DATA MONITORING COMMITTEES: A Regulator's Perspective

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SOME HISTORY

- Little in regulations/guidance address data monitoring committees (DMCs)
- Since the 60's, mostly in government-funded trials (NIH, VA)
- Increased use of DMCs over past decades
- Many different models in use
- HHS Office of Inspector General recommended in 1998 that FDA clarify appropriate role and procedures for DMCs

REGULATORY STATUS OF DMCs

- One mention in U.S. regulations: required for emergency research studies in which informed consent requirement has been waived (21 CFR § 50.24)
- Mentioned in guidance documents developed by int'l committees for conduct of clinical trials
- Draft guidance specifically on DMCs issued November 2001

GOOD CLINICAL PRACTICES

[ICH E6 5.5.2] The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
(ICH E9 Sec. 4.6)

- IDMC evaluates interim data, makes recommendations to sponsor
- IDMC should have written operating procedures and maintain meeting records
- Independence maintains confidentiality of interim data and protects integrity of trial
- Role of any sponsor representatives must be clearly defined; dissemination of interim results within sponsoring organization must be controlled

NEW FDA GUIDANCE ON DMCs

- Draft guidance issued November 2001
- Joint guidance: biologics,devices,drugs
- Open public meeting held 11/27/01
- Public comment period: 90 days

DRAFT GUIDANCE ON WEB

www.fda.gov/cber/gdlns/clindatmon.htm

GUIDANCE FOR CLINICAL TRIAL SPONSORS ON THE ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES

OUTLINE OF DOCUMENT

- Introduction and Background
- Determining Need for a DMC
- DMCs and Other Oversight Groups
- DMCs Establishment and Operation
- DMCs and Regulatory Reporting Requirements
- Independence of the DMC
- Sponsor Interaction with FDA Regarding Use and Operation of DMC

INTENT OF DOCUMENT

- Describe generally acceptable models for DMC establishment and operation
- Indicate advantages and disadvantages of different approaches
- Increase awareness of potential concerns that can arise with interim monitoring of comparative data
- Address the relation of DMCs to regulatory requirements for monitoring and reporting

THE TRIAL SPONSOR

- Document frequently refers to sponsor
- Who acts as the sponsor?
  - Holder of the IND
  - Any individual or group to whom the sponsor delegates authority for decision-making
    - Steering Committee
    - Contract Research Organization
    - Principal Investigator
- Sponsor may be company or gov't agency

INTRODUCTION & BACKGROUND

- Many different models used for DMCs
- Document highlights pro and cons of various approaches
- Different models may be appropriate in different settings

DETERMINING NEED FOR A DMC

- Risk to participants
  - favorable or unfavorable early result might warrant early termination
  - special concern about safety (novel therapies)
  - population generally at elevated risk of adverse outcome; need comparative safety data
- Practicality
- Assurance of scientific validity
  - possible need for changes in protocol after trial is initiated
  - DMC protects objectivity of trial leadership and trial investigators in conducting trial

OTHER OVERSIGHT GROUPS

- IRB
- Steering Committee
- Endpoint Assessment/Adjudication Committee
- Site/Clinical Monitoring group

These groups do not perform the same functions as a DMC, although they all contribute to safety assurance and trial integrity

ASSUMING A DMC

WHAT NEXT?

COMMITTEE COMPOSTION

- Critical - select appropriate members
  - DMC has major responsibilities
  - trial sponsor, leadership, investigators & participants rely on DMC
- Multidisciplinary
- Size varies with trial complexity

EXPERTISE ON DMCs

- Clinical medicine (appropriate specialty)
- Biostatistics
- Biomedical ethics
- Basic science/pharmacology
- Clinical trial methodology
- Epidemiology
- Law
- Patient advocate/community rep

ESTABLISHING A DMC

- Generally appointed by sponsor
- Members acceptable to trial leadership
- Generally in agreement with hypothesis, design and endpoint
- Minimize conflict of interest

SELECTING DMC MEMBERS OTHER ISSUES

- Geographic representation
- Relevant demographic characteristics
- Prior DMC experience
- Assess conflict of interest

DMC CHAIR

- Prior DMC experience
- Scientist & Administrator
- Facilitator
- Consensus builder
- Communicator
- Committed for trial duration

DMC CHARTER/SOPs

- In advance of any interim analyses
- Schedule/format of meetings
- Format for data presentation
- Delineation of data access
- Meeting attendees
- Assessment of Conflict of Interest
- Method/timing of providing reports

STATISTICAL METHODS

- Group sequential analyses
- Bayesian method
- Type I error rate
- Futility analysis
- Risk/benefit assessment

CONFIDENTIALITY OF INTERIM RESULTS

- Interim comparative data generally considered highly confidential
- Knowledge of interim data could influence trial conduct
- E.g. – unstable situations,data fluctuations may suggest emerging trend, discouraging enrollment & adherence

STANDARD OPERATING PROCEDURE
1. Meetings

- Study protocol should specify schedule of interim analyses, or considerations that will determine schedule
- Attendance at meetings should depend on confidentiality of data presented
  - discussions of comparative outcome data limited to DMC members and presenting statistician
  - "open" session can be held for discussion of non-confidential issues

STANDARD OPERATING PROCEDURE
2. Use of Treatment Codes

- Printed reports of interim analyses often use codes for treatment arms
  - ease of presentation
  - some protection of confidentiality if reports misplaced
- DMC should have access to these codes to endure their ability to make accurate benefit-to-risk assessments
  - decisions about stopping for benefit or harm usually asymmetric
  - must be able to connect safety & efficacy outcomes

STANDARD OPERATING PROCEDURE
3. Statistical Assessments

- A variety of acceptable statistical monitoring approaches are available
- DMC and sponsor should agree on statistical monitoring plan, which should be submitted to FDA prior to initiation of interim analysis
- DMC will need to exercise judgment, using monitoring boundaries as guidelines rather than "rules"

STANDARD OPERATING PROCEDURE

4. Potential DMC Responsibilities

- Interim analysis in Phase 3 studies
  - effectiveness
  - safety
  - continued feasibility vs futility
- Quality of study conduct
  - shared responsibility with sponsor/trial leadership
- Considering impact of new external data
- Monitoring safety in certain early phase studies
  - unusually high risks
  - particularly strong conflicts of interest

STANDARD OPERATING PROCEDURE
5. Meeting Minutes

- Minutes kept of all DMC meetings
- Minutes of confidential discussions maintained by the DMC and shared with sponsors at completion of trial
- Minutes of "open" sessions shared with sponsor, who may further circulate them to participating IRBs, or others
- All minutes should be submitted to the FDA with the clinical study report at the completion of the study
- Electronic interim analysis data sets archived & available to FDA on request after study is completed

DMC INDEPENDENCE

- Many advantages to independent DMC
  - ensures that DMC not influenced by sponsor interests
  - preserves ability of sponsor to make needed changes in trial without biasing results
  - protects sponsor from pressures to release interim data (e.g., SEC)
- Independent DMC does not mean sponsor has no contact with DMC
  - open sessions
  - sponsor can provide valuable information
- Having preparation and presentation of interim analyses external to sponsor & study leadership allows for interim protocol changes

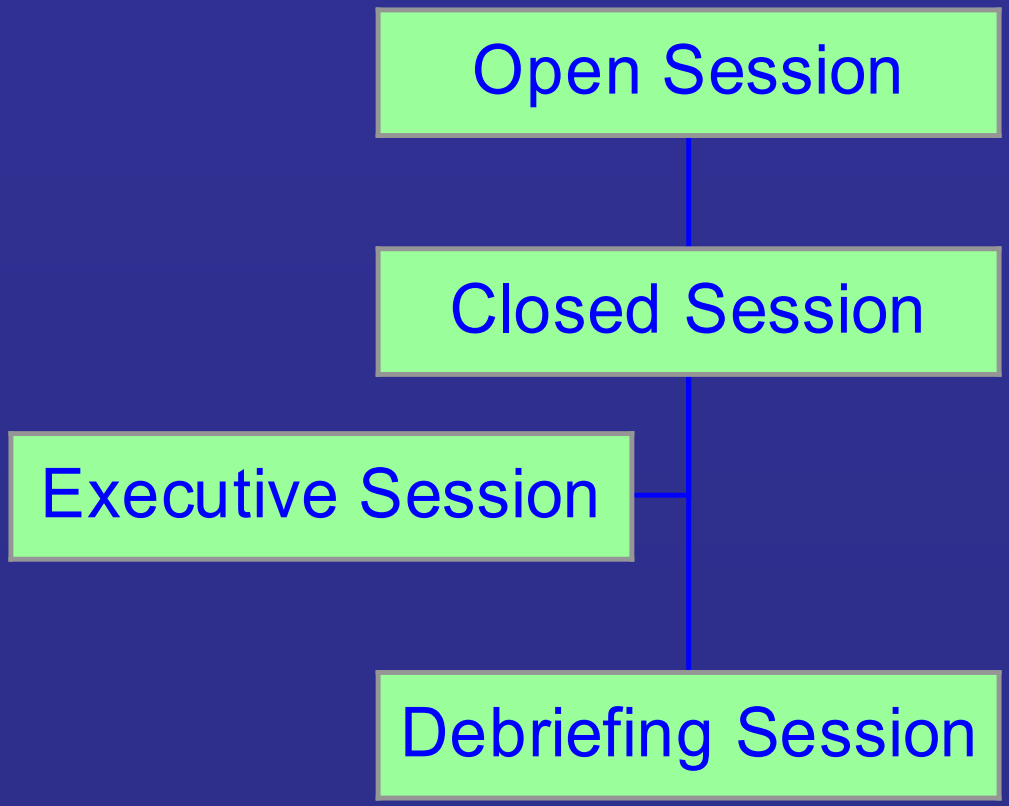
INTERIM DECISION-MAKING

- Sometimes interim changes in protocol are necessary or desirable
- Often, these changes do not directly affect trial results
  - Reduced dose due to toxicity
  - Adding sites due to unsatisfactory accrual
- Sometimes, changes would affect results
  - Change in primary endpoint
  - Change in criteria for documenting endpoint
- Changes are made by trial leadership—ability to do this without bias is compromised if they know interim results

INTERIM REPORTS

- Preparation independent of sponsor & investigators reduces risk of inappropriate access
- Based on prior analytic plan
- Agreed timing & distribution
- Comparative results coded but blind could be broken by DMC
- Separate parts for Open & Closed Sessions

DMC Meeting Structure



OPEN SESSION

- Sponsor, study chair, regulatory representative
- Only aggregate data presented
- Communicate possible problems needing clarification/action
- Discuss implications of external related research
- Communicate w/o disclosing comparative data

OPEN SESSION TOPICS

- Accrual rate, drop-outs
- Baseline characteristics
- Compliance/adherence
- Missing data
- Overall toxicity
- Trial site-specific issues

CLOSED SESSION

- DMC members & presenting statistician
- Comparative data discussed
- Recommendations to sponsor formulated

EXECUTIVE SESSION

- As needed
  - When sponsor reps participate in Closed Session
  - Other issues
- Only DMC members

DEBRIEFING SESSION

- DMC Chair, Steering Comm Rep, Sponsor
- Clarification of concerns
- Recommendations summarized

DMC RESPONSIBILITIES

- Evaluating accumulating data with regard to safety & efficacy
- Recommending trial termination or continuation
- Recommending other modifications
- Reviewing and approving protocol
- Assessing trial conduct
- Recommending additional analyses

DMC RESPONSIBILITIES

- Monitor interim data
  - Safety
  - Effectiveness
- Monitor trial conduct
- External information
- Early development
- Recommendations
- Meeting records

ACCESS TO TREATMENT CODES

- Should DMC review comparative data using treatment codes, or should treatment be identified?
- Arguments in favor of blinding
- Arguments against blinding

DMC REPORTING

- To sponsor after each meeting
- Minutes describing decision-making considerations, discussing confidential comparative data available only to DMC during the trial
- All minutes available to sponsor & FDA after trial completed

SPONSOR ACCESS TO INTERIM DATA FOR PLANNING PURPOSES

- Discuss with FDA in advance
- Request minimum data needed for planning
- SOPs to ensure that information is only available to those with a critical "need to know"
- Those accessing such information should remove themselves from further involvement in the trial
- Even if all precautions are taken, access could prove problematic in ultimate assessment and interpretation of results

SPONSOR INTERACTION WITH FDA REGARDING DMC RECCOMENDATIONS

- FDA will not tell sponsors whether or not to follow DMC recommendations
- FDA may be consulted regarding specific regulatory issues to be considered when a DMC recommends early termination or other major study modifications

GOV'T vs INDUSTRY SPONSORS

- Issues discussed in guidance document relevant to all trials
- Guidance does not distinguish between government & industry sponsors
- Differences in type & extent of conflicts of interest that exist for government & industry sponsors

REVISIONS TO DRAFT GUIDANCE

- Comments rec'd from industry, academia, other gov't agencies
- Internal review & revisions
  - **Industry vs Gov't sponsor diffs**
  - **Independent DMC report analysts**
  - **Other specific comments**

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