The Coronary Drug Project (CDP): Organization and Selected Design Issues

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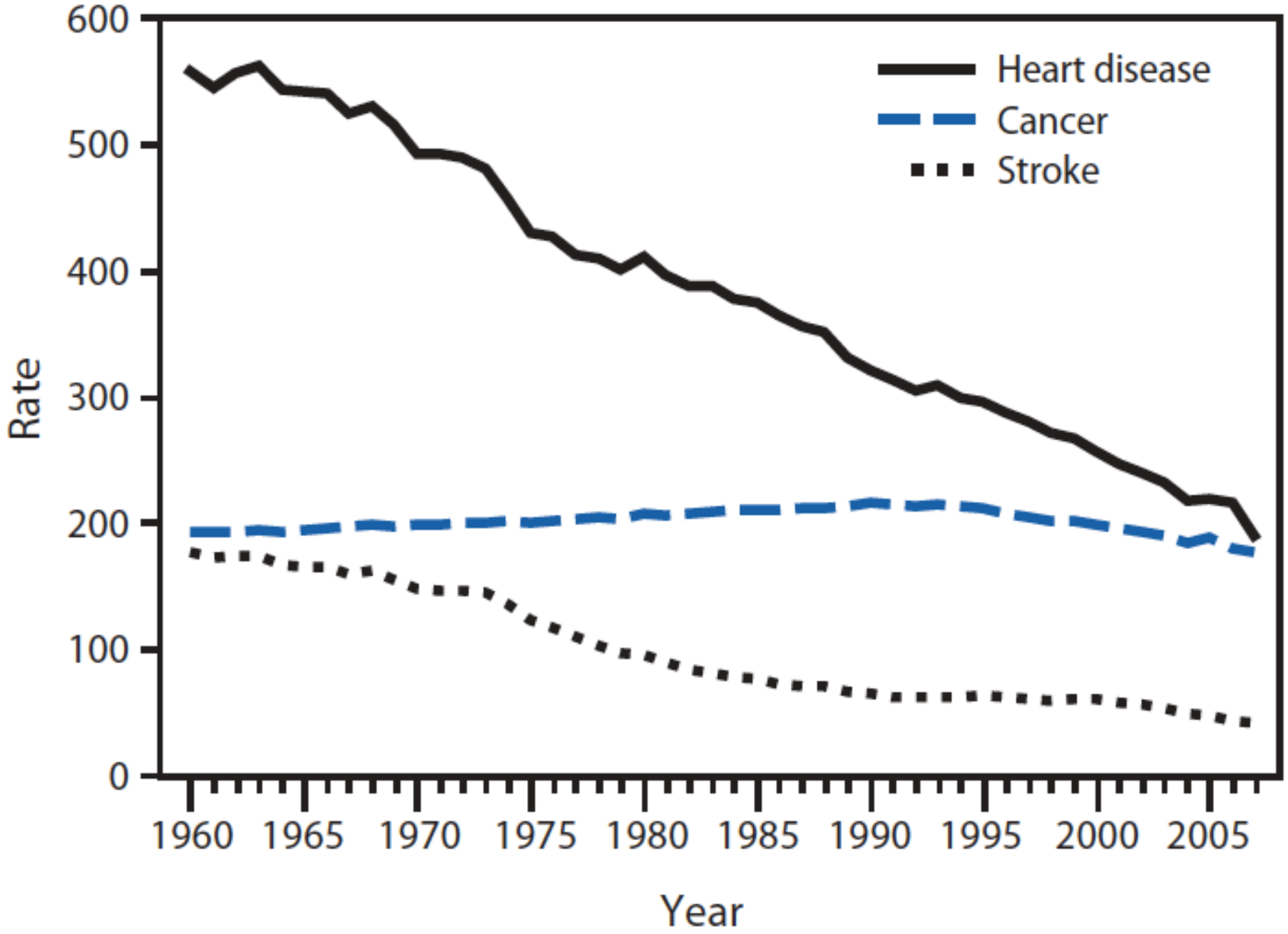
Cardiovascular Disease

- By 1950, heart disease was of epidemic proportions in the U.S.
- Largest cause of mortality, by far, as well as major morbidity
- National Heart Institute, now the National Heart, Lung, and Blood Institute (NHLBI), asked to address this epidemic

FIGURE 2. Trends in age-adjusted death rates for the leadings chronic diseases — United States, 1960–2007



Source: National Center for Health Statistics. Health, United States, 2010. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2011. Available at www.cdc.gov/nchs/data/hus/hus10.pdf.

Framingham Heart Study (1948-)
Identified Risk Factors

- Age
- Gender
- Smoking
- Blood Pressure
- Lipids
- Diabetes
- Weight

- 5,209 men & women (30-62) from Framingham, MA

- It was understood that modifying risk factors would have to be tested in a trial

Planning for Risk Factor Interventions – 1960's

- Planning for a trial on lipid lowering: Coronary Drug Project
- Trial would need to be large, long, and multicenter
- Little experience with such large multicenter trials
- Partway through CDP planning, commissioned the "Greenberg Report" (1967, published CCT 1988)
- Set the stage for many NIH & industry trials

CDP Chronology

Initial Recommendation: 1960

Protocol Development: 1961-1965

Initial Funding of Sites: 1965

Participant Enrollment: 1966-1969

End of Active Participant Follow-up: 1975

Funding for the CDP

- 1960: National Advisory Heart Council asks Dr. Robert Wilkins, senior cardiologist, to explore need and feasibility of a trial of cholesterol-modifying drugs

- 1962: Policy Board formed; Investigators asked to develop a protocol, working with NHI staff

- 1962-1967: Many Departmental and Congressional discussions and hearings to obtain funding

- 1965: Grant awards to Coordinating Center and 4 Clinics

- 1965-1967: Additional Clinics funded

CDP Design Features (a)

- Randomized, Double-Blind, Placebo Controlled Trial

- Assess Long-term Effect of Lipid-influencing Drugs in **Men** with History of Heart Disease
  - Men at the time had highest CV risk
  - Wisdom was only men had CHD

- Primary Outcome: All-Cause Mortality

CDP Design Features (b)

- Five Intervention Groups
- Placebo Group Approximately 2 1/2 Times Each Intervention
- Total Enrollment: 8341 Men With a History of Myocardial Infarction
- 53 (55) Enrollment Sites, Coordination Center, Central Laboratory, ECG Reading Center
- All enrollment sites in U.S., most were private hospitals

5 CDP Interventions

- Clofibrate -1.8 g/day
- Nicotinic Acid (Niacin) - 3 g/day
- Dextrothyroxine - 6 mg/day
- Equine Estrogens - 5 mg/day
- Equine Estrogens - 2.5 mg/day

Large Placebo Group

- Approximately 2 1/2 Times Each Treatment Group (2789)
- Enhanced Power Against Five Treatment Groups
- Allowed for “Natural History” Studies

CDP Form 07

CORONARY DRUG PROJECT PATIENT CONSENT FORM

I authorize Dr. _____, the attending physician, to treat me,

_____, with one of the drugs presently identified as Nicotinic Acid,

Dextrothyroxine, Estrogen, and Clofibrate for the following clinical condition:

_____ It has been explained to

me by the above-named doctor that the safety and usefulness of the drugs in the treatment of patients for

the above condition are being investigated and that the drugs are being supplied for the purpose of providing

further evidence of their safety and usefulness. It has been further explained to me that I may be used as a

control in this clinical investigation. I voluntarily consent to participation in this study and to treatment

with one of the above drugs and release the attending physician and this institution,

_____, from liability for any results that

may occur.

Signature of Witness

Signature of Patient (or surrogate)

Organizational Structure

- Technical Group: all investigators, met twice a year
- Steering Committee: leadership and rotating investigators
- Subcommittees: e.g., Editorial, Mortality Classification, Natural History, Laboratory
- Policy Board: protocol review, study performance, after 1968 got recommendations from DSMC, reported to NHI
- Data and Safety Monitoring Committee: after 1968 did regular data review by treatment group

Investigator Involvement

- Semi-annual Meetings of All Principal Investigators — And Coordinators ("Technical Group")
- Elections to Steering Committee
- Subcommittee Structure
- Authorship on "Natural History" Papers

External Monitoring (a)

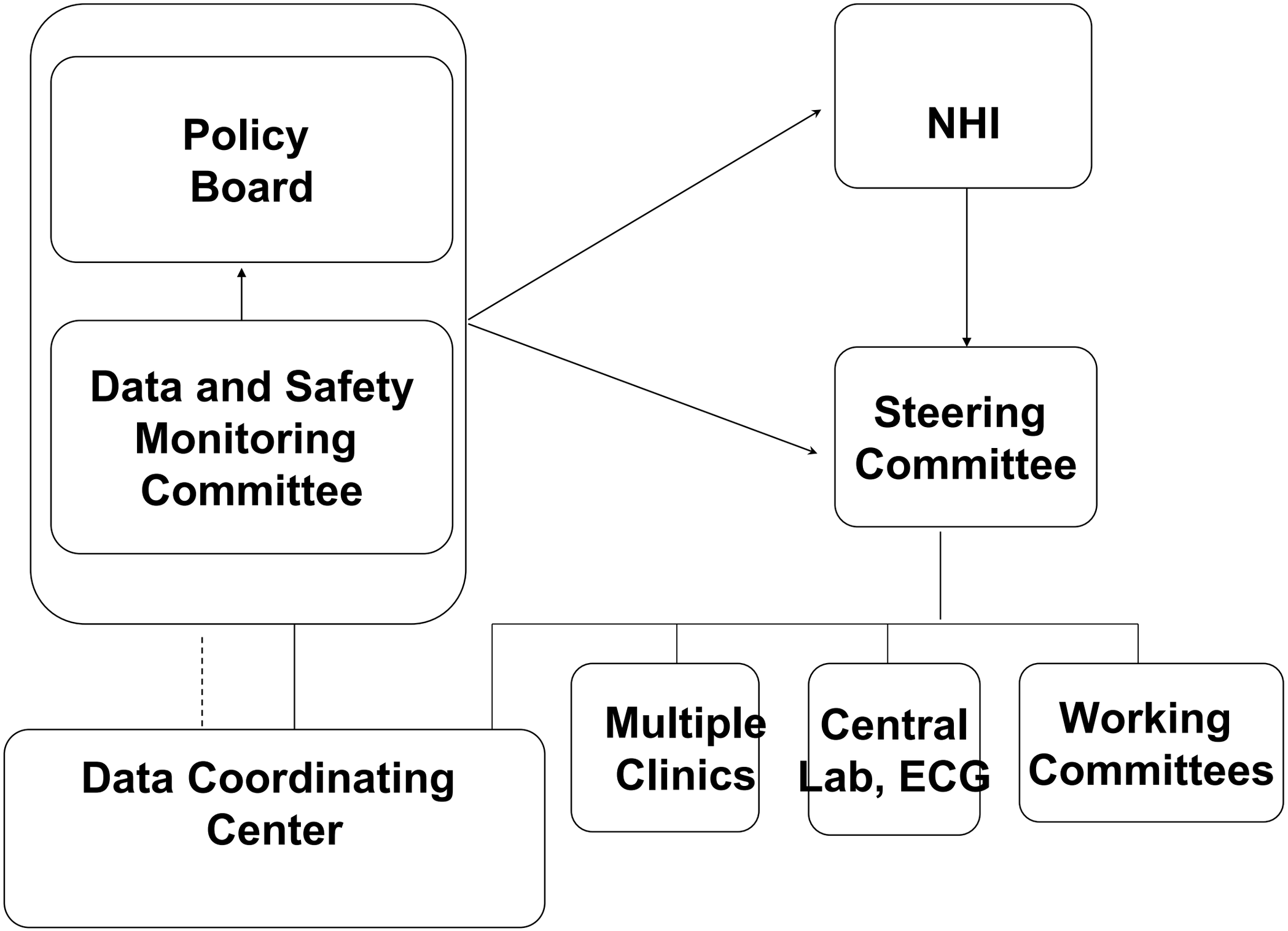
- Original Monitoring Done By All Investigators (Saw Groups “A” through “F”)

- Letter From Dr Thomas Chalmers to Dr Robert Wilkins (PB Chair) Expressing Concern About Investigators Knowing Trends

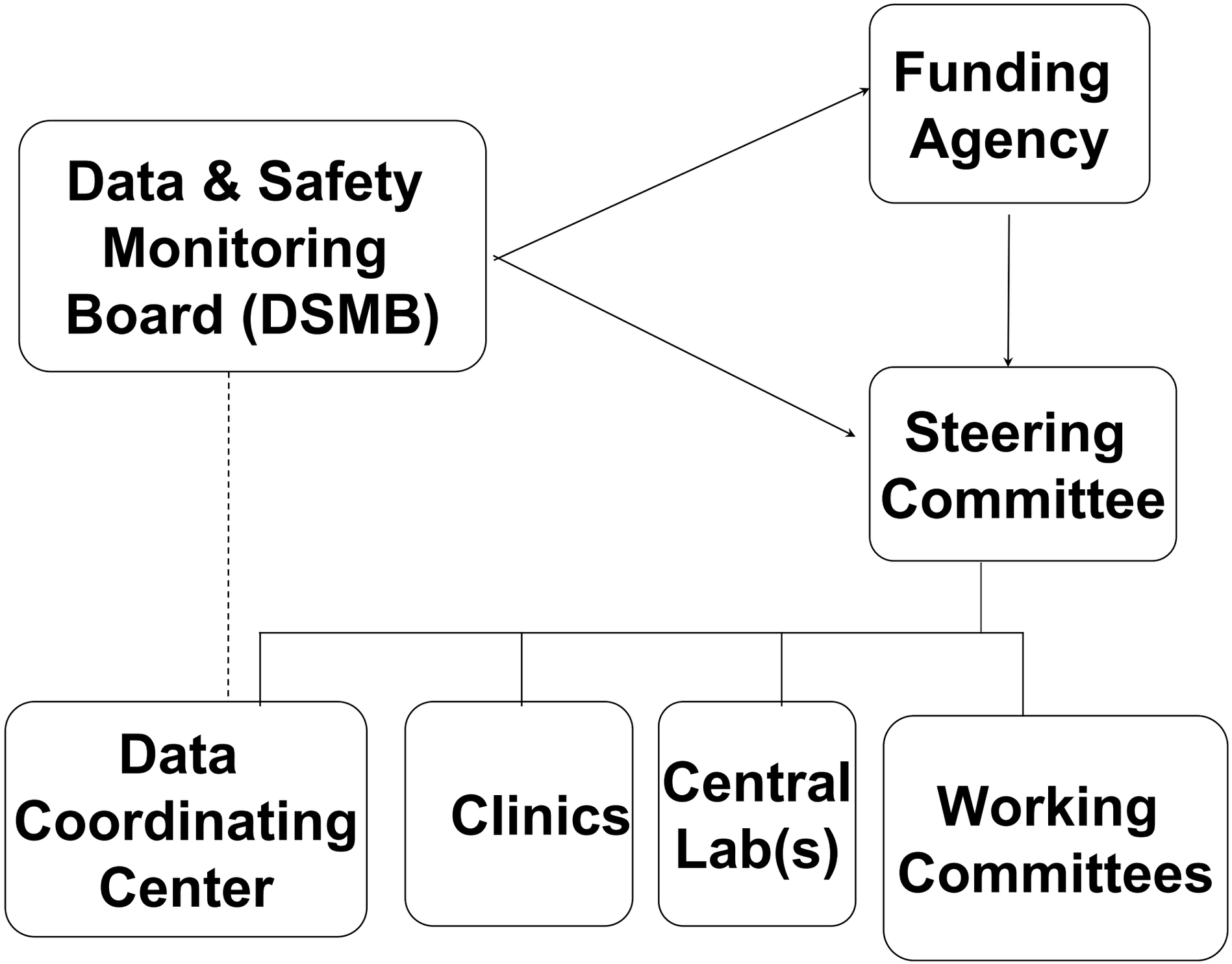
- Data and Safety Monitoring Committee (dating from 1968, included some “internal” members, not independent of NHLBI)

- Policy Board—entirely external from NHLBI (sponsor)

Early CDP CT Model



NHLBI CT Model



External Monitoring (b)

- Estrogen, 5 mg/day (ESG2): Discontinued 1970
- Dextrothyroxine (DT4): Discontinued 1971
- Estrogen, 2.5 mg/day (ESG1): Discontinued 1972
- Clofibrate and Nicotinic Acid: Continued Until scheduled end in 1975.

CDP Monitoring-ESG2

- After 18 months average follow-up, more nonfatal MI, PE, thrombophlebitis on ESG2 arm.

- Coronary death, sudden death, and total mortality trended in “wrong” direction.

- Increase in “troublesome side effects.”

- Increased mortality concentrated in high risk subgroup. DSMC voted to only discontinue the subgroup, but PB overruled.

- Stopped entire ESG2 treatment in 1970.

JAMA, 1970, vol 214, pp 1303-13

Table 1 Mortality and Morbidity in the Coronary Drug Project, May 13, 1970 Meeting

Event	Risk group[a]	ESG2		Placebo		
		n	%	*N*	%	*z*
Total mortality	All	1,118	8.1	2,789	6.9	1.33
	1	738	5.1	1,831	6.1	− 0.95
	2	380	13.9	958	8.5	3.02
Definite nonfatal MI	All	1,022	6.2	2,581	3.2	4.11
	1	684	6.7	1,689	2.9	4.30
	2	338	5.0	892	3.7	1.05

[a]Risk 1 = men with one previous MI without complications; Risk 2 = men with more than one previous MI or one MI with complications.

CDP Monitoring-DT4

- After 36 months average follow-up, strong NS trend for increased total mortality in entire DT4 treatment, but, as with ESG2, concentrated in high risk subgroup.

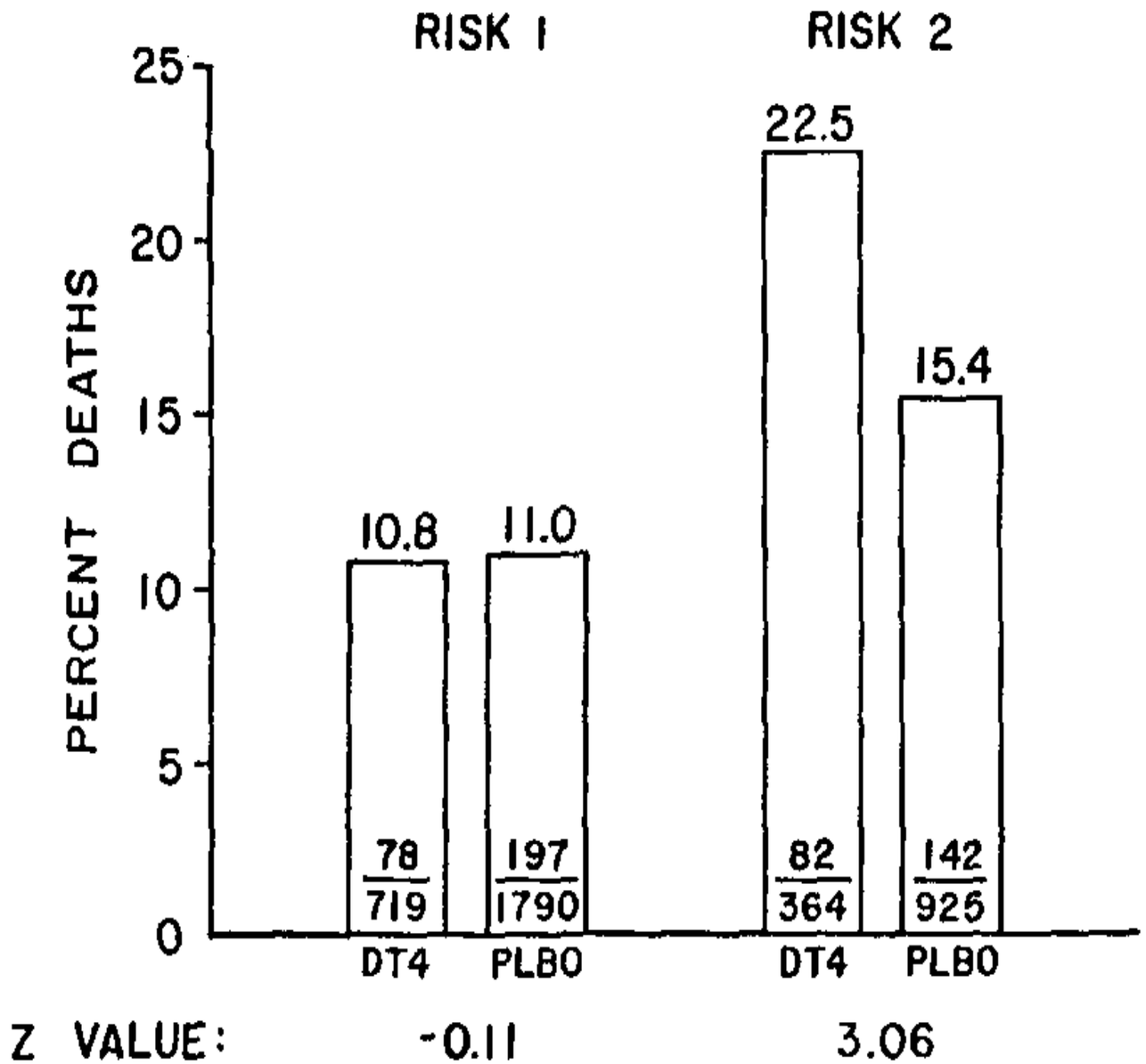
- Failure to find any subgroup in which DT4 showed any consistent benefit

- Significant increases in various other AEs.

- In 1971, DSMB and PB voted to discontinue entire treatment group.

JAMA, 1972, vol 220, pp 996-1008

Figure 1 Mortality by baseline risk group, DT4 and placebo (PLBO) groups. From Coronary Drug Research Project Group [13].



CDP Monitoring-ESG1

- After an average follow-up of 56 months, slight increase in total mortality on ESG1.

- Increases in PE, venous thrombophlebitis and troublesome side effects.

- Strong unfavorable trend for cancer mortality

- Highly unlikely that favorable finding for total mortality (primary outcome) would occur in remaining study time; a futility argument

- In 1973 DSMC and PB voted to stop entire treatment.

JAMA, 1973, vol 226, pp 652-7

Table 2 Projection of Future Mortality Experience

	ESG1	Placebo
A. Current % deaths	19.9 (219/1101)	18.8 (525/2789)
B. Current survivors	882	2264
C. % deaths at end of study, 1.96 SE difference	21.1 (232/1101)	24.0 (670/2789)
D. Future % deaths given 1.96 SE difference at end of study	1.5 (13/882)	6.4 (145/2264)

Source: Coronary Drug Research Project Group [14].

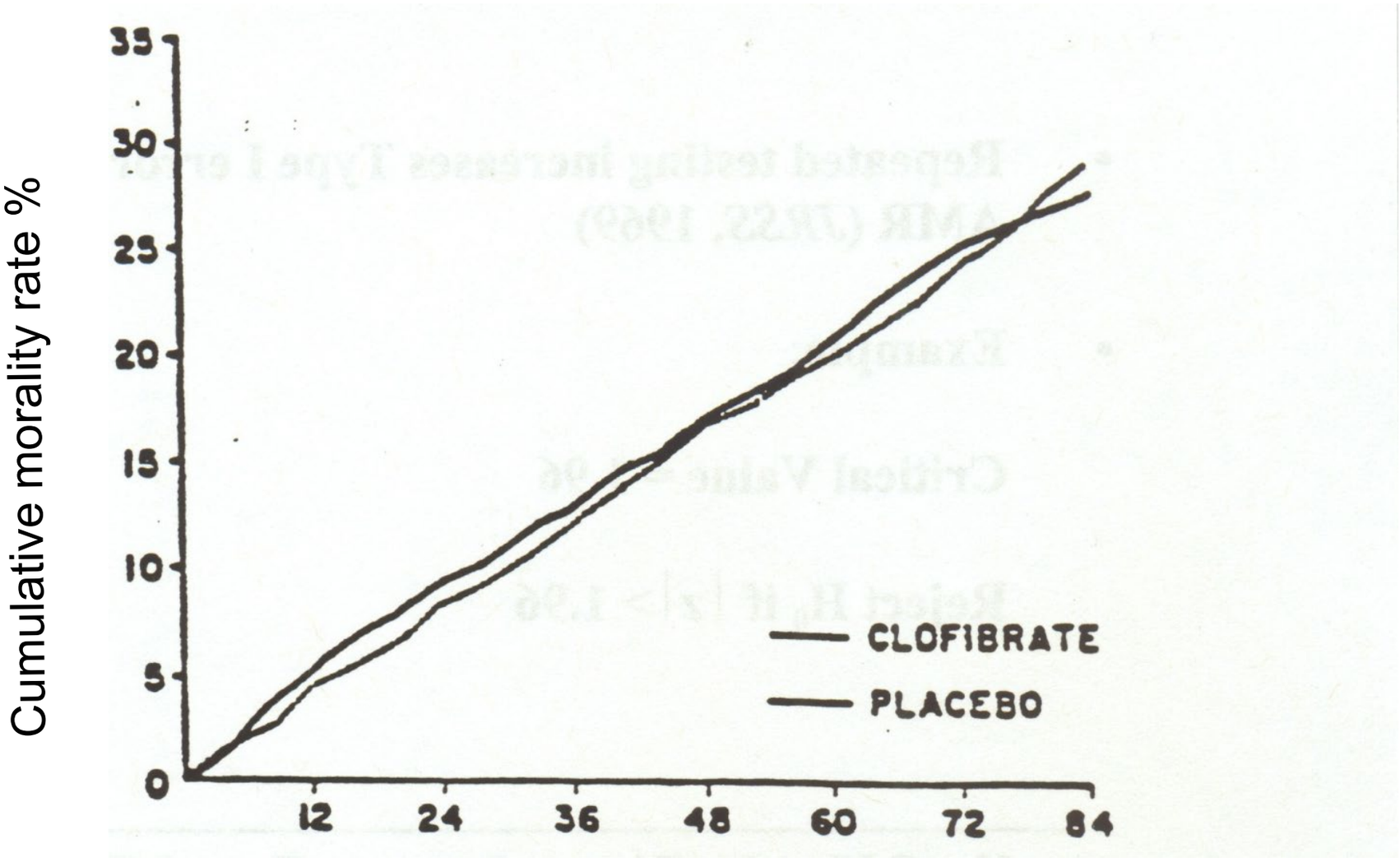
CDP Monitoring
Clofibrate and Nicotinic Acid

- Both continued to scheduled end of trial in 1975.
- Clofibrate showed no evidence of benefit for primary or major secondary outcomes.
- Nicotinic acid showed no benefit for primary outcome but did for nonfatal MI. Post-study follow-up showed reduction in total mortality.

JAMA, 1975, vol 231, pp 360-81; JACC (1987), vol 8, pp 1245-55

Coronary Drug Project (CDP)

(Canner, 1981, CCT)



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

Report to Investigators After DSMC Meetings

- Jeremiah Stamler, MD: Steering Committee Chair

"There is neither a therapeutic triumph nor a toxic catastrophe"

Adequate Support

- Regular In Person Meetings of All Investigators

- Coordinating Center Staff: Talented biostatisticians who were given time & funding

  - To develop data management procedures

  - To develop new approaches to interim monitoring and data analysis

  - To share those methods with other emerging coordinating centers

Key Points

- Large, Long-term, Multicenter, Multiple Arms
- Serious Condition with Death as the Primary Outcome
- Sample Size and Analysis Issues
- Evolving Concepts of Organizational Structure
- Evolving Concepts of Ways to Monitor
- Evolving lessons for data analysis of RCTs