Charter for the Data and Safety Monitoring Boards of the Division of AIDS National Institute of Allergy and Infectious Diseases (10/18/06)

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.

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 document chiefly describes the organization and procedures of the standing DSMBs that oversee most of the randomized trials carried out with funding from DAIDS. Currently these are the Therapeutics Trials DSMB formed in 1986, the Vaccine and Prevention DSMB created in 1998 by the merger of two DSMBs formed earlier, the International DSMBs – African formed in 2005, the Multinational DSMB created in 2003, and the Asia DSMB formed in 2006. It is expected that other DSMBs involved in oversight of DAIDS trials would have very similar characteristics, or at least conform to the same Basic Principles (see below). 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 Therapeutics Trials DSMB will oversee Phase III/IV trials conducted primarily in the US by the AIDS Clinical Trials Group (ACTG), and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), and any other network created in the future to conduct therapeutics research funded by DAIDS. Similarly, the Vaccine and Prevention DSMB will oversee Phase Phase II B and III/IV trials conducted by the HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), the Microbicide Trials Network, and any other network created in the future to conduct vaccine or prevention research funded by DAIDS. The International DSMB – African and the International DSMB – Asia will oversee adult and pediatric therapeutics, vaccine, and prevention trials funded by DAIDS and conducted primarily in Africa and Asia, respectively. Trials are

assigned by DAIDS to DSMBs according to the type of trial and geographic location of performance sites. The standing DSMBs are available to monitor Phase III/IV trials funded by DAIDS outside the networks (under investigator-initiated cooperative agreements, for instance). Requests for DSMB oversight of Phase I and II trials, whether conducted by a DAIDS network or not, can be considered by DAIDS, the investigators, and the DSMB on a case-by-case basis.

There is no presumption that the DSMB will accept responsibility for monitoring any particular trial as is. 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 all 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. It is appropriate to include expert biostatisticians, medical ethicists, regional and community representatives, and clinicians knowledgeable about the diagnosis and treatment of the diseases under study. All appointments will be made by NIAID. Terms of appointment are for 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.

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, or other interests that may affect impartial, independent decision-making by the DSMB. Members may rescue 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 Conflict of Interest certification to that effect at the time they are asked to participate and periodically thereafter. Members will be asked to disclose any new interests that involve potential conflicts prior to each meeting; the DSMB will determine the appropriate means of dealing with any such disclosures for that meeting.

Input for the appointment of a new DSMB Chair is solicited from various sources including current Board members, members of the NIAID, as well as the NIH community. The

Director of the Division of AIDS makes the final selection from a list of 3-4 eligible candidates and 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 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.

Meeting Planning

The Therapeutics Trials and the Vaccine and Prevention DSMBs will meet approximately every four months for 1-2 days in Bethesda, MD. The International DSMB – Africa, the Multinational DSMB, and the Asia DSMB will meet approximately every six months for 1-2 days. 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 the required annual review, design reviews for new protocols and interim data reviews prompted by safety concerns or *a priori* protocol specifications are added to the schedule. A draft agenda as well as logistical information will be distributed to meeting participants (through the network headquarters where possible) 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

Meetings will usually be face-to-face, occasionally by conference call (particularly for urgent reviews). Sessions will be of three types, not all of which would be needed at every meeting:

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

* 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.

demographics and other baseline characteristics, data quality control, adherence to the protocol, retention, and follow-up. Outcome results must not be discussed during this session. 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.

Closed Session: At this session, safety and efficacy data by treatment group will be reviewed. In general, this session will include only the voting members of the DSMB, the study statisticians, and the Executive Secretary, usually an NIAID biostatistician. The study chair does not attend. In some circumstances, a designated DAIDS Medical Officer/Medical Monitor may receive a copy of the closed report safety analyses and attend the part of the closed session dealing with safety. A specific procedure will be followed to determine DAIDS MO/MM access to the closed session safety data (attached). In rare circumstances, access to closed session efficacy data may be granted by the NIAID Deputy Director for Clinical Research and Special Projects. The DSMB may invite senior DAIDS Program staff to attend closed sessions to provide specific perspectives.

Reports showing data by treatment group should mask the identity of the groups, and the DSMB will determine if and when to unmask.

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.

Study Reports

Meeting reports will be prepared by the study statistician(s) and distributed at least one and preferably two weeks prior to a scheduled meeting to those DSMB members and NIAID staff who will attend the meeting. 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 open and closed session reports. Open session reports are distributed to the protocol chair and to DSMB members and appropriate NIAID staff. Information in the open report includes data on study conduct, protocol compliance, site performance, quality control, follow-up, and baseline characteristics.

Closed reports are distributed only to DSMB members and the Executive Secretary. In addition to information included in the open report, the closed report includes safety and efficacy outcome data by treatment group. Closed session reports with safety data grouped by study arm will be made available to the designated DAIDS MO/MM in circumstances when access to this safety data has been determined for a study. Ordinarily the by-treatment reports are coded as a safeguard against disclosure through lost documents, and code keys are provided separately to members.

All material presented at any session will be considered confidential, and copies of reports for closed sessions, except for archival copies retained by the study statistician and 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.

DSMB Recommendations

At the conclusion of any DSMB meeting, the Board will communicate its routine recommendations to the
trial chair and statistician. Within two weeks of the meeting, the NIAID Biostatistician with the assistance of the DSMB Chair, will prepare a report summarizing the recommendations, but none of the confidential information presented at the meeting, and circulate it to the Board, the study chair and study statistician, the director of the statistical center, the network chairs, and key DAIDS staff. The study chair is 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).

However, DSMB recommendations that involve major changes, such as stopping all or a portion of a study, will be immediately directed to DAIDS by the DSMB Chair for consideration. DAIDS will review the recommendation and the rationale (including background information/closed session data). The NIAID Director will make the decision whether to accept the recommendation. The details of the recommendation and closed session data will not be shared with the study or network investigators at this time. If NIAIDS accepts the recommendation to discontinue all or part of a trial, appropriate closed session data will be communicated to appropriate trial and network leadership and other appropriate NIAID staff.

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), NIAID will distribute a statement documenting the occurrence of the meeting and the main recommendations to the lead investigator at all participating sites. The investigator is required, in turn, to forward the statement to his/her local IRB/EC.

Basic Principles

The fundamental role of a DSMB is to examine safety and efficacy data periodically throughout the conduct of a trial and to make recommendations to DAIDS and the trial steering committee (or other leadership group) concerning continuation, termination, or other modification of the trial. The DSMB also reviews the general progress of the trial (and potential study futility in some cases) and assists DAIDS and the investigators in resolving any problems that arise. Basic principles of DSMBs and their operations are independence, confidentiality, and coordination.

Independence: DSMB members must be independent of both investigators and sponsors to avoid the perception of conflict of interest. Conflicts could arise through financial interests, collaborative professional interests, or others. Unrelated professional contact would not usually present any concern.

There are good reasons for which independent monitoring is desirable. First, the investigator, while the most knowledgeable about the protocol, in the best position to monitor, and the most highly motivated to review trial data promptly, can be too close to a trial to maintain full objectivity. In addition, the investigators often participate in recruiting and taking care of volunteers during the trial, responsibilities that may be much harder to fulfill if the investigators have access to interim data.

Included in the concept of independence is the expectation that DSMB recommendations for a given trial should be based, insofar as possible, on interpretation of the results of that trial and relevant external scientific information published or otherwise in the public domain. Every effort should be made to prevent the intrusion of other considerations into the deliberations of the DSMB. Sponsors, whether from industry or government, would often find it difficult or impossible to isolate DSMB decision making from such considerations as programmatic implications. It is for this reason that employees of the trial sponsor should never serve as voting members of a DSMB.

Despite the independence of the DSMB, it is important to remember that the DSMB, the investigators, and DAIDS are all working towards the same objective of completing trials that generate maximum knowledge at minimum risk to volunteers. The DSMB should therefore be regarded as acting on behalf of the investigators, volunteers, and sponsor; no one benefits from an adversarial relationship.

Confidentiality: Interim data from clinical trials are by definition preliminary, and reports prepared for interim reviews are done under great time pressure. It is only prudent, therefore, to treat the reports and discussions of them as confidential. This is especially important regarding summaries of safety and efficacy data separated by treatment or other randomization group. Knowledge of emerging trends by participating investigators, volunteers, potential volunteers, and others could introduce bias and is subject to overinterpretation that could interfere with the ability to complete the trial.

Limiting access to interim results extends beyond the individuals participating in the trial. No one except those involved directly in preparation of reports or the actual DSMB reviews should be allowed to see the reports or discuss them with those who have seen them, including other investigators, DAIDS staff, FDA staff, staff of industrial sponsors, and DSMBs monitoring separate but similar trials. Departures from this position may be considered, but the justification should be carefully examined and discussed in advance with the DSMB. The main exception would be to help evaluate a possible safety concern.

It is important, however, for adequate monitoring that members of the protocol team be involved in the monitoring process. Regular interactions among the study chair(s), DAIDS medical/program officer, statistician, and others on the team are required to ensure that the trial is proceeding optimally with regard to accrual of volunteers, quality of data, adequacy of

follow-up, compliance with the protocol, frequency of adverse effects, or any other issue that could affect the successful completion of the study.

Coordination: DSMB monitoring, although flexible, must follow a written plan. Plans are specific to each trial, but there are some common features. For example, DAIDS requires that no more than a year should pass between DSMB reviews of cumulative safety data. For some trials, reviews of detailed efficacy results might be somewhat less frequent than that. Any full efficacy review should be accompanied by a full safety review.

The DSMB technically is not part of the process of developing or approving new trials, because such involvement would blur the line between the DSMB and the investigators. On the other hand, it should not be assumed that the DSMB will always be comfortable assuming responsibility for protocols until they have had an opportunity to review them. Thus it is preferable to introduce new protocols to the DSMB before enrollment begins, or, if that is not possible for practical considerations, well in advance of the first review of interim results.

Coordination also acknowledges the fact that data and safety monitoring is a responsibility shared among the investigators conducting the study, the local IRB(s), and DAIDS. Often others are involved as well, such as a designated safety monitor, pharmaceutical sponsor, and the Food and Drug Administration. For example, local IRBs must be informed of the plan for interim monitoring and the role of the DSMB, which is an important reason to include this information in the final protocol.

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Attachment 1

Standard Procedures to determine DAIDS MO Access to DSMB Closed Report Safety Analyses (10/25/06)

For new trials:

- For all DAIDS trials to be monitored by a DSMB, the assigned MO/MM will assess the study for level of risk and safety concerns during protocol development.

- The MO may request access to the safety analyses from the closed report (and attendance at the DSMB closed sessions dealing with the safety) on the basis of risk and safety concerns identified for the study.

- All MO requests for access and the rationale will be discussed at the CSRC or PSRC review.

- The MO will also discuss whether to request access to the closed report safety data and the underlying safety concerns and with his/her Branch Chief, who will make the final determination based on CSRC/PSRC discussion and in consultation with the Program Director.

- The DSMB will be informed of decision and rationale to allow access to the closed session safety analyses at the study introduction session. 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 to review.

For ongoing trials:

This general process 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 access to closed safety analyses.

For trials in which MO does not have access to closed session safety data:

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

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