DSMB Chairperson will be appointed by NIAMS, and the DSMB will vote to approve the Chairperson at the first DSMB meeting. This person will be responsible for overseeing the meetings, working with NIAMS and/or the Executive Secretary (ES) to develop the agenda and summarize the meeting. One or more members will be identified as Safety Officer(s) and will be contact person(s) for serious adverse event reporting. An ES from NIAMS or a NIAMS representative may be appointed. The ES coordinates DSMB meetings and telephone conference calls, provides logistics support and meeting summaries. The ES may also provide recommendations to NIAMS, the DSMB Chair and members. The ES and NIAMS official serve as the ex-officio members of the DSMB.

[Top](#)

5. Board Process

The first meeting will take place face-to-face before initiation of the trial to discuss the protocol, approve commencement of the trial and establish guidelines for monitoring. The Chair, PI, and ES (if appointed) should prepare the agenda to address review of the Manual of Operating Procedures (MOOP), initiation of the trial, identification of the Safety Officer, reporting of adverse events, routine reports that the DSMB wishes to receive from the study statistician, stopping rules, interim analysis plan, meeting schedule and dates, and other relevant items.

Following the initial meeting, the DSMB should meet at designated intervals to review accumulated data on safety and, if appropriate, conduct an interim analysis. Meetings may be convened as conference calls or in person, although it is recommended that the initial meeting and meetings to discuss interim analyses be face-to-face. An emergency meeting of the Board may be called at any time by the Chairperson or NIAMS should questions of patient safety arise.

An appropriate format for DSMB meetings consists of an open and a closed session. The **open sessions** may be attended by investigators, institution staff, and NIAMS staff, and should always include the Principal Investigator and the study biostatistician. Issues discussed at open sessions usually focus on the conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data are not presented in the open session.

The **closed session** is normally attended only by the DSMB members and appropriate NIAMS staff representative(s) and the ES. Others, such as the study statistician, may attend if requested by the Board. If necessary, all unblinded safety data and efficacy data may be presented at this session. The discussion at the closed session is completely confidential.

The **executive session** will be held following the closed session to identify and discuss the DSMB's recommendations to NIAMS. It will be attended by three or more voting DSMB members and NIAMS staff and their representatives. The study staff may be present, at the request of the DSMB during the executive session.

Each meeting should include a recommendation to continue or to terminate the study made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, the majority vote will rule and a minority report should be appended. In the event of a 50-50 split vote, the DSMB Chair provides the tie breaker.

[Top](#)

5.a Meeting Materials

A packet of information that describes study status should be prepared by the coordinating center/statistical office and sent to the ES by email at least two weeks prior to the meeting for immediate distribution to the DSMB. The content of the reports should be determined by the DSMB at the first meeting and may be augmented as the study progresses. The need and requirements for an interim analysis may also be discussed at any time during the study. The ES will post the materials to the password-protected safety monitoring materials website. Hardcopy reports may also be express mailed to the DSMB members, if requested. Materials may be presented in two parts. Part 1 contains reports for the open session of the meeting and Part 2 contains materials for the closed session. Template reports can be located at http://niams.nih.gov/Funding/Clinical_Research/NIAMS_sample_documents.asp.

Part 1 reports for the open session of the meeting include administrative reports by site and summarize the number of patients screened and the participants screened, enrolled, completed, and discontinued. In addition, open session reports typically include baseline characteristics of the study population, listings and summaries of adverse events and serious adverse events. Other information requested by the DSMB may also be in the open session report, but none of the data should be presented in an unblinded manner. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis.

Part 2 reports for the closed session may contain safety data in aggregate or by blinded treatment group, interim analyses, or other data or formats as requested by the DSMB. The closed session reports are confidential and posted to the password-protected website. If determined necessary, hardcopies of the closed session materials may be distributed prior to and during a meeting are collected by the ES or study statistician(s) at the conclusion of the meeting. It is important that access to outcome data be limited to the study statistician and/or safety monitor and DSMB, when necessary, to protect the study from bias in patient entry and/or evaluation.

[Top](#)

5.b Recommendations and Meeting Minutes

DSMB recommendations are prepared by the ES immediately following each meeting and are submitted to NIAMS and the DSMB Chair for initial comment and approval. They are then submitted to the full DSMB for comment and approval, and the final recommendations are distributed to all DSMB meeting participants within one week. Full meeting minutes follow the same review process and are distributed to the DSMB meeting participants within 45 days of each. Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal, majority vote.

[Top](#)

5.c Mailings to the DSMB

On a scheduled basis (as agreed upon by the DSMB), blinded safety data should be communicated to all DSMB members or to the one member who serves as the designated Safety Officer. Any concerns noted should be brought to the attention of the Chair or Safety Officer who will take appropriate action.

[Top](#)

5.d Interim Analyses

If an interim analysis is determined necessary, access to this information and any accumulating endpoint data should be limited to as small a group as possible. Limiting the access of interim data to the DSMB relieves the investigators of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined.

5.e Termination of Study

A termination recommendation may be made by the DSMB at any time. Such a recommendation should be transmitted to NIAMS, who will communicate the recommendation to the Principal Investigator, business official of the grantee institution, and the FDA (if appropriate) as rapidly as possible, by immediate telephone, email and/or telefax, if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the DSMB report.

Top

[Top](#)

5.f Confidentiality

All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

[Top](#)