DSMBs: Foundations and Fundamentals

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Objectives

• Learn about the historical and ethical roots for Data Safety Monitoring Boards
• Examine the evolution and importance of DSMBs
• Answer the questions:
  – What does a DSMB do?
  – When is a DSMB needed?
  – What are the types of DSMBs?
• Understand the basic structure and content of a DSMB Charter
• Be aware of some challenges that face DSMBs today.
## Typical Oversight Bodies: Where are we now?

<table>
<thead>
<tr>
<th>Monitoring Entities</th>
<th>General Responsibilities</th>
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</thead>
<tbody>
<tr>
<td>• IRB/IEC</td>
<td>• Human subject well-being</td>
</tr>
<tr>
<td>• PI</td>
<td>• Day-to-day study performance</td>
</tr>
<tr>
<td>• <strong>DSMB/DMC</strong></td>
<td>• Statistical integrity of outcomes for efficacy and risks</td>
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<tr>
<td>• CRO</td>
<td>• Overall regulatory compliance, Data QC</td>
</tr>
<tr>
<td>• Sponsor</td>
<td>Overall Project compliance</td>
</tr>
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</table>
Sentinel events in research ethics brought about

- *The Nuremburg Code* (1947)
- *The Declaration of Helsinki* (1964 – Present)
- *The Belmont Report* (1979)
- Federal Regulations (e.g., 21 CFR Part 50, 45 CFR 46 “The Common Rule”)

The codes established the provisions and oversight requirements regarding the ethical conduct of research on humans.
Research Ethics and Human Subjects Research

• Research ethics codes and regulations enjoin investigators and IRBs to design and conduct studies with the well-being of the participant in mind.

• Specifically, investigators have an ethical responsibility toward their research subjects.

• However, monitoring of data initially took a “back-seat” to “autonomy” of participants.

• Now DSMBs have an expanded role that includes an ethical comportment.
DSMBs: How do Ethical Principles Apply?

• For example, using the ethical principles covered by the *Belmont Report* to establish an ethical foundation.
  
  — **Personhood**
  • Study design, conduct, oversight maximize the well-being and respect for all participants
  
  — **Beneficence/best-interests**
  • Benefit (efficacy reached; stop study)
  • Risk (harms too great; stop study)
  
  — **Justice**
  • Fair and equitable (evaluating enrollment)
  • Risks and benefits being equally distributed
DSMBs: Historical Roots in the U.S.

- Greenberg Report (1967) recommends to establish independent monitoring
- Coronary Drug Project convenes a DMC
- Other DMCs follow through the 60’s and 70’s
- Result: Formal consideration and eventual implementation of Data Monitoring policies
  - Interesting note: The first formation of a DMC roughly coincides with the first recognized call for the creation of an “IRB” (see memorandum issued by the Research Grants Division of USPHS (1966))
DSMBs: Historical Famous “Saves”

- BHAT study (1982) halted secondary to observed effectiveness signal of beta-blocker on mortality
- WHI/HERS study (1998) stopped for lack of improved primary outcome measure (lower incidence of MI)
- CAST study (1989) stopped early due to increased rate of adverse events
DSMBs: Evolution and Expansion

- NIH requirements (1998 Policies)
  - DSMPs (all Institutes require)
  - DSMBs (usually for “phase III” interventional studies, testing for effectiveness, risk and benefit)
- Used throughout industry sponsored trials
- Foundations (e.g., Cystic Fibrosis Foundation)
- FDA guidance on DMCs
- ICH E9: IDMCs
DSMBs: What do they do?

• DSMBs perform the following general functions:
  – Objectively appraise a study’s progress
  – Assess, via a formal and planned process, data quality
  – Provide analytical expertise and rigor
  – Determine the statistical significance of efficacy and/or risk-benefit ratio
  – Authority to halt study, recommend changes
  – Serve as “Another set of eyes.”
DSMBs: What do they do?

• In accordance with its analytic and ethical responsibilities, a DSMB is primarily tasked to determine whether a study
  – Proceeds with enrollment, as designed
  – Suspends enrollment, pending crucial changes to the protocol’s design, recruitment strategy, risk minimization, etc
  – Terminates, due to statistically significant efficacy or increased risk of harm to participants
DSMBs: When are they needed?

• Formal DS monitoring is necessary to assure confidence in a study’s interim and final outcomes:
  – To verify or validate efficacy and/or safety information significant to a novel therapy
  – To gauge data quality to confirm the research question/hypothesis in developing treatments
  – To assess efficacy and safety when “lives and well-being depend on valid results.”
DSMBs: When are they needed?

• DSMBs may be established based on any of the following features of a study:
  – Randomization:
    • e.g., a larger-scale, multicenter Phase IIb study
  – Risk to Participants:
    • e.g., when there is high risk of mortality/morbidity
    • e.g., when the research cohort is vulnerable
  – Reliability of Data:
    • e.g., when efficacy and/or safety information confidence is imperative
  – Regulatory:
    • e.g., when required by federal funding Institute
DSMBs: Various Types

• “Internal”
  – May include individuals from a PI’s department
  – Can involve trial team members, who conduct formal monitoring
  – Multidisciplinary

• Independent (“external”)
  – Typically for larger, complicated, or risky studies
  – Usually sought to minimize real or perceived bias (i.e., no interest in the outcome and not involved in the clinical trial’s design or management)
  – Members can be from different institutions
  – Multidisciplinary
**DSMB: How Many Members?**

- *Size doesn’t always matter, but expertise does*
- “Small” e.g., $>2$ may be appropriate for a DSMB on a small study, for which a DSMB is desired but not required.
- “Large”: e.g., $5+\text{ may be necessary for a larger multicenter, randomized clinical trial testing efficacy and safety for a new drug/device.*

- **Considerations related to the DSMB’s size:**
  - Is number commensurate with study size and scope
  - Adequate representation of experts
  - Logistical concerns (travel, accommodations, honoraria, etc.) and feasibility
DSMBs: Who are the Members?

• Personnel: There are many positions and roles
  – Executive Secretary
  – Chair
  – Co-Chair
  – Clinical and/or DG expert(s)
  – Biostatistician(s)
  – Bioethicist(s)
  – Participant Advocate
DSMB Charters: A Basic Approach

• Step 1: Interrogative Stage
  – Who is on the Committee/Board?
  – What are the roles or responsibilities of the members?
  – What information is to be reviewed?
  – When will the information be reviewed?
  – How will meetings be conducted?
  – How will determinations be communicated
  – Etc.
DSMB Charters: A Basic Approach

• Step 2: Formal Organization Stage
  – Introduction/Purpose
  – DSMB Membership and Responsibilities
  – DSMB logistics (scheduling, quorum, voting, etc.)
  – DSMB “Standard Operating Procedures”
    • Open meeting, if applicable
    • Close meeting
    • Schema for data and safety information review
    • DSMB conclusion
    • Minutes
  – DSMB Report Content and Distribution
  – Confidentiality Agreement/Disclosure Statements
DSMBs: Current Challenges

- A Bioethicist on the Board?
- Formal Bioethics training/knowledge for DSMB members?
- DSMBs “vs” IRBs for oversight?
- Degree of Independence?
- Transparency?
- Liability?
- Training?
- Cost?
Summary

• DSMBs have the practical position of seeing data and safety information in more frequent intervals and with typically more statistical expertise to make enhanced assessments about a study’s progress and determine the study’s future.

• Important ethical value of monitoring studies for maximization of benefit/effect and minimization of harm for current participants and future patients.
Resources


- [http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm)