

DAIDS
Bethesda, MD USA

POLICY

Charter for the Data and Safety Monitoring Boards of the Division of AIDS National
Institute of Allergy and Infectious Diseases (10/18/2012)

Approval Date: 18 OCT 2012
Effective Date: 18 NOV 2012

No.: DWD-POL-CL-018.04A4

Overview

NIH policy requiring independent data and safety monitoring boards (DSMB) for all multicenter Phase III trials has existed since 1979; the most recent restatement was issued in 1998 (NIH Policy for Data and Safety Monitoring, NIH Guide Notice 98-084). In light of the related responsibility for monitoring assigned to local Institutional Review Boards (IRB) by federal regulation (45 CFR 46), NIH added a requirement in 1999 that local IRBs be notified of the outcome of all DSMB reviews, even when no major change has been recommended, to document that data and safety monitoring is occurring as expected (Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials, NIH Guide Notice 99-107).

These NIH policies do not address implementation matters, leaving those to individual Institutes and Centers; various approaches are in use. As a result, the National Institute of Allergy and Infectious Diseases (NIAID) has issued its own policy on basic principles for DSMB operations¹. The Division of AIDS (DAIDS) monitors safety and efficacy of multicenter randomized clinical trials primarily through standing DSMBs. DAIDS believes that standing boards are both more effective and easier to manage than boards established separately for each new trial.

This Charter chiefly describes the organization and procedures of standing DSMBs that oversee most of the randomized trials carried out with funding from DAIDS. It is expected that other future DSMBs involved in oversight of DAIDS trials would have very similar characteristics to the current standing DSMBs, or at least conform to the basic principles articulated in the NIAID Policy. For trials involving collaboration between or among multiple research organizations there will usually need to be detailed discussions to arrive at trial-specific arrangements documented in a trial-specific charter.

Scope of Responsibilities

The “convening authority”² for DAIDS DSMBs is NIAID leadership who has the authority and responsibility to act upon the recommendations of the DSMBs. In unusual situations there may be a different “convening authority”.

¹ NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations, V 3.0, Effective July 2, 2009

<http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Documents/dsmbpolicyv3.pdf>.

² Ibid.

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In general, DAIDS DSMBs will review safety, efficacy, and overall study conduct as specified in the protocol and/or protocol monitoring plan for each trial. Trials are assigned by DAIDS to DSMBs according to the type of trial (i.e., therapeutics, prevention, vaccine) and geographic location of performance sites. The standing and any newly formed DSMBs are available to monitor Phase II, III and IV trials funded by DAIDS both through its networks or outside (e.g., under investigator-initiated cooperative agreements).

There is no presumption that the DSMB will accept responsibility for monitoring any particular trial “as is” (i.e., as designed by the protocol team). It is necessary, therefore, to present each study to the DSMB at the time of its initiation, preferably before enrollment begins. This initial review does not constitute participation in trial design, which would compromise the independence of the DSMB. Rather, it gives the DSMB an opportunity to communicate to DAIDS that it cannot take responsibility for oversight unless major issues and concerns are addressed. In this case, the DSMB will provide DAIDS a comprehensive list of specific issues that need to be resolved before assuming oversight responsibilities.

The DSMB’s role does not necessarily end when the opportunity for stopping enrollment early passes. The DSMB should continue to review summaries of safety data by treatment group at least annually (local IRBs will be notified of the results of these reviews) until either safety follow-up ends or another entity assumes this responsibility.

The DSMB normally will have no role or responsibility for final analyses and preparation of manuscripts for publication.

Membership and Appointment Procedures

Membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the trial, including medicine, statistics and potentially ethics. Selection of DSMB members should include consideration of clinical trials experience, relevant expertise, prior DSMB service, and absence of significant conflict of interest (COI). Terms of appointment are for two to four years and can be renewed. *Ad hoc* members may be added for reviews of specific studies to expand expertise or geographic representation as appropriate for the trial. To hold an official DSMB meeting a quorum consisting of at least three voting members must participate, including at least one clinician and one biostatistician.

No member of the DSMB should have any involvement in the conduct of the studies to be reviewed. Furthermore, no member should have certain financial, proprietary, professional,

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or other interests that may affect impartial, independent decision-making by the DSMB. Members may recuse themselves in the case of such potential conflicts. In general, it is best to avoid appointing individuals who work in the same institution as the investigators. A lead investigator on one trial should not be a member of the DSMB for a different but similar trial. All regular and ad hoc DSMB members will sign a COI certification prior to being asked to participate initially and at least once per year thereafter. Members will be asked to disclose any interests that involve potential conflicts for studies under review prior to each meeting of the DSMB. Consideration of and decisions regarding potential COI will follow the NIAID policy on COI for data and safety monitoring³.

Input for the appointment of a new DSMB Chair is solicited from various sources including current Board members and NIAID staff. The Director of the Division of AIDS appoints the Chair.

Suggestions for potential Board members are similarly sought from various sources. In consultation with the appropriate Board Chair, network or study investigators, and NIAID staff, the NIAID Biostatistician, who acts as Executive Secretary, makes the final decision to appoint a Board member.

As indicated above, selection of members is more complicated when DAIDS networks collaborate with others. When the collaborator is another established research organization, appropriate representatives of each partner will develop plans jointly. For some studies, one of the existing DSMBs may not have representation from a country or region with a substantial number of participating clinical sites. In such cases, DAIDS policy is to add *ad hoc* members representing these countries, or regions, as necessary. These *ad hoc* members are identified in consultation with trial investigators, national ministries of health, and others.

Coordination of DSMB activities is the responsibility of a senior NIAID biostatistician, who acts as Executive Secretary. This individual oversees meeting planning and development of the meeting agendas, prepares the official meeting summaries and notifications of local IRBs, and serves as primary point of contact for inquiries regarding the DSMB.

³ NIAID Policy for Identifying Potential Conflict of Interest for Individuals Serving on Advisory Committees or Independent Safety Monitors Responsible for Data and Safety Monitoring of Clinical Trials, Version 1.0, dated 08/09/2012, effective 11/01/2012
<http://www.niaid.nih.gov/labsandresources/resources/toolkit/guidance/Pages/guidance.aspx>.

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Meeting Planning

DSMBs are expected to meet at least once per year and can convene in the U.S. (typically in Bethesda, MD) or outside of the U.S (e.g., Africa). The agenda for the meetings will be developed by the NIAID in conjunction with the statistical centers and the DSMB Chair. In addition to studies scheduled for a required annual review, protocol initiation reviews and interim data reviews prompted by safety concerns or protocol specifications are added to the schedule. A draft agenda as well as logistical information will be distributed to meeting participants (possibly through the network headquarters) two months in advance of the meeting. Two weeks prior to the meeting, NIAID will distribute the final agenda, copies of the protocols, summaries of previous DSMB reviews, as well as review assignments to the Board.

Meeting Conduct and Data Reports

Meetings will usually be face-to-face, occasionally by conference call (particularly for time-sensitive reviews). Sessions will be of three types, open session, closed session and closed executive session, not all of which would be needed at every meeting (depending upon the trial under review).

Study data reports will be prepared by the study statistician(s) and distributed at least one and preferably two weeks or two weekends prior to a scheduled meeting to those DSMB members and NIAID staff who will participate in the review. The protocol team will determine contents and format initially; the DSMB may request additions and other modifications for subsequent reports. Reports for the meetings consist of separate open and closed session reports.

All material presented at any session will be considered confidential, and copies of reports for closed sessions, except for archival copies retained by the NIAID, will be collected and destroyed following the meeting. In general, closed reports are expected to be declassified not later than seven years after study completion.

I. Open Session: This session is open to observers, including members of the protocol team, coordinating/data center staff, NIAID staff*, representatives of industrial

* Some trials overseen by an NIAID DSMB are supported jointly by other NIH components and/or other federal agencies. In such cases, each supporting agency would be entitled to participate in meetings and receive reports under the same conditions as NIAID staff.

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collaborators, or representatives from the Food and Drug Administration. This open session will deal with issues relating to the general conduct and progress of the study, such as accrual, patient demographics and other baseline characteristics, data quality control, adherence to the protocol, retention, and follow-up. Unless Senior DAIDS Program Staff approve an exception, outcome results must not be discussed during the open session nor included in the open data report even if data are pooled. Discussion should be limited to the DSMB members, protocol chair, and statistician, and observers should refrain from participating unless asked a question or to volunteer a clarification.

Open Data Report: This report is reviewed in the open session. It is routinely distributed to the protocol chair, to DSMB members and to appropriate NIAID staff. Information in the open report includes overall data on study conduct, protocol compliance, site performance, quality control, follow-up, and participant baseline characteristics exclusive of data by treatment group. Note: Pooled safety data may also be reported with limited distribution to the study Chair(s), DAIDS Medical Officer, Branch Chief and Program Director, and may require a session with restricted attendance to discuss this data.

II. Closed Session: At this session, safety and efficacy data by treatment group will be reviewed. Comparative results are presented to the DSMB in closed reports and closed sessions are normally attended only by voting members of the DSMB and one member of the NIAID staff or contractor serving as DSMB Executive Secretary (apart from the statistician who prepared the reports, who may in some instances be a NIAID employee or contractor, and a staff person to assist with taking notes). The study chair does not attend. Reports showing data by treatment group should mask the identity of the groups, and the DSMB will determine if and when to unmask.

In other scenarios where DSMBs have documented significant deficiencies in closed data reports that impact their ability to perform an adequate review, the Division may need to provide support to the study statistician in order to maintain the integrity of the trial. Access to draft closed reports in these specific cases may be granted by the NIAID Deputy Director for Clinical Research and Special Projects to a qualified independent reviewer when needed to ensure quality of reports prior to DSMB submission. The independent reviewer will not perform any study safety monitoring functions, have any interactions with the study team, or be a member of the Program or Branch sponsoring the study. This reviewer may consult with a representative of the DSMB if needed to ensure that concerns of the Board are being fully addressed, but otherwise will have no interactions with the DSMB. Ideally, the Division should explore options of having the study coordinating/statistical center contract directly with a qualified expert in lieu of an NIAID employee or contractor serving in this role. (In this scenario, a request for exception to policy would not be needed.) This type of exception

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should be requested only in critical situations where trial integrity could be compromised; future long term solutions need to be actively explored.

Closed Data Report: This report is distributed to DSMB members and the Executive Secretary only and is reviewed in the closed session. In addition to information included in the open report, the closed report includes safety and efficacy outcome data by treatment group. Ordinarily the by-treatment reports are coded as a safeguard against disclosure through lost documents, and code keys are provided separately to DSMB members and the Executive Secretary.

To address an emerging safety issue, the designated DAIDS Medical Officer/Medical Monitor (MO/MM) for the trial should provide a written request for access to closed safety analyses (in a manner that minimizes unblinding) and attendance at the DSMB session dealing with safety analyses to the DAIDS Director for review and approval [See Attachment 1, Standard Procedures to Determine DAIDS Medical Officer/Monitor Access to DSMB Closed Safety Analyses (10/18/2012).] The DAIDS Director is strongly encouraged to consult with the DSMB Chair [through the NIAID Executive Secretary] before approving the MO/MM's request.

III. Closed Executive Session: This session involves only the DSMB members in order to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding a study.

The DSMB will have the option to invite other participants to attend any part of the meeting to assist in fulfilling its responsibilities.

DSMB Recommendations

Within two weeks after the meeting, the DSMB Executive Secretary works closely with the DSMB Chair to prepare and distribute a report summarizing the DSMB's recommendations, but none of the confidential information presented at the meeting. After approval of the summary recommendations by the full DSMB, the DSMB Executive Secretary forwards the final version to the DAIDS Medical Officer, or other senior DAIDS staff as appropriate, to ensure clarity of the summary prior to its distribution to: the study chair, study statistician, director of the statistical center, network chairs, as relevant, and to other key DAIDS staff. The study chair is then responsible for disseminating the DSMB summary report to other team members as necessary. In the case of trials conducted by networks, the network headquarters may take responsibility for distribution within the network (e.g., posting the meeting summary to a website and notifying investigators where to find it).

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It is encouraged and acceptable for the DSMB to verbally share any recommendations of a routine nature with the team representatives and program officials at the meeting.

Major Recommendation

In circumstances when there is a major recommendation (e.g., to stop a study arm), the Board instead first communicates its formal recommendations only to the DSMB convening authority. After consulting with relevant NIAID staff as deemed necessary by NIAID leadership, the DSMB convening authority's responsible official makes the final decision to accept the recommendations or not. The convening authority may consult with trial leadership prior to making a final decision to accept recommendations or not. If approved, the Executive Secretary circulates the DSMB recommendations as described above. Otherwise, a decision to reject a major recommendation will be communicated to the DSMB with appropriate rationale, after which the DSMB will reach a final determination on the recommendation, and in consultation with senior DAIDS staff, determine its distribution.

Reporting to IRBs

In fulfillment of the NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (release date: June 11, 1999), the NIAID will distribute the final DSMB meeting summaries documenting the occurrence of the meeting and the recommendations to Institutional Review Board (IRB)/Ethics Committee (EC) via the site investigator who forwards to their IRB/EC or directly as appropriate.

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Attachment 1

**Standard Procedures to Determine DAIDS Medical Officer/Monitor Access to
DSMB Closed Safety Analyses⁴ (10/18/2012)**

(1) For New Trials Not Yet Undergoing DSMB Review

- For all DAIDS trials to be monitored by a DSMB, the assigned Medical Officer/Medical Monitor (MO/MM) will assess the study for level of risk and safety concerns during protocol development.
- The MO/MM will also discuss whether to request access to closed safety data and analyses and the underlying safety concern with his/her Branch Chief and Program Director.
- All MO/MM requests for access to closed safety data and analyses pertinent to a safety issue and the rationale will be discussed at the DAIDS's Clinical Science Research Committee (CSRC) or Prevention Science Review Committee (PSRC) review.
- The designated MO/MM should then provide a written request for access to closed safety data/analyses and attendance at the DSMB session dealing with safety analyses to the Director, Division of AIDS [through their Branch Chief and Program Director] for a final decision. The Division Director is strongly encouraged to consult with the DSMB chair [through the NIAID Executive Secretary] before approving a request.
- The DSMB will be informed of decision and rationale to allow access to the closed session safety analyses at the protocol initiation review. The protocol statistician will be present and will be able to ensure that the study safety monitoring plan includes the proper reports for the MO/MM to review.

(2) For Trials Currently Undergoing DSMB Review

⁴ This procedure should be followed for MO/MM requests of any additional restricted information.

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The general process described above will also be applied to trials currently reviewed by DSMBs. The request for access will be discussed at the Branch level and Program level before going forward. Discussion at the CSRC and PSRC is not required. Each DSMB will be informed of these requests for ongoing trials as soon as possible. Program will then provide the Statistical Centers with a list of ongoing studies that will have MO/MM access to closed safety analyses.

(3) For Trials in which MO/MM Does not have Access to Closed Session Safety Data

When the MO/MM does not have access to the closed session safety data/analyses for a DSMB-monitored study, the MO/MM will receive interim reports with aggregated safety data as directed by the study safety monitoring plan. The MO/MM may request access to closed data analyses per the above approval process, if any new information indicates a substantial safety concern. The DSMB and Statistical Center will be informed of approved requests as soon as possible.