

# **Interim Analysis of Randomized Clinical Trials**

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# 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

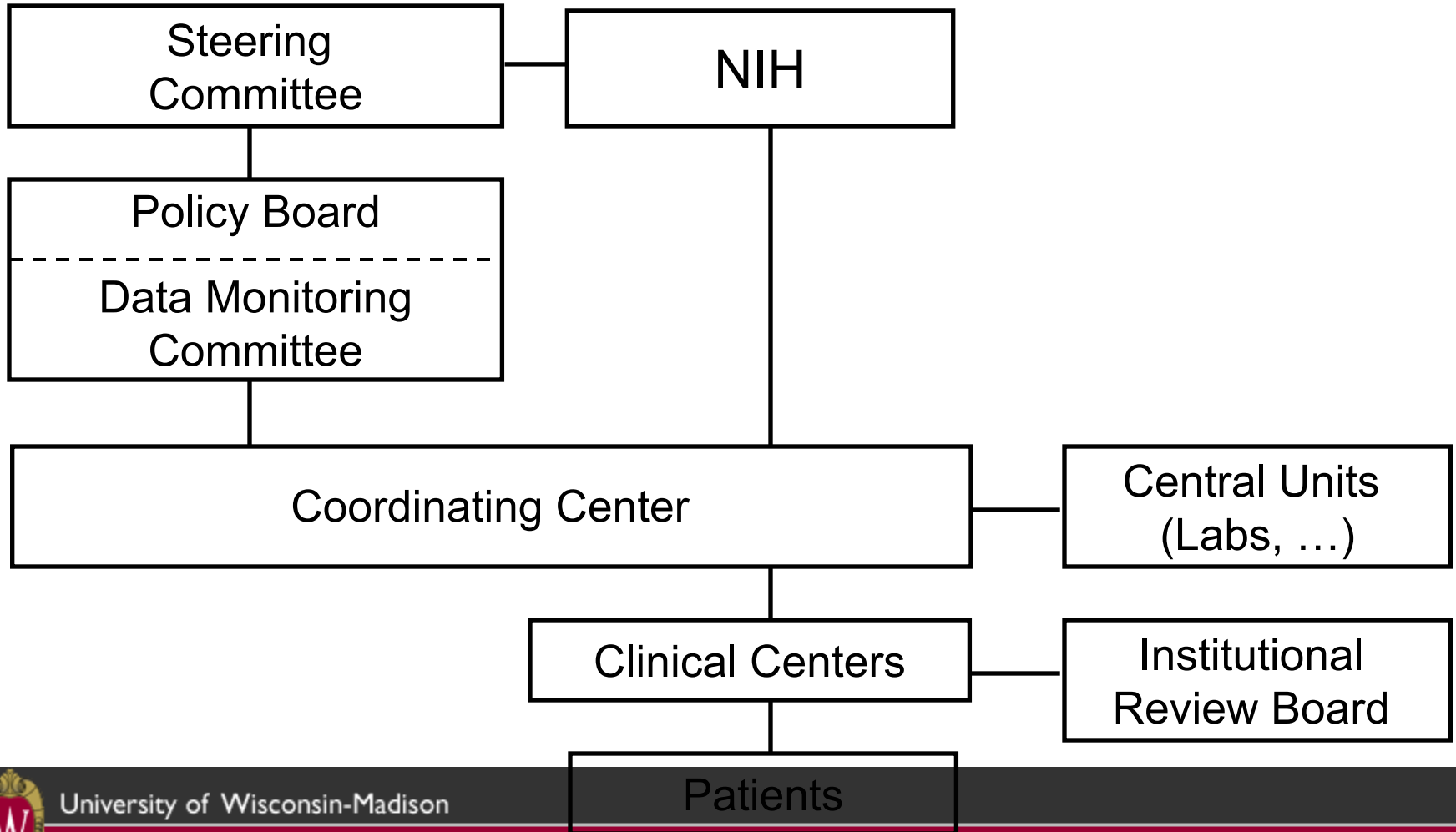


# Greenberg Report Recommendations (2)

- 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)



# DMC

A committee with responsibility to review accumulating results for:

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

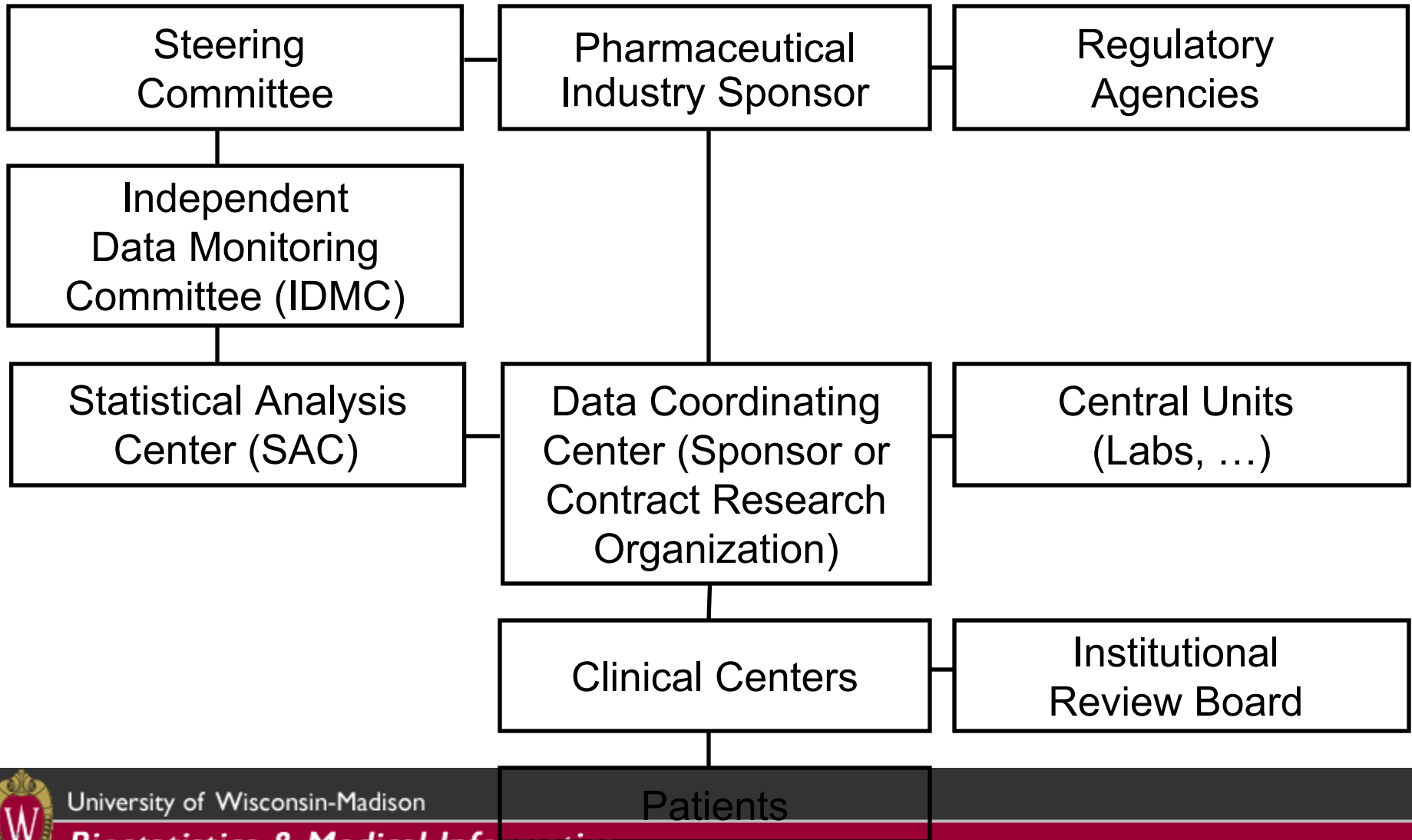


# NIH DMC Activity

- 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



# 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**

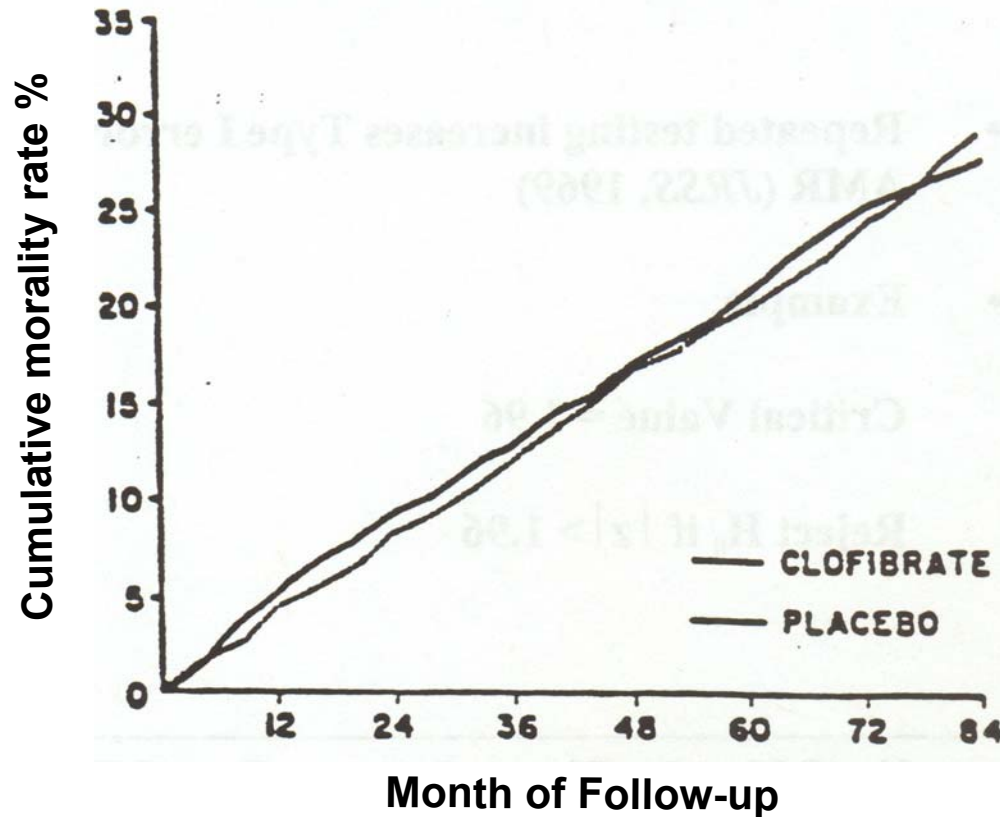


# Reasons for Early Termination

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



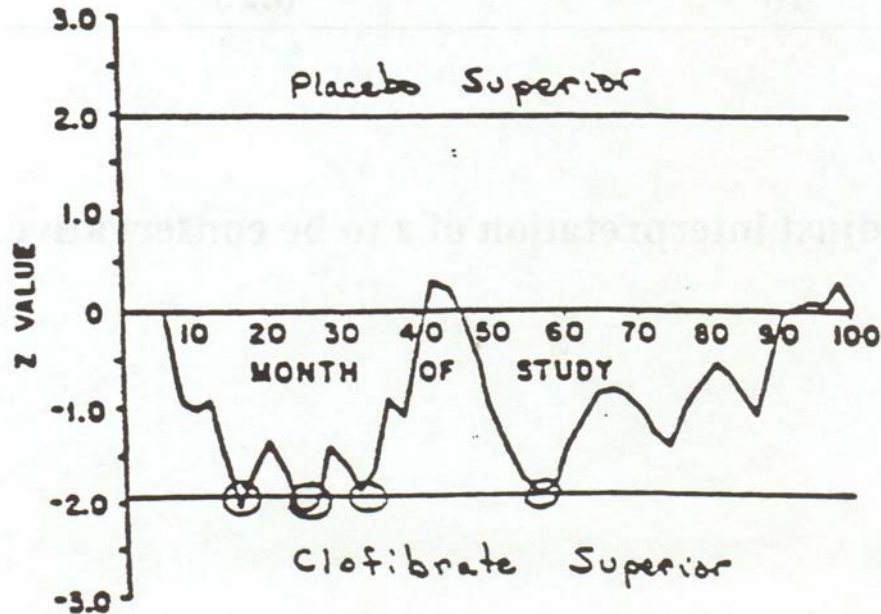
# Coronary Drug Project



Life-table cumulative mortality rates,  
Coronary Drug Research Project Group



# Coronary Drug Project Research 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

- **HHS Office of Inspector General issued report June 1998: “Institutional Review Boards: A Time for Reform”**
- **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
  - [www.grants.nih.gov/grants/guide/notice-files/not98-084.html](http://www.grants.nih.gov/grants/guide/notice-files/not98-084.html)
- FDA Draft DMC Guidelines web site
  - [www.fda.gov/ohrms/dockets/98fr/010489gd.pdf](http://www.fda.gov/ohrms/dockets/98fr/010489gd.pdf)
- Ellenberg, Fleming & DeMets, (2002) Data Monitoring Committees in Clinical Trials, Wiley

