Data Safety Monitoring Boards: An Education & Familiarization Module

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The intent of this presentation is to provide a brief educational familiarization of the Roles and Responsibilities of DSMBs and their members.
**Definition:** Data Safety Monitoring Boards (DSMBs) are small groups of independent experts charged with (1) reviewing proposed Research Controlled Clinical Trials (CCTs) for ethical conduct and safety; and, (2) periodically considering interim data in order to protect CCT participants’ safety in the interest of preserving the integrity of the CCT and reproducibility of results.

The jurisdiction of DSMBs includes following an CCT completely or partially to make recommendations of (1) continuation, (2) modification, or (3) termination.

Their justification is they are more objective than CCT investigators and sponsors in conducting interim analyses evaluating CCT conduct and will prevent inferior and unsafe conduct, and they are more germane than IRB/CPHSs.
Therefore, DSMBs have far reaching current and future consequences and implications for CCT participants, researchers, sponsors, the generalized body of knowledge, and the course of future research and treatment. The work of their members is critical and members should be familiar with how DSMBs operate and their Roles and Responsibilities as DSMB members.
DSMBs vs. IRB/CPHSs

Most DSMB members or potential members are more familiar with the work of Institutional Review Boards or Committees for the Protection of Human Research Subjects (IRB/CPHSs) than DSMBs, because IRB/CPHSs are more common, pervasive, and, as researchers, they probably had more exposure to them than DSMBs.

Though IRB/CPHSs and DSMBs compliment each other, the focus of their activities and conduct are independent and vastly different. However, comparing between the two may provide insight into the less commonly known and secretive aspects of DSMBs. (One way to know what a DSMB is, is by learning what it is not.)
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## IRB/CPHSs vs. DSMBs

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DSMB Charter

There are no DSMB regulatory requirements except those imposed by the Sponsor. At minimum, the DSMB’s existence is justified by its deliberations and reports. Members should be well-acquainted with the DSMB Charter, which spells out rules and procedures as well as their roles and responsibilities. DSMB members should have been involved with the design and establishment of the Charter. A well-designed Charter should detail DSMB operations but permit operational flexibility, and it should be considered a checklist or reference for:

- normative monitoring guidelines;
- DSMB roles and composition and structure;
- jurisdiction and responsibilities;
- Adverse Event, and (AE) reporting;
- event triggers for unscheduled reviews, termination guidelines, data unmasking, and data review.
DSMB meetings should be forums for free discussion to take advantage of valuable discourse as a “committee of peers,” and DSMB members should be able to comment on all reports. Recommendations should be by consensus and, when issues are particularly difficult to resolve, by vote. DSMBs should be constituted by odd numbers to allow a vote to break a deadlock. A range of issues and recommendations should be available to members in advance of meetings. Recommendation errors can be avoided through:

- thorough and informed review;
- clarity on study protocol;
- procedures for discourse;
- active participation by all members;
- resolution of differences amicably; and,
- systematic consideration of recommendation options.

A Recommendation error is one that failed to achieve the intended outcome: safer CCTs.

Meetings can be open with non-members and PIs and closed with members’ and sponsors only. Optimally they should be face-to-face but can be teleconferences. Usually one face-to-face meeting a year is required.
Conflict of Interest

A critical element of DSMBs and their members is **Independence**: an absence of a Conflict of Interest, real or perceived. There should be a formal Conflict of Interest policy among members. Before the DSMB is first convened there should be a formal declaration of Conflicts of Interest. Conflicts of Interest must be re-visited before meetings and reviews. Conflict of Interests are in terms of an CCT outcome (financial or non-financial). DSMB Members with Conflicts of Interest should not participate or influence proceedings. Those with unmanageable Conflicts of Interest may be dismissed. **To avoid Conflicts of Interest, DSMBs usually remunerate their members for their time** (usually a gratuity or honorarium), **travel, accommodations, and communications.**
DSMBs are lead by Chairs. Chairs are responsible for facilitating meetings and ensuring they are well-coordinated and conducted orderly. Chairs ensure a conduit between the DSMB, Principal Investigators, and CCT sponsors in that protocols, data, and Adverse Events (AEs) are communicated between CCTs and the DSMB. Chairs should be nominated and chosen by DSMB members with the consent of sponsors. There is consensus in the literature that Chairs should have previous DSMB experience.
The DSMB Biostatistician is responsible for developing, designing, and drafting a statistical plan of analyses at the start of the CCT. This member prepares interim and formal reports to the DSMB in a “digestible and standard format” and orally presents a summary of the reports at meetings. They may make recommendations or Courses of Action in reports. They guide the DSMB in discussions, if statistical or data issues arise. They may provide commentary on CCT publications too, and their work should be acknowledged in CCT publications. They must be competent to apply the methods chosen by the DSMB.

**Note:** The CCT Sponsors own the results of analyses, they are confidential, and DSMB members are appointed their guardians.
Bio-Ethicist

This member helps to ensure that “commonsense” is considered. They may represent the interests of vulnerable populations. They should be aggressive, aware, and constantly vigilant.
DSMB Members

Membership is varyingly defined as those who can participate in proceedings and make recommendations. They are Subject Matter Experts (SMEs) in their fields or vocations. They review and discuss CCTs with circumspection toward: (1) CCT procedures; (2) Data Quality; (3) Safety and Efficacy; and, (4) Protocol Compliance.

DSMBs should be multi-disciplinary but with a focus toward the subject matter of the CCT they are monitoring, and they should:

- Exercise good judgment.
- Have practical experience.
- Be reputable for objectivity, impartiality, and being unbiased.
- Be well-respected and credible.
- Demonstrate knowledge about CCTs and some statistics.
- Have a concern for safety and the objectives of CCTs.
- Work-well under pressure from sponsors and media.
- Demonstrated competency with research oversight.
- Have familiarity with how DSMBs work.
DSMBs must underwrite Staff to ensure coordination and communication between PIs and DSMBs and support of DSMB activities. DSMB members should not have independent contact with CCT PIs. Staff organizes meetings and provides members with CCT materials and communications at least 2 weeks prior to meetings to consider relevance and implications, and drafts reports and meeting notes. They also maintain the DSMB files and records protecting confidentiality.
The DSMB product is its reports on its reviews and deliberations that describe key issues and the rationale for DSMB decisions. Since DSMBs and their members are legally culpable, their reports are brief summaries in comprehensible style and avoiding excessive jargon. Any delay between findings and reporting must be addressed. DSMB reports can be requested through legal proceedings of Discovery and the Freedom Of Information Act. There are 4 possible mutually exclusive Report Recommendations:

- Continue CCT.
- Continue CCT w/ modifications;
- Stop CCT for safety concerns; or
- Stop CCT for lack of efficacy.

DSMB members must be satisfied with the timeliness, completeness, and accuracy of CCT data submitted and subsequent reports.
Recommendations: The task in which DSMB members engage does not have obvious correct answers. However, members must consider the evidence, each others’ viewpoints, assess the relative risks vs. benefits, and achieve a consensus. A DSMB meeting quorum must be present to make Recommendations.

Equipoise: This is the “ideal” to which DSMB members strive. This is defined as the belief that uncertainty exists concerning effectiveness of health interventions, especially those in the CCT.
DSMBs are ultimately responsible for recommending stopping CCTs if the health intervention is clearly harmful or not beneficial. This recommendation is reported to the CCT sponsor. The DSMB establishes stopping rules prior to the CCT based on comparative predicted outcomes between Cases and Controls. There is usually a cut-point between risks and benefits with emphasis on pre-defined Adverse Events (AEs). These are unfavorable or unintended symptoms, signs, and outcomes that may or may not be related to the CCT. PIs are required to report all AEs and their severity and whether they were related to the CCT. DSMBs decide how these are reported, and how other CCTs are alerted to safety hazards. Before a CCT can be stopped, DSMBs should consider:

• Prognostic differences
• Assessment errors
• Missing data
• Side effects & intervening factors
• Adherence
• CCT consistency between groups
• Impact of early termination on DSMB’s credibility
• Statistical error and competence.
DSMB Process and Information Flow

CCT

DSMB

Sponsor

Peter G Kaufmann and Nina Schooler
The Fourth Annual Summer Institute on Randomized Clinical Trials
Airlie, Virginia
July 21, 2004
References
Whitehead J., 1999. On being the statistician on a Data Safety Monitoring Board. Statistics in Medicine, 18 (24), 3425-34.

Resources
http://deainfor.ci.nih.gov/grantspolicies/datasftyltr_dsmbirb.htm
http://www.nhbli.nih.gov/funding/policies/ae_multi_center.htm
http://www.niams.nih.gov/rtac/clinical/conflictofinterest.htm
http://www.nihtraining.com/ohsrsite/irb/Attachments/5-1_DSMB.htm
http://www.nhlibi.nih.gov/funding/policies/dsmb_inst.htm
http://www.niad.nih.gov/dmid/clinresearch/dsm.htm