

# **FDA DRAFT GUIDANCE ON CLINICAL TRIAL DATA MONITORING COMMITTEES**

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# DATA MONITORING COMMITTEE (DMC)

A DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

# TERMINOLOGY

A

B

C

Data

Monitoring

Committee

Safety

Review

Board

Policy

Advisory

Panel

Efficacy

Endpoint

# BACKGROUND

- Little in regulations and guidance address data monitoring committees
- DMCs used since the 1960's, mostly in government-funded trials (NIH, VA)
- Increased use of DMCs over past 10-15 years
- Many different models in use
- HHS Office of Inspector General recommended in 1998 that FDA clarify appropriate role and procedures for DMCs

# NEW FDA GUIDANCE ON DMCs

- Draft guidance issued November 2001
- Joint guidance: biologics, drugs, devices
- Open public meeting held 11/27/01
- Public comment period: Closed 2/19/02
- Comments will contribute to development of final document

# REGULATORY STATUS OF DMCs

- Only 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 recently developed by international committees for conduct of clinical trials
  - ICH E6: Good Clinical Practice
  - ICH E9: Statistical Principles for Clinical Trials
- Draft guidance specifically on DMCs issued November 2001

# **WEB PAGE FOR DRAFT GUIDANCE**

[www.fda.gov/cber/gdlns/clindatmon.htm](http://www.fda.gov/cber/gdlns/clindatmon.htm)

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

# INTENT OF GUIDANCE DOCUMENT

- Describe generally acceptable models for data monitoring committee establishment and operation
- Indicate advantages and disadvantages of different approaches
- Increase awareness of potential concerns that can arise in trials 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 government agency

# **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**

# INTRODUCTION AND 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 TRIAL 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

# DMC ESTABLISHMENT AND OPERATION

## 1. Committee Composition

- Critical to select appropriate committee members
  - DMC has major responsibilities
  - trial sponsor, leadership, investigators and participants rely on DMC
- Membership is multidisciplinary
  - relevant clinical specialties
  - biostatistics
  - medical ethics, other scientific disciplines as necessary
- Size varies with trial complexity

# DMC ESTABLISHMENT AND OPERATION

## 2. Conflicts of Interest of Committee Members

- DMC members should be free of major conflicts of interest
  - financial
  - intellectual
  - trial conduct responsibilities
- Sponsors should establish procedures for assessing conflicts of interest of potential DMC members

# 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 PROCEDURES

## 2. Use of Treatment Codes

- Printed reports of interim analyses for DMC meetings often use codes for treatment arms
  - ease of presentation
  - some protection of confidentiality if reports misplaced
- DMC members 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 and efficacy outcomes

# STANDARD OPERATING PROCEDURES

## 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 PROCEDURES

## 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 PROCEDURES

## 5. Meeting Minutes

- Minutes should be kept of all DMC meetings
- Minutes of sessions in which confidential interim data were discussed should be maintained by the DMC and 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, study investigators or other interested parties
- All minutes should be submitted to the FDA with the clinical study report at the completion of the study
- Electronic data sets used for interim analyses should be archived and should be 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

# 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

# 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

# NEXT STEPS

- FDA workgroup will review comments that have been submitted
- Revised document will be developed
- Difficult to predict time frame for publication of final document
  - Many complex issues have been raised
  - Completion of revision seems unlikely within this calendar year