

**National Institutes of Health (NIH)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Data and Safety Monitoring Board (DSMB) Charter**

[STUDY/TRIAL NAME]

Grant No: [GRANT NO]

Contract No: [CONTRACT NO]

Cooperative Agreement No: [COOPERATIVE AGREEMENT NO]

[PI NAME AND CREDENTIALS], Principal Investigator

[INSTITUTION]

Last Approved Date: TBD

INTRODUCTION

This Data and Safety Monitoring Board (DSMB) acts in an advisory capacity to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH) to review safety data and [study/trial] progress for “[STUDY/TRIAL NAME].” This [study/trial] is funded partially or in whole by the NIAMS. The purpose of this document is to outline the NIAMS charge to the DSMB regarding its responsibilities, composition, and processes for “[STUDY/TRIAL NAME].” The NIH mandate requires safety oversight and monitoring for all interventional studies to be commensurate with risks, nature, size, and complexity of the [study/trial]. The Charter is intended to be a living document to be modified at any time. Annual review, modification, and approval of the Charter are facilitated by KAI Research, the Executive Secretary.

NIAMS RESPONSIBILITIES

NIAMS staff have stewardship responsibilities for oversight of the data and safety monitoring of its [studies/trials]. Responsibilities of the NIAMS include, but are not limited to:

- Ensuring that a monitoring system is in place and is appropriate for the [study/trial].
- Selecting DSMB members that have relevant expertise for the [study/trial].
- Providing DSMB members access in a timely manner to study documents and milestones, and masked/unmasked data.
- Attending all DSMB meetings and meeting sessions. A limited, designated number of NIAMS staff attend the meetings. NIAMS staff are not members and do not have voting privileges. The NIAMS may not influence or provide input into the DSMB recommendations. They may, however, raise questions to or seek clarification from the DSMB and the investigators during the meeting.

- Serving as the decisional authority and accepting or rejecting recommendations from the DSMB.

Other NIH program staff who attend the DSMB meetings are held to the same responsibilities.

EXECUTIVE SECRETARY

A NIAMS contractor, KAI Research, Inc., serves as the Executive Secretary and drafts meeting agendas in consultation with the PI, DSMB Chairperson, and the NIAMS Program staff. KAI coordinates the DSMB meetings and telephone conference calls, and provides logistics support and meeting summaries. KAI transcribes the meeting recommendations and minutes and distributes them to the NIAMS, the DSMB Chairperson, and DSMB members. KAI is the primary contact point for DSMB communication with the NIAMS and the PI.

DSMB RESPONSIBILITIES

Responsibilities of the DSMB are to:

- Review the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, including all proposed revisions. The Manual of Operating Procedures (MOOP), which may contain the sections included above, is also reviewed.
- Evaluate the progress of the [study/trial] (s) on an ongoing basis, as needed, including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of [study/trial] site(s), and other factors that can affect the outcome.
- Evaluate safety throughout the course of the [study/trial] through the routine review of aggregated adverse event safety data, in addition to expedited review of unanticipated problems, serious adverse event reports, and protocol deviations/violations impacting participant safety. The DSMB Safety Officer reviews the documentation provided by the study team and makes recommendations to the NIAMS regarding protection of the [study/trial] participants.*
- Evaluate proposals of new sites (that differ from the approved application) and make a recommendation to the NIAMS as to whether the enrollment at the site(s) is expected to enhance overall enrollment. Activities include evaluating the patient population pool, catchment area description, recruitment plan, and target enrollment for any new clinical sites.
- Consider the impact of factors external to the [study/trial] when new information, such as scientific or therapeutic developments, becomes available and may affect safety of

*Questions from the investigators regarding individual participants, such as those involving eligibility, patient care, or unblinding, are outside the purview of the DSMB. The PI is encouraged to consult with a designated study medical monitor and/or the IRB for guidance in these cases.

participants, their willingness to participate in the [study/trial] or the ethics and conduct of the [study/trial].

- Assist the NIAMS by commenting on any problems with study conduct or performance.
- Ensure that the plan for maintaining the confidentiality of the [study/trial] data and the results by the investigative team is appropriate.
- Review and evaluate requests for protocol modifications.
- [Review data after completion of each cohort to approve dose escalation.]
- Review in advance of the [study/trial] initiation the [study/trial] specific stopping rules and plans for interim analyses as established by the PI and selected members of the study team. These plans outline the conditions under which a [study/trial] may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures, or other issues).
- Review the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate, or modify the [study/trial] based on observed benefit or harm in accordance with the planned stopping rules.

The NIAMS may discharge one or all of the DSMB members from their duties when:

- a) “[STUDY/TRIAL NAME]” is complete;
- b) a member is not able to fulfill the DSMB responsibilities as outlined in the Charter;
- c) the NIAMS no longer has oversight responsibilities of the [study/trial] and/or;
- d) a member is found to have a Conflict of Interest.

Additionally, a DSMB member may resign at any point during the [study/trial], when a member:

- a) is not able to fulfill the responsibilities of the position, as outlined in the Charter;
- b) believes a Conflict of Interest exists.

DSMB MEMBERSHIP

This DSMB consists of [NUMBER] members who have been appointed by the NIAMS. [NUMBER] members will constitute a quorum for voting. In the event that quorum is lost during the meeting, the NIAMS decides whether to continue with the remaining members or adjourn the meeting. If quorum is lost during the meeting, a vote may not take place and must be conducted electronically after the meeting with all members.

Membership consists of persons independent of the [study/trial] who have no financial, scientific, or other conflict of interest with the Principal Investigator (PI) or any Co-

Investigators. This DSMB includes experts in or representatives from the fields of [e.g., Orthopedics, Dermatology, etc.):

Ad Hoc Membership

Individuals with additional expertise may be invited by the NIAMS to participate as non-voting members in the DSMB meeting in certain situations. These members do not constitute quorum for voting. Non-voting members must also be independent of the [study/trial] and have no financial, scientific, or other conflict of interest with the PI or any Co-Investigators.

DSMB Chairperson

The DSMB Chairperson is appointed by the NIAMS, and confirmed by DSMB vote at the first meeting. The DSMB members must provide a full consensus vote when electing the DSMB Chairperson. The Chairperson is responsible for overseeing the meetings, working with the NIAMS and/or KAI to develop the agenda, and summarizing all DSMB recommendations to the DSMB, NIAMS, and KAI, with input from the DSMB in Executive Session. The Chairperson is the primary contact person for the DSMB.

Dr. [NAME] has been appointed as the DSMB Chairperson.

DSMB Safety Officer

The DSMB Safety Officer is appointed by the NIAMS and confirmed by DSMB vote at the first DSMB Meeting. The DSMB must provide a full consensus vote when electing the DSMB Safety Officer. The Safety Officer is the DSMB contact person for expedited reports (e.g., serious adverse events (SAEs), protocol violations, and unanticipated problems). Expedited reports must be reported to the NIAMS DSMB Safety Officer, KAI, and the NIAMS Program Officer within 48 hours of the study personnel receiving notification of the event. The Safety Officer provides an assessment of the action taken by the investigative team and makes a recommendation to the NIAMS as to whether further action should be taken (e.g. collection of follow-up information or a full DSMB discussion).

While the NIAMS requires expedited reporting of SAEs through KAI, the Safety Officer and NIAMS do not provide real time assessment of SAEs. It is the responsibility of the Investigator(s) to provide real time assessment and take the necessary, immediate action with regard to participant safety.

Dr. [NAME] has been appointed as the DSMB Safety Officer.

CONFLICT OF INTEREST

Individuals invited to serve on the DSMB must disclose any potential conflicts of interest, whether real or perceived, to the NIAMS. Conflicts of interest can include, but are not limited to, professional, proprietary, and miscellaneous interests. Any real or potential conflicts that develop during a member's tenure on a DSMB must be disclosed for the NIAMS consideration at the time the potential conflict is realized. In addition, written documentation attesting to an absence of conflict of interest is required annually.

Confidentiality

Each member of the DSMB must sign a statement of confidentiality annually. All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

DSMB PROCESSES

Prior to commencement of recruitment, the study team drafts or revises [study/trial] materials (the MOOP, protocol, DSMP, report templates, and any other materials required for the DSMB's review). The study team delivers relevant materials to KAI, who facilitates the review process with the NIAMS and the DSMB through email and a secure website.

- Upon completion of the initial review, the DSMB members are asked to send KAI their comments for consideration by the NIAMS. Accepted comments and recommendations are sent to the PI for review and revision.
- KAI concurrently schedules an introductory teleconference among the PI, DSMB, and NIAMS. All discussions are confidential.

The first meeting is held either by teleconference or in-person before initiation of the [study/trial] to discuss the materials and whether the [study/trial] is ready to commence, establish guidelines for monitoring, and determine the format for future meetings. The NIAMS and KAI prepare the agenda to 1) review the study materials, 2) appoint the DSMB Chairperson and Safety Officer, 3) discuss the plan and timing for safety monitoring, 4) make recommendations to initiate the [study/trial] and/or modify the [study/trial] materials, and 5) review the charter. During the initial DSMB meeting, a NIAMS representative provides a training session outlining the DSMB process and procedures for all meeting participants (DSMB members, study staff, and NIAMS staff).

Reports for both the open and closed sessions and plans for interim analyses (if applicable) should be established at the initial DSMB meeting, although changes throughout the [study/trial] may be requested by the DSMB. In addition, the DSMB members will vote to recommend commencement of the [study/trial].

Routine meetings of the DSMB are generally held two times a year (or at other intervals determined by the DSMB), in-person or via conference call. Attendance at all meetings, both in-person and by teleconference, is highly critical for all DSMB members. Each DSMB member is specifically selected for his/her expertise and thus the member's consistent participation ensures rigorous monitoring throughout the course of the [study/trial]. To facilitate its role as the decisional authority, NIAMS staff attends all DSMB meetings and meeting sessions (i.e., open, closed, and executive sessions) as an objective observer, not a DSMB member. KAI also attends all DSMB meetings and meeting sessions in order to provide logistical support and transcribe meeting summaries. Meetings are closed to the public because of participant confidentiality considerations.

All DSMB discussions are confidential. An ad hoc meeting of the DSMB may be called at any time by the Chairperson or by the NIAMS should ethical or patient safety issues arise. The suggestion to convene an ad-hoc meeting should be transmitted to KAI, who will notify the NIAMS and the Chairperson. Depending on the situation, this meeting may include the Chairperson alone, a quorum of the DSMB, or the full DSMB.

Safety data are reviewed regularly by the DSMB. The DSMB decides how frequently it needs to review safety data and the level of details to be provided.

Meeting Format

DSMB meetings consist of open, closed, and executive sessions. Discussion held in all sessions is confidential. All invited meeting participants, including the investigators, institution staff, the NIAMS staff, and KAI, may attend the **open sessions**. All sessions are normally attended by a minimum of [quorum #] voting DSMB members. The PI and the study statistician must be present. The number of NIAMS staff attending DSMB meetings should be minimized and only include experienced and trained Program Officials, Medical Officers, and Clinical Coordination staff. Other NIAMS staff may be invited to attend only when appropriate. Open session discussion focuses on the conduct and progress of the [study/trial], including patient accrual, protocol compliance, and problems encountered. **Unmasked data are not presented in the open session.**

The **closed session** is normally attended by the DSMB members, the NIAMS staff, KAI, and the unmasked study statistician or unmasked study team designee. **If necessary, all unmasked safety data and efficacy data by treatment group may be presented during the closed session.** The DSMB determines in advance in what format it wishes to see the data during the closed session. The discussion during the closed session is completely confidential, and thus attendance is limited to the particular members listed in this section, 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 is attended by DSMB members, the NIAMS staff, and KAI.

If necessary, a second **open session** to clarify any questions that arise from the DSMB may be held with the study staff. A second **closed or executive session** may also be held, if needed.

Ad-hoc meetings may be held at any time should ethical or safety issues arise. The suggestion to convene an ad-hoc meeting should be transmitted to KAI, who will notify the NIAMS and the Chairperson.

Each meeting, whether routine or ad-hoc, must include a recommendation made by a formal DSMB majority or unanimous vote in the Executive Session to initiate, continue, place on hold, or to terminate the [study/trial]. The decision is ultimately made by the NIAMS, taking into consideration the recommendation of the DSMB. The vote may be postponed until further information is acquired. Should the DSMB decide to issue a termination recommendation, the full DSMB must vote. In the event of a mixed vote, majority vote will rule and a minority report will be appended. The NIAMS Institute Director provides the final decision. KAI will transmit the NIAMS's decision to the PI as soon as possible. Specific recommendations will be transmitted in writing at a later date.

Meeting Materials

DSMB report templates are prepared by the study staff, typically the statistician and/or the data coordinating center in consultation with the [study/trial] PI, to be reviewed by the DSMB; modifications to the reports can be requested at any time throughout a [study/trial]. The reports list and summarize safety data, as relevant, and describe the status of the [study/trial]. All meeting materials must be sent to KAI at least two weeks prior to the meeting for distribution to the DSMB. KAI posts the materials on the NIAMS Safety Monitoring website for access by the DSMB members, study staff, and NIAMS staff. Materials are divided into two parts if requested: Part 1 contains open session materials, which may be shared with the study staff and meeting participants and referenced during any session of the meeting; Part 2 contains closed session materials, which may contain sensitive or unmasked data and should be discussed in closed and executive sessions only.

Part 1 – Open session materials include administrative reports by [study/trial] site that describe patients screened, enrolled, completed, and discontinued, as well as baseline characteristics of the [study/trial] population. Listings and summaries of adverse events and SAEs, along with any other information requested by the DSMB, may also be in the open session report, but none of the data should be presented in an unmasked manner.

Part 2 – Closed session materials may contain safety data in aggregate, by masked treatment group (A/B presentation), by unmasked treatment group, or in other formats as requested by the DSMB. The closed session reports are confidential. Printed copies of the closed reports should be destroyed immediately following the meeting. Hard copies distributed prior to and during an in-person meeting are collected by the study statistician or KAI at the conclusion of the meeting.

It is important that access to outcome data, when necessary, be limited to the study statistician and/or unmasked study team designee and the DSMB to protect the [study/trial] from bias in patient entry and/or evaluation. Any unmasked study personnel should be pre-designated and described in the MOOP.

Meeting Recommendations

Meeting recommendations are drafted by KAI within two working days after the meeting and are distributed for review to the full DSMB. KAI receives comments from DSMB members within two working days. KAI will send one reminder to the DSMB members who have not provided a response within the two-day window. After the two-day window has passed, KAI will send DSMB comments and the recommendations to the NIAMS for review and acceptance. KAI will copy the DSMB Chairperson. The NIAMS may request KAI to follow-up with any DSMB member who has not responded to the request for review of the recommendations.

The NIAMS carefully considers all DSMB recommendations and accepts the recommendations at its discretion. The NIAMS has the decisional authority. Once finalized, the recommendations are posted to the NIAMS Safety Monitoring website and circulated to the DSMB and the PI for their reference.

Once received in writing, the PI has 30 calendar days to submit a formal, written response to the recommendations. If the DSMB and the NIAMS have any further questions or concerns, KAI will notify the PI for further clarification via email. It is the responsibility of the PI and at his/her discretion to distribute the DSMB recommendations or other information from the meeting to all co-investigators and to assure copies are submitted to all the IRBs associated with the [study/trial]. The PI's response will also be discussed at the following DSMB meeting.

Meeting Minutes

KAI drafts the full meeting minutes within 5 working days after the meeting and distributes the full meeting minutes to the full DSMB for review and approval. The DSMB has 3 working days to review and provide comments. KAI will send one follow-up reminder to the DSMB members who have not responded allowing them an additional two days to respond. After two days, KAI will send DSMB comments and the full meeting minutes to the NIAMS for review. KAI will copy the DSMB Chairperson. The NIAMS may request KAI to follow-up with any DSMB members who have not responded, in instances when a DSMB member has not reviewed the minutes. The minutes will be finalized no later than 30 calendar days after the meeting. Once approved by the DSMB and the NIAMS, KAI posts three separate versions (open, closed, and executive) of the approved minutes to the NIAMS Safety Monitoring website and notifies all participants according to the session(s) they attended. Note: Blinded study team members will only have access to open session minutes, whereas unblinded study team members will have access to the closed session minutes. A formal vote to approve the minutes is held at the next DSMB meeting.

Additional Reporting

Monthly Status Updates (pre-enrollment)

A status update regarding recruitment/enrollment start-up should be provided to the NIAMS by the study team through KAI on a monthly basis until the first participant is enrolled.

Monthly Enrollment Reports (during active enrollment)

All clinical trials must provide monthly enrollment reports by the 5th of each month once the first participant is enrolled into the study. These reports will contain an Actual versus Expected graph and a CONSORT diagram and should be submitted to the NIAMS through KAI. The reports will be shared with the DSMB for their reference.

Unanticipated Problems

Unanticipated problems are 1) unexpected events that are 2) related or possibly related to participation in the research that 3) place subjects or others at greater risk of harm than was previously known or recognized. All three criteria above must be met to qualify the event as an unanticipated problem. The Office for Human Research Protections (OHRP), the Department of Health and Human Services (HHS) provides a complete definition and the following guidance for reporting unanticipated problems to the Institutional Review Board(s) (IRBs): *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* (<http://www.hhs.gov/ohrp/policy/advevntguid.html>).

Unanticipated problems must be reported to the NIAMS within 48 hours of the PI receiving notification of the event. The DSMB Safety Officer reviews the unanticipated problems to determine if further action is required.

Serious Adverse Events

All SAEs (regardless of expectedness, relatedness, or if they meet the definition for unanticipated problems) must be reported to the DSMB Safety Officer and the NIAMS through KAI within 48 hours of the PI receiving notification of the event. The report will include a description of the event, as well as the investigator's assessment of expectedness, relatedness, and other relevant information. The investigative team should report any actions taken. The DSMB Safety Officer will receive this information and provide an independent assessment on attribution and expectedness, as well as recommendations for further action, if any (e.g., collection of follow-up information).

Discrepancies with Assessments Concerning Unanticipated Problems

On occasion, there may be disagreements between the investigator and the DSMB regarding the assessment and/ or management of an event that qualifies as an unanticipated problem. The

following excerpt gives guidance for cases where there is a difference of opinion among the DSMB (referred to as the “monitoring entity” in the excerpt below) and the investigator <http://www.hhs.gov/ohrp/policy/advevntguid.html>.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).

Please note: The DSMB and the investigator may have iterative discussions regarding the assessment and may later come to agreement regarding the assessment and/or management of an AE. In cases where the DSMB and investigator come to an agreement after discussions and the event is determined not to be an unanticipated problem, the investigator is not required to report the event as an unanticipated problem to the IRB. Such discussions should take place promptly so as not to delay appropriate reporting to the IRB.

Please also note that if the study is testing an intervention that is regulated by the Food and Drug Administration (FDA), there may be additional reporting requirements to the FDA and the IRB that are not part of the NIAMS DSMB process and are the PI’s responsibility.

Protocol Deviations/Violations

Protocol deviations/violations that impact participant safety should be reported to the NIAMS and the DSMB Safety Officer (through KAI) within 48 hours of the PI becoming aware of the event. Protocol deviations/violations that occur but do not affect participant safety are submitted with the routine DSMB meeting report. The investigator must also adhere to the Institution's policy on reporting protocol deviations/violations to the IRB.

Please note: Additional reporting may be required if the violation meets the definition of an unanticipated problem as described in the OHRP, HHS guidance (<http://www.hhs.gov/ohrp/policy/advevntguid.html>).

Protocol Amendments

Requests for protocol amendment approvals may be submitted by the PI for review by the NIAMS and the DSMB between regularly scheduled meetings. Approvals may be conducted via email correspondence, deferred until the next regularly scheduled meeting, or a call may be scheduled if immediate discussion is warranted. The PI is notified by KAI of the approved changes. IRB review of protocol amendments are separate from this process and are the PI’s responsibility.

Communication with the DSMB

To maintain the independence of the DSMB, the PI and study staff shall only communicate DSMB-related requests, questions, or concerns through the NIAMS or KAI. The DSMB members should only communicate with the PI through KAI and the NIAMS.

Release of [Study/Trial] Data

Publications and abstracts containing primary [study/trial] results are the responsibility of the investigator(s) and prior review or approval by NIAMS or the DSMB is not required. However, the perspective of the DSMB and NIAMS staff can add value to such publications/abstracts, and their comments may be useful to the investigator(s). Therefore, the PI is encouraged to provide the NIAMS with a copy of all abstracts or manuscripts reporting primary [study/trial] results well in advance of submission to a journal or scientific meeting. The NIAMS will distribute the manuscript/abstract to the DSMB members and collect and provide their comments to the PI. The PI may then consider changes to the abstract or manuscript based on comments received from NIAMS.

NIAMS DSMB Ombudsman

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