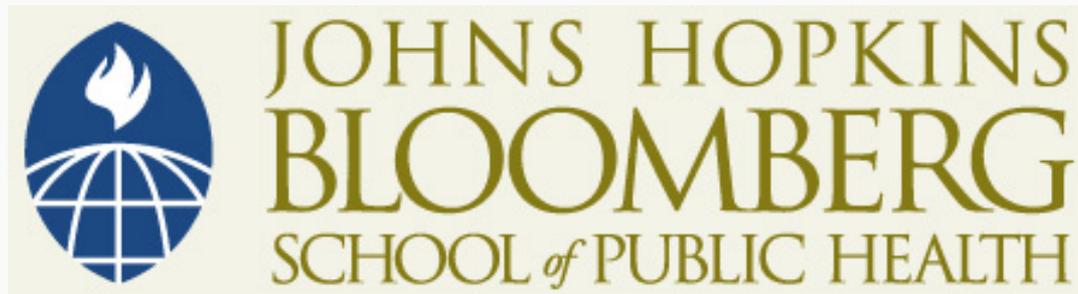


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Interim Monitoring

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Section A

Interim Monitoring

Some History

- Little in regulations/guidance address data monitoring committees (DMCs)
- Since the 1960s, mostly in government-funded trials (National Institutes of Health, MRC)
- Increased use of DMCs over past decades
- Many different models in use

Regulatory Status of Data Monitoring Committees

- 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 international committees for conduct of clinical trials (ICH E6 & E9)

Regulatory Status of DMCs

- Food and Drug Administration—draft guidance specifically on DMCs issued in November 2001
- Committee for Medicinal Products for Human Use (CHMP) points to consider
- World Health Organization
- FDA—guidance March 2006

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 the 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 a private company or government agency

Introduction and Background

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

Monitoring

- All trials need monitoring but not all trials need DMCs

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

- Institutional Review Board (IRB) / EC
- 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?

DMC Committee Composition

- Critical—select appropriate members
 - DMC has major responsibilities
 - Trial sponsor, leadership, investigators, and 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 reputation

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 and administrator
- Facilitator
- Consensus builder
- Communicator
- Committed for trial duration

- 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

In the Next Section We'll Look at . . .

- Data monitoring committees
 - Statistical considerations
 - Confidentiality
 - Independence
 - Reports, communication



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Section B

Operational Aspects of DMCs

Statistical Methods

- Group sequential analyses
- Bayesian method
- Type one 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 and/or data fluctuations may suggest an emerging trend, discouraging enrollment, and adherence

Standard Operating Procedures (SOPs): 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

SOPs: 2.) Use of Treatment Codes

- Printed reports of interim analyses for DMC meetings often use codes for treatment arms
- DMC members should have access to these codes to ensure their ability to make accurate benefit-to-risk assessments

SOPs: 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”

SOPs: 4.) Potential DMC Responsibilities

- Interim analyses in phase three studies
- Quality of study conduct
- Considering impact of new external data
- Monitoring safety in certain early phase studies

SOPs: 5.) Meeting Minutes

- Document DMC deliberations
- Maintained by the DMC, can be shared with sponsors at the completion of the trial
- Minutes of “open” sessions may be shared with the sponsor, who may further circulate them (or a summary of relevant items) to participating IRBs and study investigators
- Minutes and electronic data sets used for interim analyses may be requested by regulatory agencies at the completion of the study

DMC Independence

- Many advantages to independent DMC
- Independent DMC does not mean that a sponsor has no contact with DMC
- Preparation and presentation of interim analyses external to sponsor and study leadership allows for protocol changes

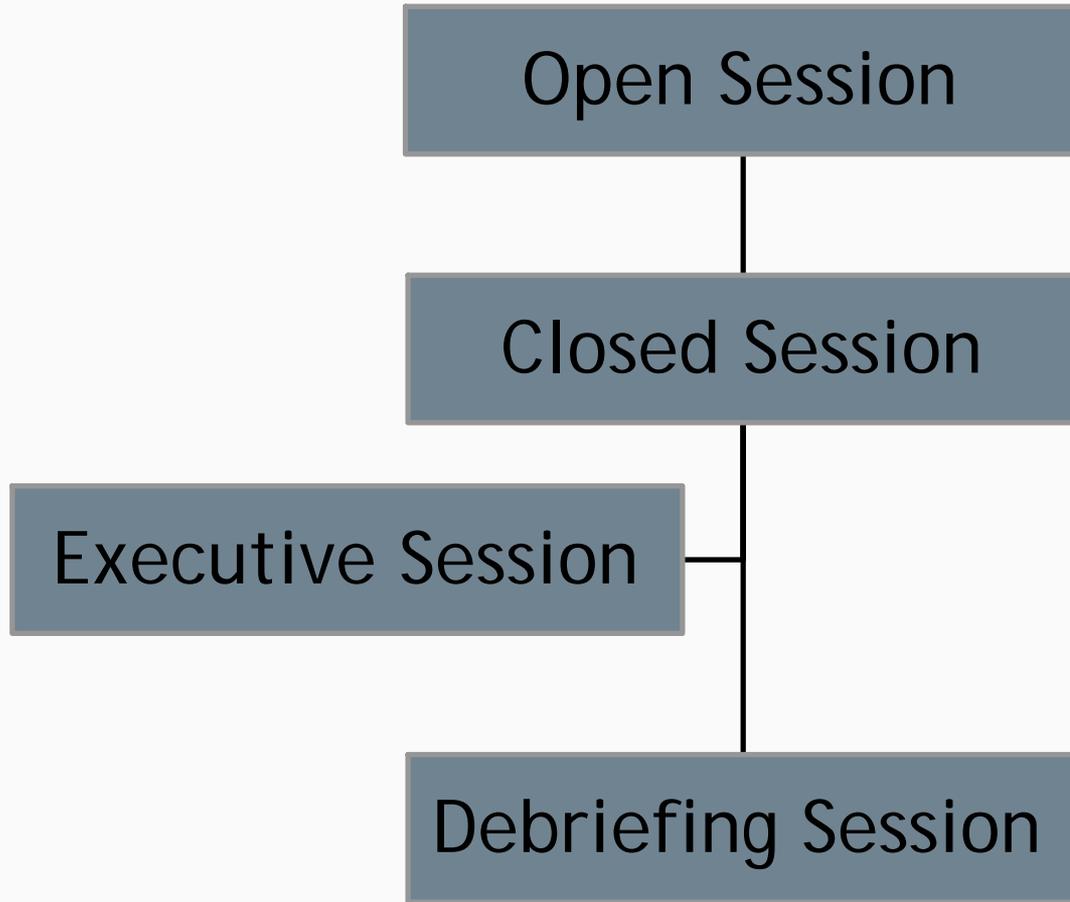
Interim Decision-Making

- Sometimes interim changes in protocol are necessary or desirable
- Often, these changes would not affect efficacy
- Sometimes, changes could affect efficacy
- Changes are made by trial leadership (ability to do this without bias is compromised if they know interim results)

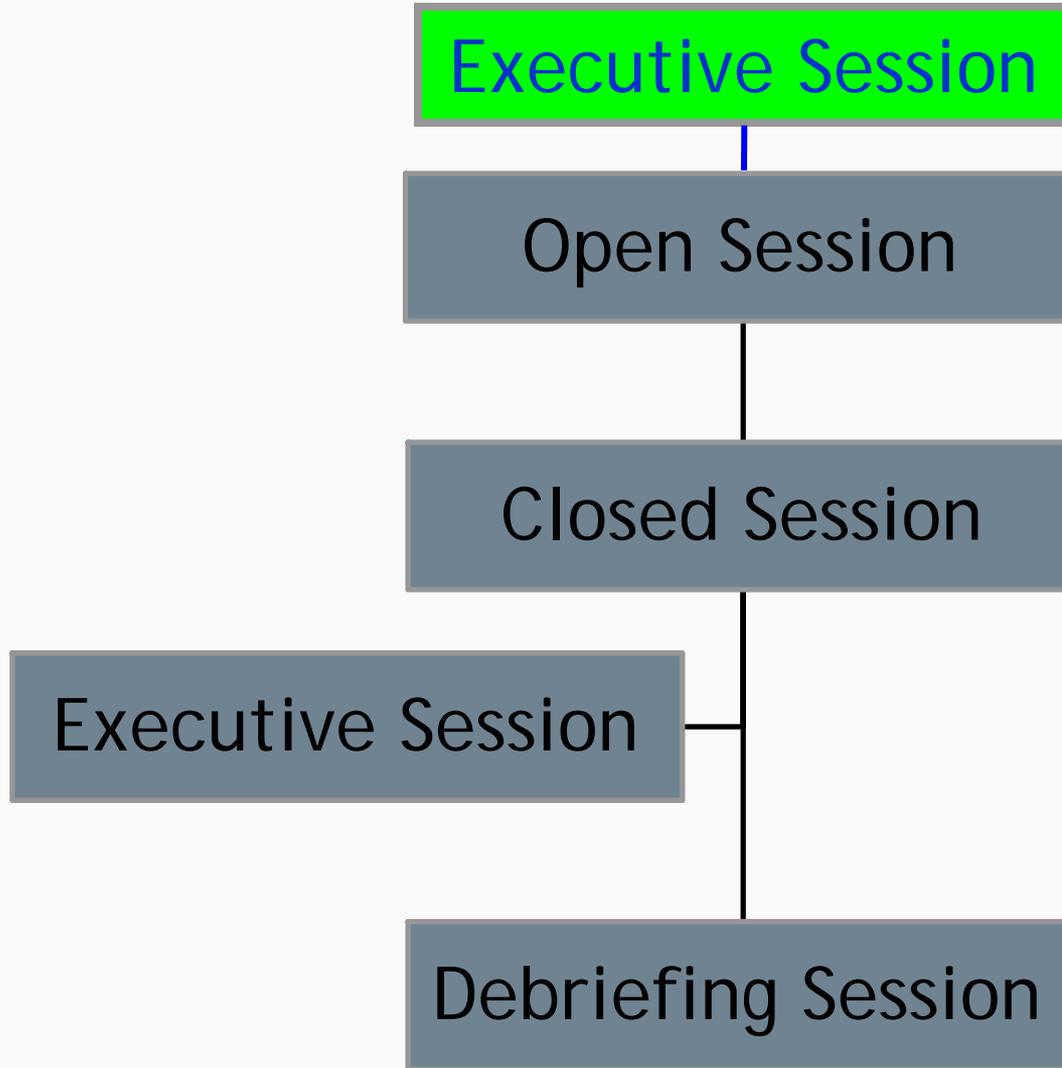
Interim Reports

- Preparation independent of sponsor and investigators reduces risk of inappropriate access
- Based on prior analytic plan
- Agreed timing and distribution
- Comparative results coded but blind could be broken by DMC
- Separate parts for open and closed sessions

DMC Meeting Structure



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 and presenting statistician
- Comparative data discussed
- Recommendations to sponsor formulated

Executive Session

- As needed
 - When sponsor representatives participate in a closed session
 - Other issues
- Only DMC members

Debriefing Session

- DMC chair, Steering Committee representative, sponsor
- Clarification of concerns
- Recommendations summarized

DMC Responsibilities

- Evaluate accumulating data with regard to safety and efficacy
- Recommend trial termination or continuation
- Recommend other modifications
- Review and approve protocol
- Assess trial conduct
- Recommend 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 and to regulatory authorities after trial is completed

Sponsor Access to Interim Data for Planning Purposes

- Discuss with regulators 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 Regulators

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

Government vs. Industry Sponsors

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

Guidance on Web

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