Behind Closed Doors: Functions of the Data Safety Monitoring Board

Roxana Mehran, MD

Columbia University Medical Center
Cardiovascular Research Foundation

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Disclosures: Roxana Mehran

Clinical Research Support: Sanofi/Aventis, Bracco

Educational Support: The Medicines Company, Boston Scientific, Abbott, Medtronic, and Cordis

Consultant/Honoraria: TMC, BSC, Abbott, Medtronic, Sanofi/Aventis, Lilly/Diachi Sankyo, Astra Zeneca, Cordis, Therox, Bracco, Guerbert, Regado

History of DSMB

- First used for large randomized multicenter trials in 1960s that were federally funded in the U.S.
- Recognition that interim monitoring of accumulating study data was essential to ensure the ongoing safety of participants
- Involvement of expert advisors external to trial would address problems in an unbiased way

Functions of DSMB

- Reviews the accumulating data from clinical trial on an ongoing basis
- Advises sponsor regarding continuing safety of trial subjects
- Advises sponsor regarding continuing validity and scientific merit of the trial

Determining Need for DSMB

- What is the risk to trial participants?
  - An interim analysis of a study endpoint could be so highly favorable or unfavorable that study termination would be required
  - Reasons exist for a safety concern
  - Fragile population
  - Large, long duration and multicenter trial

Determining Need for DSMB (2)

- Is DSMB review practical?
  - Short duration of trial would limit the meaningful impact of DSMB
  - Limited value for early studies (Phase I or early Phase 2) where accumulating results are known to sponsor and statistical interpretation of interim data is less relevant

Determining Need for DSMB (3)

- Will DSMB help assure scientific validity of the trial?
  - Changes over time in understanding of disease, affected population and standard of care during long duration can lead to modifications to trial – best if recommended by unbiased group
  - Accumulating event rates may suggest need for modifications

DSMB Relation to Other Groups

- IRBs / Ethics Committees
- Clinical Trial Steering Committee
- Endpoint Adjudication Committee or Clinical Events Committee (CEC)
- Site / Clinical Monitoring
- Investigators
- Sponsor

DSMB Composition

- Clinicians with expertise in relevant clinical specialty
- Statistician familiar with statistical methods for clinical trials and sequential analysis of data
- Others might include epidemiologist, ethicist, pharmacologist
- No conflicts of interest (financial, intellectual, influence on trial)

DSMB Charter

- Procedural issues
  - Meeting schedule, format, structure, quorum, minutes
  - Report formats and codes
- Statistical methods
  - Group sequential methods with interim analyses defined by time intervals or amount of information
  - Stopping rules

DSMB Responsibilities

- Interim monitoring
  - Monitoring for effectiveness
  - Monitoring for safety
  - Monitoring study conduct
  - Consideration of external data
- Making recommendations
- Maintaining meeting records

Independence of DSMB

- Independence from sponsor
  - DSMB remains objective
  - Increases credibility of trial's conclusions
  - Sponsor maintains ability to make trial modifications in response to external data without introducing bias

Independence of DSMB (2)

- Sponsor interaction with DSMB
  - "Open" part of meeting to review enrollment, compliance, event rates in aggregate as well as sponsor goals, plans, and resources
  - DSMB can address questions from interim comparative data review to sponsor

Independence of DSMB (3)

- Independence of statistician
  - Primary trial statistician has most knowledge about trial but doing interim analysis and participating in DSMB would compromise objectivity of DSMB as well as statistician's objectivity with ongoing study management
  - Recommendation is to employ a contractor statistician

Blinding

- **Prior to study start**
  - **Develop list of personnel**
    - **Their roles**
    - **Access rights to study information**
    - **When they have access to information**
  - **Develop rules for unblinding**
    - **When it should occur**
    - **Who will have access to the unblinded information**

Blinding

- **During the study**
  - Use different site personnel (Investigator and Site Coordinator) to perform the procedure vs. the follow-up so the treatment will remain blinded during the follow-up
  - Develop a script for follow-up personnel to use in obtaining information from patients
  - Train follow-up personnel to avoid sections of the patient's record that would cause unblinding
- **Control communication channels**
  - Who can send and/or receive information
  - By what methods (phone, email, reports, letters) and password protection
  - What information can be provided by each method

Blinding

- **Managing data**
  - Limit access to data
  - Develop list of assigned personnel and their roles
  - Limit printing of data including where to print
  - Shred printed items unless required for recordkeeping
    - do not place in trash (too easy for others to pick up and read)
  - Provide isolated area for data review, analysis, data entry, source document collection for safety monitoring
  - Use computer screen shades when working in open areas

Blinding

- **Safety monitoring**
  - Limit access to incoming source documentation
  - Redact key identifiers (patient information, product usage)

Reference:

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees

US Food and Drug Administration (FDA)
OMB Control No. 0910-0581 (March 2006)