

# SAE Reporting and Data Safety Monitoring Boards

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# Specific Topics for Today

1. What is the main missions and purpose of a DSMB?
2. Describe the monitoring activities of the DSMB related to reviewing Serious adverse event reporting. What are the guidelines for a DMSB when assessing SAEs?
3. What interactions should occur between IRBs and DSMBs/DMCs with regard to adverse events and unanticipated problems?
4. What interactions should occur between the sponsor and DSMBs/DMCs with regard to adverse events and unanticipated problems?



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# Different DSMBs

## ■ Institutional:

- ☐ meet regularly
- ☐ used by HCC to monitor early phase trials
- ☐ HCC has monitoring plan which includes a DSMB

## ■ Independent:

- ☐ convened for specific study
- ☐ generally for phase III (comparative) studies
- ☐ Sponsor can come in many forms



# Guidelines for initiating DSMB

- for phase III trials of therapies for diseases with significant morbidity and mortality rates
- when a therapy has a known risk of severe side effects even if being used for a different indication
- when the results of the study will be used to recommend therapy to large populations of patients at risk for major events.
- where the participants are at an elevated risk for major adverse outcomes, a DSMB should be considered even if the study only addresses lesser outcomes such as relief of symptoms.



# Purpose

- The fundamental responsibility of every DSMB is to ensure patient safety and study validity by monitoring the accruing interim data of the study and making recommendations based on its analyses as to the continuation of the study.



# DSMBs: *An Education & Familiarization* *Module*

- *Written by Jay Johnson, Ph.D., M.A.H.S & Dianna M. Milewicz, M.D., Ph.D.*

# Data Safety Monitoring Boards

**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 a 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 IRBs.





# Data Safety Monitoring Boards

- DSMBs have far reaching current and future consequences and implications for
  - CCT participants
  - researchers
  - sponsors
  - the generalized body of knowledge
  - the course of future research and treatment.



# DSMBs vs. IRBs

Most DSMB members or potential members are more familiar with the work of IRBs than DSMBs, because IRBs are more common, pervasive, and, as researchers, they probably had more exposure to them than DSMBs.

The focus of their activities and conduct are independent and vastly different.

Comparing between the two may provide insight into the less commonly known aspects of DSMBs.

# IRBs vs. DSMBs

	<b><u>IRB</u></b>	<b><u>vs.</u></b>	<b><u>DSMB</u></b>
<b>Incorporation:</b>	<b>Government Regulation Registration and Assurance of Compliance</b>		<b>Charter</b>
<b>Product:</b>	<b>Decisions Executive</b>		<b>Recommendations Advisement</b>
<b>Timeline:</b>	<b>Final Step to Study Start</b>		<b>Interim Step to Study Start</b>
<b>Jurisdiction/ Sponsor:</b>	<b>Institution, where research conducted</b>		<b>Funding Stream (or Independent Investigator)</b>

# IRBs vs. DSMBs

	<u>IRB</u>	<u>vs.</u>	<u>DSMB</u>
<b>Reports to:</b>	<b>Institution</b>		<b>Funding Sponsor</b>
<b>Structure:</b>	<b>Committee</b>		<b>Board</b>
<b>Membership:</b>	<b>Peers Diverse Group 5 or &gt; w/ study group or vulnerable pop rep (optional)</b>		<b>Experts 3-8, 1 statistician and 1 bio-ethicist &amp; experienced clinicians investigators</b>
<b>Member Service:</b>	<b>Voluntary/Community Service (unless “Hired IRB”)</b>		<b>Remunerated (some Voluntary)</b>
<b>Tenure:</b>	<b>Decided by Institution</b>		<b>Project/Study Delimited</b>



# IRBs vs. DSMBs

	<b><u>IRB</u></b>	<b>vs.</b>	<b><u>DSMB</u></b>
<b>Schedule:</b>	<b>Regular and Continuing (Annual) Reviews</b>		<b>Determined by Project/Study Timetables</b>
<b>Proceedings:</b>	<b>Face-to-Face, Teleconference Consensus and Votes Confidential</b>		<b>Face-to-Face, Teleconference Consensus and Votes Sensitive &amp; Classified</b>
<b>Leadership:</b>	<b>Chair</b>		<b>Chair</b>
<b>Support:</b>	<b>Dedicated Staff Executive Coordinator</b>		<b>Dedicated Staff Executive Secretary</b>

# 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

**DSMB meetings should be forums for free discussion to take advantage of valuable discourse as a “committee of peers,”**

**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.**



# DSMB Chair

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.





# Biostatistician

The DSMB Biostatistician oversees the development, design, and drafting of a statistical plan of analyses.

This member oversees the preparation, reviews, and revises interim and formal reports to the DSMB in a “digestible and standard format” and orally presents a summary of 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  
“common sense” 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.



# DSMB Coordination

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.

They also maintain the DSMB files and records protecting confidentiality.

# DSMB Reports

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, or efficacy is determined before the CCT stopping point.

DSMB members must be satisfied with the timeliness, completeness, and accuracy of CCT data submitted and subsequent reports.



# Recommendations & Equipoise

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.



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# AEs and CCT Stopping Rules

- As part of the ongoing monitoring process performed by a DSMB, it is responsible for reviewing adverse event data.
- The trial sponsor normally provides adverse event data to the DSMB in summary form.
- However, as discussed earlier with regards to IRBs, the ultimate responsibility lies with the sponsor to review such events promptly and to report serious, unexpected adverse events to FDA
- The benefit of DSMB involvement in this process comes from its ability to help distinguish whether or not the adverse event resulted from the disease being treated or the intervention itself



# AEs and CCT Stopping Rules

- 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
- 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.

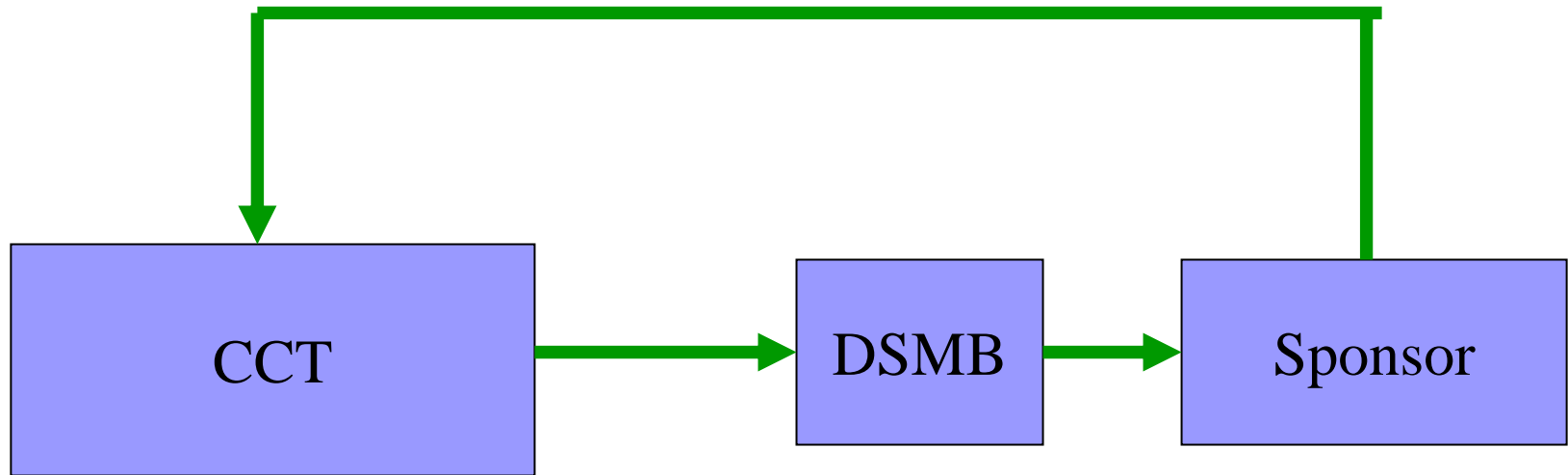


# AEs and CCT Stopping Rules

**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



Cf. Peter G Kaufmann and Nina Schooler  
The Fourth Annual Summer Institute on  
Randomized Clinical Trials  
Airlie, Virginia  
July 21, 2004



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# Interactions between IRB and DSMB

- Monitoring plan should be established a priori and IRB approved
- DSMB or sponsor should report to PIs and IRBs (at each site) in regards to AEs
- Reports should be submitted
  - when adverse events occur and are problematic
  - periodically even when there are no concerns



# Interactions between IRB and DSMB

- Major role comes in multicenter trials
- AEs from other sites not available to local IRBs
- DSMB and sponsor provide reports for local IRBs that describe study-wide AEs



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# Interactions between DSMB and Sponsor

- While the DSMB is charged with many great responsibilities, in the end it is still an advisory board.
- The sponsor must approve DSMB recommendations, particularly on discontinuation of a trial.
- In some situations, FDA may act as a useful second opinion to the sponsor with regards to the implementation of a DSMB recommendation that might affect subsequent regulatory decision-making.



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# Resources

<http://leda.law.harvard.edu/leda/data/685/Corkery05.html>

[http://deainfor.ci.nih.gov/grantspolicies/datasftyltr\\_dsmbirb.htm](http://deainfor.ci.nih.gov/grantspolicies/datasftyltr_dsmbirb.htm)

[http://www.nhbli.nih.gov/funding/policies/ae\\_multi\\_center.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.nihtraining.com/ohsrsite/irb/Attachments/5-1_DSMB.htm)

<http://grants1.nih.gov/grants/guide/notice-files/not98-084.html>

[http://www.nhlibi.nih.gov/funding/policies/dsmb\\_inst.htm](http://www.nhlibi.nih.gov/funding/policies/dsmb_inst.htm)

<http://www.niad.nih.gov/dmid/clinresearch/dsm.htm>