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Clinical Research

DATA AND SAFETY MONITORING BOARD (DSMB) GUIDELINES

I. Roles and Responsibilities

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises DMID and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DMID concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;

- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB should conclude each review with their recommendations to DMID as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrollment;
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
- Optional approaches for DMID and investigators to consider when the DSMB determines that the incidence of primary study outcomes is substantially less than expected such as recommendations to increase the number of trial centers or extend the recruitment period; and,
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. Usually, only voting members of the DSMB should have access to interim analyses of outcome data by treatment group. Exceptions may be made when the DSMB deems it appropriate. DSMB members must maintain strict confidentiality concerning all privileged trial results ever provided to them. The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the identities of the groups are necessary for their decision-making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

II. Membership

The membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

DMID staff without direct involvement in study implementation and who meet other membership criteria may participate as *ex officio*, non-voting members. DMID staff serving in these positions must have a current confidential financial disclosure report on file with the Deputy Ethics Counselor, NIAID. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the DSMB although they may attend open sessions of the DSMB meetings.

Conflict of Interest

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Letters of invitation to prospective DSMB and *ad hoc* members should include the following: "Acceptance of this invitation to serve on the xxx DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all DSMB and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix I). At the beginning of every DSMB meeting, DMID program staff or the DSMB Chair will reconfirm that no conflict of interest exists for DSMB members. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any discussion. The DSMB will determine how to handle such potential conflict. The DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss a

member of the DSMB in the event of unmanageable potential conflict.

Selection and Invitation to Participate

The PO holds primary responsibility for the formation of the DSMB unless the Clinical Terms of Award for a grant specifically identify this as the responsibility of the grantee. The PO (or grantee as specified) is responsible for developing the roster of potential DSMB members. Recommendations for proposed members are solicited from many sources. Study investigators and the industrial collaborators should have the opportunity to review the list of proposed members before the candidate's interest and availability are confirmed by the PO (or grantee as specified). The proposed roster of members must be submitted to the Chief, Office of Clinical Research Affairs (OCRA), DMID or designate for review and approval before invitations are issued.

The PO (or grantee as specified) is responsible for identifying the DSMB Chair. He/she may select the Chair or ask DSMB voting members to select the Chair.

Terms of membership are also determined by the PO (or grantee as specified). Participation is generally for the duration of the study. Participation for standing DSMBs convened to monitor multiple protocols or lengthy studies may be for fixed terms. As continuity of review is essential, the duration of fixed terms should be staggered so that no more than one third of the membership changes at any one time.

III. Meetings

The frequency of DSMB meetings depends on several factors including the rate of enrollment, safety issues or unanticipated side effects, availability of data, and, where relevant, scheduled interim analyses. Unless the Clinical Terms of Award for the grant specifically identify this as the responsibility of the grantee, the PO or designee is responsible for convening meetings, selecting a venue, and coordinating the distribution of meeting materials to DSMB members and other meeting participants. The agenda for each meeting is generally developed jointly by the PO, the Principal Investigator (regardless of whether a contract, cooperative agreement, or grant), the study statistician, and DSMB Chair.

The initial DSMB meeting should occur preferably before the start of the trial or as soon thereafter as possible. At this meeting the DSMB should discuss the protocol, set triggers for data review or analyses, define a quorum, and establish guidelines for monitoring the study. Guidelines should also address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol.

At this meeting, the DSMB should also develop procedures for conducting business (e.g., voting rules, attendance, etc.). DMID staff may discuss DMID's perspective on the study at this initial meeting.

Once a study is implemented, the DSMB should convene as often as necessary, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed. A DSMB meeting may be requested by DSMB members, the PO, industrial collaborator, IRB, or study Principal Investigator at any time to discuss safety concerns. Decisions to hold *ad hoc* meetings will be made by the PO and DSMB Chair. Face-to-face meetings are preferable but conference calls or videoconferences are acceptable alternatives with the agreement of the DSMB members and PO. In the event a DSMB member cannot attend a meeting, he/she may receive a copy of the closed session DSMB report (see below) and either participate by conference call or provide written comments to the DSMB Chair for consideration at the meeting.

A. SMB meeting format

The recommended meeting format consists of three sessions: Open Session, Closed Session, and Closed Executive Session.

1. Open Session

   Issues relating to the general conduct and progress of the study are discussed including adverse events and toxicity issues, accrual, demographic characteristics of enrollees, disease status of enrollees (if relevant), comparability of groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. Any data provided must be presented without grouping by treatment assignment or otherwise by preserving the masking of all subjects. Outcome results must not be discussed during this session.

   DSMB members, voting and *ex officio* members, NIAID staff members and *ad hoc* experts attend this session. The lead investigator and the study biostatistician should be in attendance in order to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industrial collaborators, representatives from the Food and Drug Administration (FDA), and DMID program and regulatory staff.

2. Closed Session

   Grouped safety data and, if appropriate, efficacy data are presented by the study statistician(s) at this session. Grouped data should be presented by coded treatment arm. This session is normally attended only by voting members, study statisticians, and invited *ex officio* members. The DSMB may invite the participation of other individuals for all or part of the session.

3. Closed Executive Session

   This final session involves only DSMB voting members to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding the study. If treatment codes have been made accessible to the DSMB, then the DSMB may unmask the data based on procedures identified in advance.

B. Voting

A quorum, as defined by the DSMB in the initial meeting, must be present either in person or by conference call. After a thorough discussion of DSMB members' opinions and rationale and an attempt to reach clarity regarding individual recommendations, the final recommendations of each DSMB member should be solicited in Closed Executive Session (*ex officio* members shall not vote and shall not be present at this voting session). The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc.

IV. Study Reports for DSMB Meetings

It is the responsibility of the PI to ensure that the DSMB is apprised of all new safety information relevant to the study product and the study. This includes providing the DSMB with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the DSMB. The DSMB should receive all protocol revisions and may receive other documents relating to the study.

Reports are prepared by the study statistician(s). The study statistician should provide suggested formats or templates for data presentation for the initial meeting of the DSMB. The DSMB and DMID must review and approve the data elements

to be presented. At subsequent meetings, additions or modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Written reports should be sent to DSMB members prior to the meeting and should allow sufficient time for review.

Reports for meetings of the DSMB consist of two separate parts: Open Session Report and Closed Session Report. Open Session reports are distributed to DSMB members, selected DMID staff, and other appropriate persons as directed by the DSMB at least one week prior to a scheduled meeting. Closed Session reports are distributed on the same schedule but only to DSMB members and others as designated by the DSMB Chair. The data presented in the reports must reflect both the need for the fullest possible information on trial results and the need to assure reliability and accuracy of the information included.

A. Part 1 (Open Session Report)

This report provides information on study conduct, as outlined in Section III.A.1 above, such as accrual, appropriate demographic representation, baseline characteristics, protocol compliance, site performance, quality control, and currency of follow-up. General (ungrouped) adverse events and toxicity issues are also included in the open report.

B. Part 2 (Closed Session Report)

This report may contain data on study outcomes, including safety data and, depending on the study, efficacy data coded by group. It may also contain data from the Open Session report but presented separately for each study arm. Interim analyses of efficacy data are presented only when planned in advance and appropriate statistical criteria for assessing evidence of efficacy have been clearly addressed. Supplemental information may need to be furnished immediately after the meeting if the DSMB decides that such follow-up is needed in order to conclude their deliberations.

The Closed Session Report is **confidential** and marked accordingly. Copies of reports distributed prior to and during a meeting are collected by the study statistician(s) at the end of the Closed Session. Procedures for securing closed reports distributed to telephone and videoconference participants should be specified in advance of the meeting.

V. Other Reports of Study Progress

Masked safety and enrollment data may be forwarded

periodically to all DSMB members or to the member who serves as the Independent Safety Monitor. The DSMB receives all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters. Appropriate follow-up procedures, such as for directing concerns or requests for further information to the PO or designated DMID staff, should be identified in advance.

VI. Reports from the DSMB

A. Verbal Report

At the conclusion of a DSMB meeting, the DSMB should discuss its findings and recommendations with DMID representatives and the study investigators. If DMID is not represented at the meeting, the DSMB Chair should contact DMID immediately after the meeting to debrief the PO, the Chief, Office of Clinical Research Affairs (OCRA), and Chief, Office of Regulatory Affairs (ORA).

B. Summary Report

The DSMB will issue a written summary report that identifies topics discussed by the DSMB and describes their individual findings, overall safety assessment and recommendations. The rationale for recommendations will be included when appropriate. This report will generally not include confidential information. The DSMB Chair or designee is responsible for drafting, circulating and obtaining approval from other DSMB members within two (2) weeks of the meeting.

The final summary report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff. The study team representative is responsible for disseminating the DSMB summary report to site investigators who must, in turn, submit the report to their local IRBs. If under an IND, the sponsor will forward the summary report including routine and nominal findings to the Food and Drug Administration (FDA) and to any other industrial collaborators.

C. Closed Session Report (optional)

The DSMB may also prepare confidential minutes that include details of closed session discussions. Meeting minutes are to be held in strict confidence, accessible only to voting members of the DSMB until such time when the study is closed or the DSMB recommends early termination or in the event the minutes are requested by the FDA or NIAID for participant safety reasons or for regulatory purposes.

D. Immediate Action Report

The DSMB Chair will notify the PO of any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial. The PO will immediately inform appropriate DMID staff, including: the Chief, OCRA, the Chief, ORA, and the Deputy Director of DMID or designate. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DMID in writing by e-mail, fax, or courier on the day of the DSMB meeting. This written, confidential report may contain unmasked supporting data and include the DSMB member's rationale for their recommendations. The report should be submitted to OCRA and ORA for submission to the FDA, if under an IND.

See Appendix IV for the DMID sign-off sheet for the above reports.

VII. Relationship Between DSMBs and IRBs

NIH policy has explicitly identified required communications that must occur between DSMBs and Institutional Review Boards (IRBs) ("Guidance on reporting adverse events to IRBs for NIH-supported multicenter clinical trials" dated June 11, 1999 (**http://grants.nih.gov/grants/guide/notice-files/not99-107.html**)). The DSMB should provide feedback at regular and defined intervals to the IRBs. After each meeting of the DSMB, the DSMB's Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to his/her local IRB.

VIII. Executive Secretary

An Executive Secretary (ES) may be designated to coordinate the effective functioning of the DSMB. The DSMB Chair may designate an ES for DSMBs established by grantees. The PO may serve as the ES for DSMBs. The ES may not vote or be present during Closed or Closed Executive Sessions and should not have access to the closed session reports and materials.

Responsibilities include:

- Coordinating communications between DSMB members

and other meeting participants such as *ex officio* and *ad hoc* members;
- Overseeing meeting logistics including: selecting meeting dates and locations, providing reimbursement for per diem and DSMB honorarium, and assisting with other travel arrangements;
- Assisting the DSMB Chair with preparation and dissemination of meeting summary reports and other appropriate non-confidential documents;
- Obtaining conflict of interest statements; and,
- Preparing thank you letters/letters of appreciation to recognize and acknowledge DSMB members' contributions.

IX. Reimbursement

1. Per diem

   DSMB members should be intellectually and financially independent of trial investigators. If the reimbursement of DSMB members for their participation is not directly from the NIAID, then reimbursement must be provided by funds restricted for this purpose. DSMB members will receive per diem and travel expenses in accordance with Standard Government Travel Regulations. Members who are officers or employees of the United States shall not receive compensation for service on the DSMB.

2. Honorarium

   If deemed appropriate by the PO and funds are available, an honorarium of up to $200 per day may be offered to members who are not full-time Federal employees. Members who are employees of the United States Government shall not receive an honorarium for service on the DSMB.

CONFLICT OF INTEREST CERTIFICATION
FOR MEMBERS OF DATA AND SAFETY MONITORING BOARDS (DSMB)

Confidential

DSMB for the ABC Trial on XYZ

- I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;

- I do not have any financial interests or assets that exceed $10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;

- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,

- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

PLEASE COMPLETE BELOW.

☐ No relevant interests or activities.
☐ I will disclose exception(s) to the DSMB prior to any discussion so that they can be reflected in the minutes along with the DSMB's determination as to how to handle such exception(s).

I will notify the DSMB's Executive Secretary promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

Member's name (please print)	Signature	Date

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