

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Data and Safety Monitoring Guidelines

September 30, 2014

- 1...[Introduction](#)
- 2...[The NIH and the NIAMS Requirements for Data and Safety Monitoring](#)
- 3...[Data and Safety Monitoring](#)
- 4...[Board Process](#)

DEFINITIONS:

Clinical Research¹ - Research with human subjects that is:

1. Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes:
 - mechanisms of human disease
 - therapeutic interventions
 - clinical trials
 - development of new technologies
2. Epidemiological and behavioral studies.
3. Outcomes research and health services research.

Studies falling under 45 CFR part 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition.

Clinical Trial² - A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Data and Safety Monitoring Plan (DSMP)³ - 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. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted

¹ NIH, *Glossary*. Accessed at <http://grants.nih.gov> on September 18, 2014.

² Ibid

³ Ibid

to the applicant's IRB and subsequently to the awarding IC for approval prior to the accrual of human subjects.

Masked Data – Study data which are reported in aggregate (summary) so that the assigned treatments and study outcomes are not revealed.

NIAMS-appointed Safety Officer (SO) – An independent individual, often a clinician who is appointed by the NIAMS and performs data and safety monitoring activities in low-risk, single site clinical studies. The Safety Officer advises the NIAMS regarding participant safety, scientific integrity and ethical conduct of a study. The SO is advisory to the Institute Director.

NIAMS-appointed Data and Safety Monitoring Board (DSMB) - A group of individuals appointed by the NIAMS who are independent from the study investigators and have relevant study expertise to monitor participant safety, data quality and to assess clinical trial progress on a regular basis from one or more ongoing clinical trials. The DSMB is advisory to the Institute Director.

NIAMS-appointed Observational Study Monitoring Board (OSMB) – A group of individuals appointed by the NIAMS to provide ongoing review for an observational study to help assure the integrity of the study. The OSMB closely monitors data acquisition for comprehensiveness, accuracy, and timeliness; and monitors other concerns such as participant safety and confidentiality

Program Official (PO) -The NIAMS Program Officer Representative who attends the DSMB meetings. The PO is not considered a DSMB member.

Unmasked Data by Group – Study data which are reported by group (e.g., A and B) and reported in such a way that the intervention and study outcomes are not revealed.

Unmasked Data by Intervention - Study data which are reported by intervention (e.g., placebo and steroid) to the monitoring body under certain circumstances (e.g., a planned interim analysis or concerns about accumulating adverse events).

1. Introduction

The purpose of this document is to outline the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) requirements for data and safety monitoring of clinical research studies funded in whole or in part by the NIAMS. The audience of these guidelines is intended to be members of the data and safety monitoring (DSM) bodies, current and potential Principal Investigators, and NIAMS staff. These guidelines comply with the National Institutes of Health (NIH) mandate for requiring safety oversight by outlining the NIAMS responsibilities for ensuring the appropriate monitoring is in place. These guidelines inform the DSM bodies of the stewardship and logistical responsibilities of the NIAMS staff and the staff who provides Executive Secretarial support for DSM operations. They also outline the activities necessary to ensure the high quality, validity and scientific integrity of the study results, and allow for the appropriate termination of studies for which significant benefits or risks have been found that impact the conduct of the trial. They emphasize that the DSM activities may evolve as new information is known about the trial, research area and intervention under study.

This document summarizes DSM activities required by the NIAMS and the NIH. It emphasizes that the DSM bodies are advisory to the Institute Director, and the NIAMS carefully considers all DSM recommendations. Additional reporting requirements [e.g., to the Institutional Review Board (IRB), the Office for Human Research Protections (OHRP) and/or the U.S. Food and Drug Administration (FDA)] are

separate from these guidelines and are the responsibility of the Principle Investigator and/or the institution receiving NIH funding, as appropriate.

2. The NIH and the NIAMS Requirements for Data and Safety Monitoring

It is the policy of the NIH that clinical trial monitoring activities for studies supported by the NIH be commensurate with the risks, nature, size, and complexity of the trial. The NIH requires that the NIAMS retains critical stewardship responsibility for the clinical trials it supports and in this role, 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 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.

Each clinical trial funded by the NIH must have a Data and Safety Monitoring (DSM) plan. The DSM plan describes monitoring by various entities including an independent Safety Officer (SO) or a committee, also known as a Data and Safety Monitoring Board (DSMB). Monitoring activities should be appropriate to the study, study phase, population, research environment, and degree of risk involved. The DSM is developed by the Principal Investigator and may be revised with NIAMS, DSMB, or SO input once a study has been awarded. The NIAMS ultimately determine the appropriate type of monitoring body for safety oversight. Observational studies with large (typically greater than 1000 participants) or vulnerable populations or risks associated with tests or standard of care are likely to require monitoring oversight either through an Observational Study Monitoring Board (OSMB) or SO.⁴ (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 participant safety.

The DSM is submitted as part of the research application. Refer to the application instructions and Sections 4.1.5 and 5.3: http://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf#Part_II. 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 plan should include a description of the following elements:

- The entity responsible for monitoring the trial. These can include, but are not limited to, monitoring by a:
 - a) PD/PI (required)
 - b) Institutional Review Board (IRB) (required)
 - c) Independent individual/Safety Officer (SO)
 - d) Designated medical monitor
 - e) Internal Committee or Board with explicit guidelines
 - f) Independent, NIAMS-appointed Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative plans may

⁴ Note that reference to a DSMB may also include an Observational Study Monitoring Board (OSMB).

be appropriate. Please note that the NIAMS requires that all multi-site clinical trials involving interventions that entail any risk to participants have a DSMB appointed by the NIAMS. In addition, all Phase III studies and masked and/or high risk Phase I or II intervention studies must also be monitored by a NIAMS-appointed DSMB.

- How frequently will the monitoring occur?
- What is the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations?

In addition to the above, please also include the following information in the DSM plan:

- How often are the safety data examined?
- What types of reports and data will the safety monitoring entity review?
- What safety signals, trends, or triggers does the monitoring entity look for?
- How does the monitoring entity provide its feedback and what are the timelines?
- What is the oversight by institutional committees?
- What procedures are in place for coordinating multi-site activities?
- If applicable, has the appropriate investigational new drug application (IND) or investigational drug exemption (IDE) been obtained prior to study initiation?

“Guide for Developing a Data and Safety Monitoring Plan for Clinical Studies Funded by the NIAMS” can be located at http://www.niams.nih.gov/Funding/Clinical_Research/guidelines_monitoring_plan.pdf

2.a. Types and Frequency of DSM Document Review

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

- DSM Charter outlining the charge to the NIAMS-appointed monitoring body
- Study materials (e.g., the Manual of Operating Procedures (MOOP), the DSM plan, research protocol)
- Routine DSM reports (i.e., recruitment/retention, safety (e.g., Adverse Event) and laboratory data)
- Serious Adverse Event (SAE) reports or other expedited reports (e.g., protocol violations that impose serious safety risks)
- Interim analysis reports for safety, efficacy and/or futility
- Ad hoc reports, as requested

DSM Charter - The Charter outlines the charge to the NIAMS-appointed monitoring body and is intended to be a living document to be modified at any time if any processes or procedures were to change. A formal review and DSMB vote to approve the charter takes place at the initial meeting and on an annual basis or as needed.

Study materials - The monitoring body must review and may make recommendations regarding the study materials (e.g., the MOOP, DSM plan, research protocol) prior to the start of the study or at any time as new information during the study is collected.

Routine DSM Reports - The Investigator will routinely report ongoing study activities with emphasis on data integrity and participant safety issues. The NIAMS Safety Report templates can be located at

http://www.niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp. The reports must be customized to each study and the DSMB or SO may request additional reports, as necessary. The DSM body has the ability to review masked and unmasked clinical trial data by group (e.g., A vs. B) or intervention (e.g., placebo vs. steroid) at its discretion.

Serious Adverse Event (SAE) or other expedited reports - The monitoring body will review SAEs or other expedited reports (e.g., protocol violations impacting the safety of the research participants) and relatedness of events to study/intervention and communicating recommendations regarding SAEs to the NIAMS through the NIAMS Executive Secretary (ES). Expedited reports are submitted to the ES within a predetermined interval (generally within 48 hours). An assessment and action plan proposed by the monitoring body is sent to NIAMS and the Principal Investigator, through the Executive Secretary.

Interim Analyses Reports – Interim analysis may be conducted either due to pre-specified stopping rules as outlined in the protocol and at predetermined intervals, or as determined necessary by the monitoring body to assess safety concerns or study futility based upon accumulating data. An interim analysis may be performed for safety, efficacy and/or futility, and the reports are prepared by the unmasked study statistician or data coordinating center responsible for generating such reports. Interim analysis reports are presented in closed session to the DSMB in an unmasked format and in closed session, without the masked study personnel in attendance.

- Interim analysis for safety: The DSM body may review unmasked interim safety data and recommend termination or modification of a trial due to a trend toward showing harm to the research participants.
- Interim analysis for efficacy: The DSM body may review unmasked interim efficacy data and recommend termination of the trial, based on the interim data, where there is overwhelming evidence that the intervention is highly beneficial.
- Interim analysis for futility: The DSM body may review unmasked interim efficacy data and recommend termination of the trial with the likelihood that the treatment effect being sought, based on the interim data, is very unlikely to be established even if fully enrolled.

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 (e.g., safety problems encountered, interim analysis review). If the trial is being monitored by a Safety Officer (SO) and not a full DSMB, an initial meeting with the SO is held, as needed, by teleconference prior to the study start, and subsequent review of reports can be conducted by email on a biannual basis or at other intervals, as determined necessary. The monitoring body will review ongoing study activities with emphasis on recruitment/retention, data integrity and participant safety issues and make recommendations to the NIAMS. The NIAMS Institute Director holds the final decisional authority and will take the DSM body's recommendations into consideration. DSM activities include:

- Reviewing plans for and implementation of dose escalation
- Providing recommendations to the NIAMS on the adequacy and completeness of the documents and milestones needed to begin the trial. The NIAMS will give approval to allow the study to begin.
- Advising NIAMS on continuing, or stopping the trial(s) or modifying the study protocol based on accumulating data and information. The NIAMS Institute Director holds the decisional authority.

- Ensuring proper protections are in place to safeguard 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.
- Monitoring data and study quality.
- Assessing safety reports during routine intervals and in an expedited manner, as appropriate.

3. Data and Safety Monitoring

The remainder of this document addresses DSM activities and logistics as they relate to a DSMB. However, the activities described may also apply to a single, NIAMS-appointed safety officer after determining a full DSMB is not required. The DSM responsibilities and operating procedures, including the intervals at which the reports are reviewed and the types of data and format (masked and unmasked), are guided by a charter. The NIAMS will draft the charter and ask for the DSMB's input. The charter is intended to be a living document and can be modified at any time. A formal review and DSMB vote to approve the charter takes place at the initial meeting and on an annual basis or as needed.

3.a. Responsibilities

The DSMB is advisory to the NIAMS and is responsible for reviewing data to assure that the study participants are not exposed to unnecessary or unreasonable risks, and the investigator conducts the clinical trial according to the highest scientific and ethical standards.

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. All NIAMS-appointed DSMBs have the ability to review unmasked clinical trial data in during regular or predetermined interim reports or as determined necessary.
- 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.
- Ensure protections are in place for the safety and privacy of study participants.
- Make recommendations to the NIAMS concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment intervention under study. .
- Review data after completion of each cohort to approve dose escalation.
- Request and review interim analyses, if in the statistical plan, 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 the 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 the NIAMS as to whether a study should continue as approved or undergo a protocol modification.

3.b. DSMB Membership and Participation

Appointment of the members of the DSMB is the responsibility of the NIAMS. However, the study investigators may have input into the selection of members with the approval of the NIAMS program staff. 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, such as those in the 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. DSMB members are paid an honorarium by the NIAMS for contributing their time and efforts in DSMB meetings.

In small, single-site studies, safety monitoring is often performed by a NIAMS-appointed SO. While the SO is appointed by the NIAMS, the Principal Investigator and affiliates may provide suggestions of individuals who are qualified to serve in this capacity. The SO will usually be independent of the institution(s) and investigator(s) participating in the trial. The SO must have no financial ties to the outcome of the trial to avoid any conflict of interest. The SO will be paid an honorarium by the NIAMS for contributing their time and efforts to the review of the study materials and biannual safety reports.

A DSMB Chairperson will be appointed by the 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 the NIAMS and/or the ES to develop the agenda, and summarize the meeting. One or more members will be identified as the DSMB Safety Officer (SO) and will be contact person(s) for serious adverse event reporting.

NIAMS staff has stewardship responsibilities for oversight of trial data and safety monitoring and to ensure that a monitoring system is in place and is appropriate for a study, and the Institute is informed of recommendations emanating from monitoring activities. However, NIAMS staff is not, even in an informal capacity, considered DSMB "members" and does not have voting privileges. A limited, designated number of NIAMS staff attends the DSMB meetings and may not influence or provide input into the DSMB recommendations.

The NIAMS ES coordinates the DSMB meetings and telephone conference calls, and provides logistics support and meeting summaries. The ES will transcribe the meeting recommendations and minutes and will distribute them to the NIAMS, the DSMB Chairperson and members.

4. Board Process

The first meeting will take place before initiation of the trial to discuss the protocol, approve commencement of the trial and establish procedures for monitoring. The NIAMS, DSMB Chair, PI, and ES will prepare the agenda to address review of the study protocol, Manual of Operating Procedures (MOOP), initiation of the trial, identification of the SO, reporting of adverse events, types and format of the reports that the DSMB wishes to receive from the study PI and statistician, stopping rules, interim analysis plan, the ability of the DSMB to request and circumstances under which the members can review unmasked clinical trial data, meeting schedule and dates, and other relevant items. The DSMB charter will outline the Board Process. During the initial DSMB meeting, a NIAMS representative will provide a training session outlining the board process and DSMB procedures for all meeting participants (DSMB members, study staff and NIAMS staff).

Following the initial meeting, the DSMB should meet at designated intervals to review accumulated data on safety. 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 in-person. To facilitate its role as the decisional authority, NIAMS staff who are directly involved in the NIH stewardship and clinical oversight of the clinical trial attend all DSMB meetings and meeting sessions (i.e., open, executive, and closed sessions) as objective observer, not a DSMB member. The NIAMS ES also attends all DSMB meetings and meeting sessions in order to provide logistical support and transcribe meeting summaries. Should questions of participant safety arise, the Chairperson or the NIAMS may call an emergency meeting of the Board at any time.

4.a. DSMB Meeting Sessions

An appropriate format for DSMB meetings consists of open, executive and closed sessions. The **open sessions** may be attended by investigators, institution staff, NIAMS staff, the ES 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 participant accrual, compliance with protocol, and problems encountered. Participant-specific data and treatment group data are not presented in the open session. The number of NIAMS staff attending DSMB meeting should be minimized and only include experienced and trained Program Officials, Medical Officers, and Clinical Coordination staff.

The **closed session** is normally attended only by the DSMB members, the NIAMS staff representative(s), the ES, and the unmasked study statistician. If necessary, all unmasked safety data and efficacy data by treatment group may be presented at this session. The DSMB determines in advance what format it wishes to see the data in the closed session. The discussion at the closed session is completely confidential and thus attendance is limited to the particular members listed above, based on their safety monitoring and oversight roles and responsibilities.

The **executive session** will be held after the closed session to identify and discuss the DSMB's recommendations to the NIAMS. It will be attended by three or more voting DSMB members, the non-voting NIAMS staff representative(s) and the ES. The NIAMS must not influence or provide input into DSMB's recommendations.

Each meeting should include a recommendation to the NIAMS 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. The decision is ultimately made by the Institute Director, taking into consideration the recommendation of the DSMB.

4.b. DSMB Meeting Materials

A packet of information that describes study status should be prepared by the study data coordinating center or other study staff, such as the study statistician, 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.

4.c. Recommendations and Meeting Minutes

DSMB recommendations to the NIAMS are prepared by the ES immediately following each meeting and are submitted to the NIAMS and the DSMB for comment and acceptance to ensure that they reflect the discussion at the meeting.

4.d. Interim Analysis

If an interim analysis is pre-specified or 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 unmasked, interim data to the DSMB relieves the investigators of the burden of deciding whether it is ethical to continue to randomize participants, and helps protect the study from bias in participant entry and/or evaluation. Data files to be used for an interim analysis 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.

Stopping rules should be pre-specified in the research protocol at the onset of the study and documented in the DSMB's charter. If the DSMB decides to remain masked for a certain period of time and/or if an interim analysis is not planned, the DSMB charter and study MOOP should clearly outline the stopping rules and the point at which the DSMB will become unmasked.

Examples of when unmasking may be required:

- At the request of the Data and Safety Monitoring Board (DSMB) or Safety Officer for a safety concern.
- Clinical treatment decisions are necessary or when a serious adverse event occurs and the treatment allocation must be made known. This is called emergency unmasking.
- During an unmasked analysis in accordance with the study Statistical Analysis Plan (e.g., an interim analysis).
- At the conclusion of the study to determine the effect of the intervention.

4.e. Termination of Study

A termination recommendation may be made by the DSMB at any time. Such a recommendation must be transmitted to the Institute Director, who will make a final determination. If the NIAMS concurs with the recommendation, the Institute 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 minutes.

4.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.

4.g. NIAMS DSMB Ombudsman

Any concerns related to the NIAMS staff attendance or participation in DSMB meetings may be directed to the NIAMS Deputy Director.