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• Draft guidance specifically on DMCs issued November 2001
[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.
• 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- Draft guidance issued November 2001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DRAFT GUIDANCE ON WEB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 COMPOSITION

• **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
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 ensure 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
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

Closed Session

Executive Session

Debriefing Session
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 RECOMMENDATIONS

- 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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