Interim Analysis of Randomized Clinical Trials

David L DeMets, PhD
Need for Data Monitoring

- **Phase I Trials** (dose)
  - Monitoring usually at local level
- **Phase II Trials** (activity)
  - Most monitoring at local level
  - Some randomized, blinded, multicenter Phase II trials may need IDMC
- **Phase III & IV** (effectiveness, risk, benefit)
  - Most frequent user of IDMC
- **Structure of monitoring depends on risk**
  (e.g. Phase I-IV)
Data Monitoring

Rationale

1. Ethical

2. Scientific

3. Economic
A Brief History

• A 35-year history
• Greenberg Report (1967)
• Coronary Drug Project (1968)
• NIH Experience and Guidelines (1998, 2000)
• Industry and ICH Guidelines
• Department of Health & Human Services (Shalala, 2000)
• FDA Draft Guidelines (2001)
Greenberg Report

• Commissioned by National Heart Institute (1967)

• Task: Organization and Review of Multicenter Trials

• Report Published in 1988 (Controlled Clinical Trials)
Greenberg Report
Recommendations (1)

• Develop a mechanism to terminate early if
  – Question answered
  – Trial can’t achieve its goals
  – Unusual circumstances
  – Hypothesis no longer relevant
Greenberg Report Recommendations (2)

- National Heart Institute (sponsor) should not terminate early without advise of external consultants
- No mention of a formal DMC
- Suggested an oversight Policy Advisory Board
NIH Model (Greenberg, 1967)

- Steering Committee
- Policy Board
- Data Monitoring Committee
- Coordinating Center
- Clinical Centers
- Central Units (Labs, ...)
- Institutional Review Board
- Patients

NIH
DMC

A committee with responsibility to review accumulating results for:

- Satisfactory Progress
- Protocol Compliance
- Data Quality
- Patient Safety
- Early Intervention Effectiveness
NIH DMC Activity

• Ref: *Statistics in Medicine* (1993)

• CDP became model for National Heart, Lung, and Blood Institute (NHLBI)
  – heart, lung, blood disease trials

• National Eye Institute (NEI) (1972)
  – Diabetic Retinopathy Study

• National Institute Diabetes, Digestive and Kidney (NIDDK)
  – Diabetes Complication and Control Trial (1980)

• National Cancer Institute (NCI)
  – Prevention Trials, Cooperative Group Therapeutic Trials

• National Institute Allergy and Infectious Disease (NIAID)
  – AIDS Clinical Trial Group (ACTG) (1986)
Industry-Modified NIH Model

- Steering Committee
- Independent Data Monitoring Committee (IDMC)
- Statistical Analysis Center (SAC)
- Pharmaceutical Industry Sponsor
- Data Coordinating Center (Sponsor or Contract Research Organization)
- Clinical Centers
- Central Units (Labs, …)
- Regulatory Agencies
- Institutional Review Board
- Patients
DMC Decision Making Role

- DMC makes recommendations, not final decisions
- Independent review provides basis for DMC recommendations
- DMC makes recommendations to
  - Executive Committee who recommends to sponsor, or
  - Sponsor
- DMC may, if requested, debrief Executive Committee and/or sponsor
- Rarely are DMC recommendations rejected
DMC Data Review
Interim Analysis

1. Recruitment
2. Baseline Variables
   - Eligibility
   - Comparability
3. Outcome Measures
   - Primary
   - Secondary
4. Toxicity/Adverse Effects
5. Compliance
6. Specified Subgroups
DMC Decision Process Complex

• Recruitment & Compliance
• Risks and Benefits
• Internal/External consistency
• Current vs future patients
• Clinical/Public impact
• Statistical issues
DMC Recommendations

1. Continue Protocol Unmodified

2. Modify Protocol

3. Terminate Trial
Reasons for Early Termination

1. Serious toxicity
2. Established benefit
3. Futility or no trend of interest
4. Design, logistical issues too serious to fix
Coronary Drug Project

Life-table cumulative mortality rates,
Coronary Drug Research Project Group
z values for clofibrate-placebo differences in proportion of deaths by calendar month since beginning of study
(Month 0 = March 1966, Month 100 = July 1974)
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 via International Conference on Harmonization (ICH)

• Draft guidance specifically on DMCs issued November 2001
Motivation for FDA Guidance on DMCs

- Included recommendation that DMCs be required for trials under NIH and FDA purview meeting specified conditions
  - Definition of these conditions
  - Requirements for DMC composition
Intent of FDA Guidance Document

• Describe generally acceptable models for DMC establishment and operation
• Indicate advantages and disadvantages of different approaches
• Increase awareness of potential concerns
• Address the relation of DMCs to regulatory requirements for monitoring and reporting
FDA Comments On When External DMCs Are Needed

- Trials with mortality or major morbidity endpoints
- Trials for which assessment of serious toxicity requires comparison of rates
- Trials of novel, potentially high-risk treatments
DMC Summary

• NIH Clinical Trial Model – 40 year history of success
• Adaptation for industry can be made
• SC, DMC, SAC or DCC are critical components
• Independence of DMC essential
• FDA draft guidance consistent with NIH practice for most issues
• Some issues need further discussion
Some recent references

• NIH DMC Guideline web site

• FDA Draft DMC Guidelines web site