Data and Safety Monitoring Board (DSMB)

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Overview

- Why monitor data?
- Why a DSMB?
- Statistical issues.
- DSMB composition.
- DSMB meetings.
- Study team responsibilities.
The Name Game

- Data & Safety Monitoring Boards (DSMB).
- Independent Data Monitoring Committee (IDMC).
- Data Monitoring Committee (DMC).
- Data Review Board (DRB).
- Etc.
Why monitor data?

ICH E9 on Statistical Principles describes two types of data monitoring:

- Monitoring quality of the study.
- Monitoring treatment group comparisons of outcome data (interim analysis):
  - Safety.
  - Efficacy.
Monitoring for Quality

- Identify logistical or data quality issues:
  - Recruitment, retention.
  - Protocol violations.
- Identify need for additional data to clarify endpoints.
- Identify problems with the study assumptions used for planning and design (e.g., sample size reviews).
Monitoring Outcome Data

Ethical responsibility to study participants:

- If interim data indicate an intervention is harmful, the trial may be stopped.
- If interim data demonstrate a clear benefit from an intervention, the trial may be stopped.

Futility.
Why a DSMB?

ICH E9 on Statistical Principles:

“The independence of the IDMC is intended:

to control data sharing of important comparative information; and

to protect the integrity of the clinical trial from adverse impact resulting from access to trial information.”
Why a DSMB? (cont-d)

NIH Policy for Data Safety and Monitoring (DSM) June 10, 1998

"...each Institute and Center should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials.”
Why a DSMB? (cont-d)

NIH DSM  June 10, 1998 Policy (continued)

"...The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants."
Why a DSMB? (cont-d)

Further guidance issued June 5, 2000:

“For earlier trials (phase I and phase II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.”
Statistical Issues in Interim Review

Repeated testing of outcome data increases the chance of a type I error.
Interim analysis

Test for difference in proportions failing in two groups without adjustment for multiple testing

**Decision Rule:** *Reject null if $|Z| \geq 1.96$*

- Single test at end of study $\rightarrow 0.05$
- Two tests, equally spaced $\rightarrow 0.08$
- Five tests, equally spaced $\rightarrow 0.14$

*(Friedman, Furberg and DeMets, 1996)*
Five equally spaced tests of two proportions

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<tr>
<td></td>
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<td>First look</td>
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<td>Second look</td>
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<td>Third look</td>
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*Reject null hypothesis if \(|Z| \geq this value*
Who should be in a DSMB?

- DSMB should be multidisciplinary:
  - Clinician(s).
  - Statistician(s).
  - Bioethicist?

- Different trials might require the inclusion of different disciplines on a DSMB.
DSMB meetings

- Initial meeting before study initiation.
- Subsequent meetings throughout the course of the study.
Initial meeting (Study preview)

- Protocol (IRB approved?).
- CRFs and DM plans.
- Informed Consent Forms.
Initial meeting (Study preview) cont-d

Data Safety Monitoring Plan:
- Adverse Event system
- Content of interim reports (key efficacy and safety outcomes of interest)
- Procedures to manage access to reports
- Frequency of interim reports
- Statistical methods and stopping rules
Subsequent meetings

Operational Plan:
- The structure of the meeting: Open session and closed sessions.
- Discussion and voting procedures.
- Reports.
Open session

Trial performance:

- Accrual.
- Follow-up.
- Protocol violations.
- Summary of GCP site monitoring reports.
- Baseline characteristics.
- Safety and efficacy outcomes, all treatment groups combined.
Closed sessions

Review interim analyses:
- continue as originally designed,
- be modified, or
- be terminated.

No single statistical test should be used as a strict rule for decision-making.
DSMB recommendations

After each meeting, the DSMB should provide the study leadership with written information concerning findings and recommendations (through the Executive Secretary, and corresponding NIH program officer).
Study Team Responsibilities

- PI is required to transmit the final summary of DSMB findings and recommendations to the appropriate IRBs (per NIH June 1999 guidance on AEs).
- Respond to all DSMB recommendations in writing in a timely manner.
Information Flow for interim reviews
Key points

- All clinical studies need a DSM plan.
- Some need a DSMB.
- Implications of Interim Analysis:
  - Access, confidentiality, blinding issues.
  - Statistical Issues.
- Plan, plan, plan.
- ICSSC can help (www.icsssc.org/DSMB.htm).