Society for Clinical Trials 34th Annual Meeting

Workshop P3
So You've Said "Yes" – Now What? Sitting On or Chairing a Data Safety Monitoring Board

Sunday, May 19, 2013
8:00 AM - Noon
Fairfax A Room

So you are invited to join a Data Safety Monitoring Board: Now what?

DG: David Gordon, MD, NHBLI
JW: Janet Wittes, PhD, Statistics Collaborative, Inc.

Workshop at the Society for Clinical Trials
May 19, 2013

Outline

- Our first DSMBs – DG and JW
- History & responsibilities of DSMBs –JW
- Anatomy of a DSMB Charter- DG
- Looking for
  - Safety + Trial #1 to monitor - DG
  - Study integrity - JW
  - Efficacy + Trial #2 to monitor – JW
  - Futility + Trial #3 to monitor – DG
- Monitoring a complex trial – Trial #4 - JW

My First DSMB

David Gordon, MD, PhD, MPH

Special Assistant for Clinical Studies

NHLBI-Div Cardiovascular Science

May 19, 2013

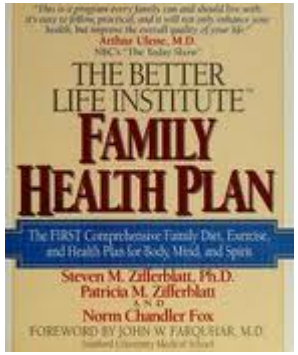
National Heart, Lung, and Blood Institute

Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT)

- Landmark trial to test the “cholesterol hypothesis” that lowering cholesterol would prevent coronary heart disease (CHD)
- Embedded in $100 M + project supporting population and laboratory science in 12 LRCs.
- 3806 men, aged 35-59, with high LDLc but no clinical CHD
- 1973-1983

The LRC-CPPT DSMB


Basil Rifkind.



Joslin Diabetes Center

Overseers
Caroline S. Lurie - New York, NY

Residency Reform: A Perspective from the Association of Professors of Medicine
Harold J. Fallon, MD
Ann Intern Med. 1992;116(12_Part_2):1041.

NIH National Heart, Lung, and Blood Institute

Janet's first DSMBs

CDP (Coronary Drug Project)

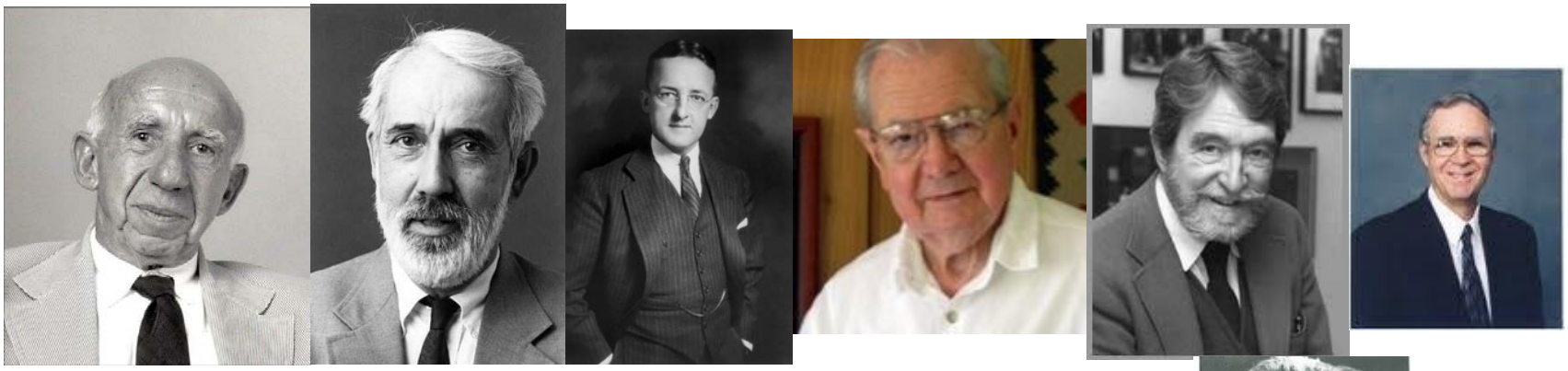
- 1966 to 1974
- Randomized, double-blind, placebo-controlled
- 8341 men with previous MI
- Primary outcome: all-cause mortality
- 5 lipid-modifying agents vs. placebo
  - High dose estrogen (5.0 mg/day)
  - Low dose estrogen (2.5 mg/day)
  - Dextrothyroxine sodium (6.0 mg/day)
  - Clofibrate (1.8 mg/day)
  - Niacin (3.0 gm/day)
  - Placebo (3.8 mg/day lactose)

DSMB and Policy Board (PB)

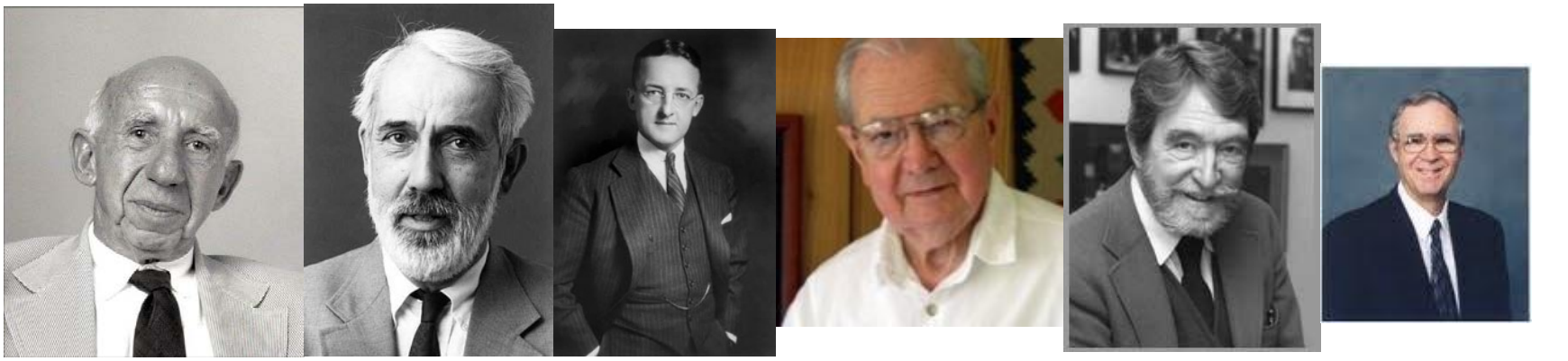
- Data and Safety Monitoring Committee
  - Most members directly involved in daily operations
- Policy Board: only persons not involved in study.
- DMC: recommendations to be ratified or overturned by PB.

- Ref: Appendix - Coronary Drug Project Personnel: *Controlled Clin Trials* 4:523-36, 1983.

DSMB



DSMB+1-time guests of Jerry Cornfield



Andreas Gruentzig and streptokinase

- Trial of intracoronary SK - ~1968
- DSMB would be 3 people – 2 cardiologists + JW
- Applied as grant to NHLBI
  - Paul Meier was on study section
  - Pink sheet: get rid of JW – she has no experience

My experience at NHLBI - 1972

- Advice from Kent Bailey and Gordon Lan
  - Go to as many DSMBs as you can!

Topic #1: History & responsibilities of DSMBs

- History of DSMBs
- DSMB membership and responsibilities
  - NIH, VA, and other publically funded trials
  - Industry-sponsored trials
- Regulatory guidance from FDA and EMA
- Therefore, what you must know as
  - Member
  - Chair

External Data Monitoring Committee

- DMCs are known by other names:
  - NIH: Data Safety & Monitoring Boards (DSMBs)
- Name may or may not define scope of functions
  - Data Monitoring Board/Committee (DMB)
  - Data & Safety Monitoring Board (DSMB)
  - or, Drug (Device?) Safety Monitoring Boards
  - Independent Data Monitoring Committee (IDMC)
  - Safety Monitoring Committee
  - Efficacy and Safety Monitoring Board

Rationale for DSMB

- Ethical compact protecting participants in trials
- Sponsor: regulatory responsibilities for reporting during trial
- Sponsor: Financial incentive to end trial early
  - If drug has no effect
  - If drug is a smashing success
- May advise about change in protocol, change in procedure

Purpose of DMC:
In decreasing order of importance

1. Protect the safety of participants
   - "evaluate trial equipoise"
2. Ensure the integrity and credibility of the trial
   - Ensure that research objectives & questions can be met and answered
3. Identify beneficial treatments early
4. Stop trial early if treatment ineffective
   - Ensure that reliable results are available to the medical community in a timely fashion

History of DSMBs

- 1960s: NIH started multicenter randomized trials
- National Heart Institute (NHI) [later NHLI & NHLBI
  - Task force to describe structure of multicenter trials of new treatment interventions
  - Chair: Dr. Bernard Greenberg
- Greenberg Report – issued 1967; published 1988
  - Recommended group of experts, not involved in trial, to advise NHI about conduct of trial
  - Coronary Drug Trial among the first that used this model

Pre-1990

- Evolution of clinical trial methodology, larger trials and NIH Clinical Trial Committee Guide, 1979
    - "every clinical trial should have provision for data and safety monitoring… [M]onitoring should be commensurate with risks"
- 1980's: Many large trials, many data monitoring models …variable practices in U.S. & Europe

1990 on

- Early 1990's : Joint NIH Conference on Data Monitoring Boards...Statistics in Medicine, '93
- 1994 NIH Committee on Clinical Trial Monitoring:
  - "all trials, even those that pose little likelihood of harm, should *consider* an external monitoring body." (My emphasis)

Current practice

- Any trial conducted under NIH auspices expected to conform to ’79 guidance
- ICH E9 4.5 (interim analysis) and 4.6 (role of the IDMC) from: Statistical Principles for Clinical Trials, FR 63:Sept 16, 1998
-
- FDA: Guidance for Industry

At NIH and VA

- Became standard at NHBLI
  - Policy Advisory Boards
  - DSMBs
- Other institutes adopted it (e.g., NEI)
- Now standard at all of NIH
- Also standard for VA trials

What do the guidances etc. mean to you?

- A DMC is a group of individuals with pertinent expertise that regularly reviews accumulating data from an ongoing clinical trial

- The DMC advises the trial 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

What are your responsibilities

- Unbiased recommendations (at least the perception)
- Scientific objectivity
- Members must be leading experts in field
  - generally not part of Sponsor organization
  - You are responsible for conveying your knowledge

What is not your role

- You are not designing the trial
- You don't make final decisions
  - Sponsor decides how to respond to DMC recommendations
  - Difficult to make an informed decision
    - The sponsor is blinded and has not seen the data
  - Difficult for regulators to aid in the decision for the same reason

Composition of NIH and VA DSMBs

- Collectively: expertise in evaluating product
  - Physicians expert in specialty
  - Biostatistician(s)
  - Medical scientist (sometimes)
  - Epidemiologist (sometimes)
  - Ethicist (sometimes)
  - Patient advocate (sometimes)
- If you sit on a DMC, ask yourself why you are there

In industry

- Unusual until the 80's
- Some early examples of outside DSMBs
  - The HA1A trial in sepsis
  - Cimetidine Stress Ulcer Clinical Trial
- As time passed, became more usual
  - Composition: physicians and statisticians

ICH Guidance E6 sect. 5.5 (April'96)

- Sponsor may use an IDMC to assess the progress of a clinical trial (safety and efficacy)
- recommend to the sponsor whether to
  - continue
  - modify
  - stop a trial
- IDMC should have written operating procedures and maintain written records of all its meetings

ICH E9: IDMC responsibilities

- Written operating procedures
- Maintain records of meetings and interim results, available for review when trial is completed
- Independence necessary to:
  - Control sharing of important comparative information
  - Protect integrity of the trial from adverse impact of access to trial information

ICH E9: IDMC Procedures

- ...Sponsor representatives on the IDMC should be clearly defined in the operating procedures (e.g., voting)
- ... the procedures should address the control of dissemination of interim trial results within the sponsor organization

Goals of interim analysis (ICH E9, *4.5*)

- To stop the trial early if:
  - the superiority of the treatment is clearly established
  - the demonstration of a relevant treatment difference has become unlikely (futility)
  - unacceptable adverse effects are apparent

DMC

- Unblinded when necessary
- Does not generally
  - Actual electronic database
  - perform analyses
- Receives DMC reports from “independent” statistician”
- Makes recommendations to the “Executive Committee” (aka, steering committee)

What do you as member need to know?

- Understand protocol
  - Review it ideally before finalization
  - DMCs can make important contributions in design
- Know what data are being collected
- Read informed consent document
- Know what the molecule has done thus far
- Understand study's organizational structure

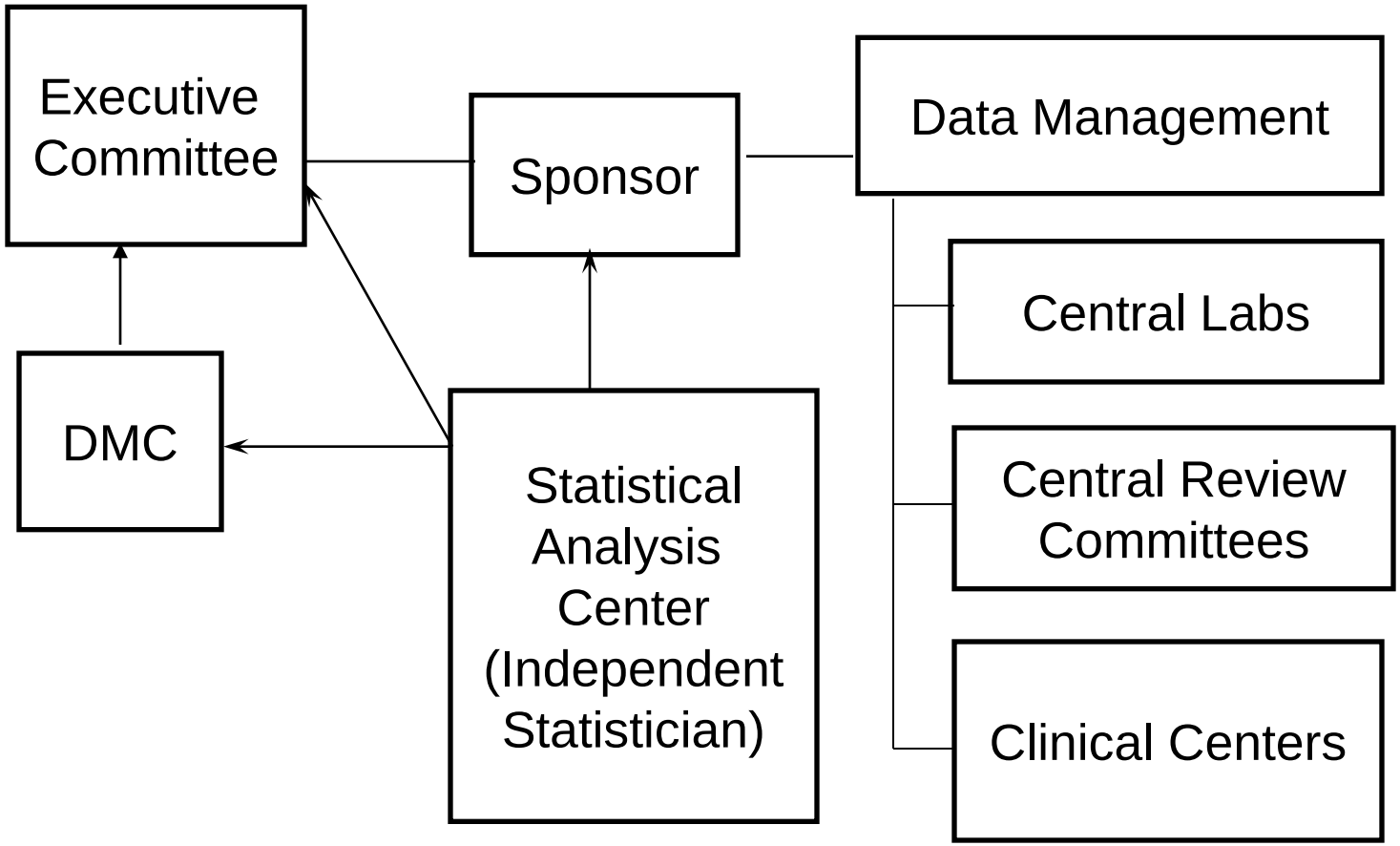
DMC role in assessing protocol design

- Common in NIH. Uncommon in industry.

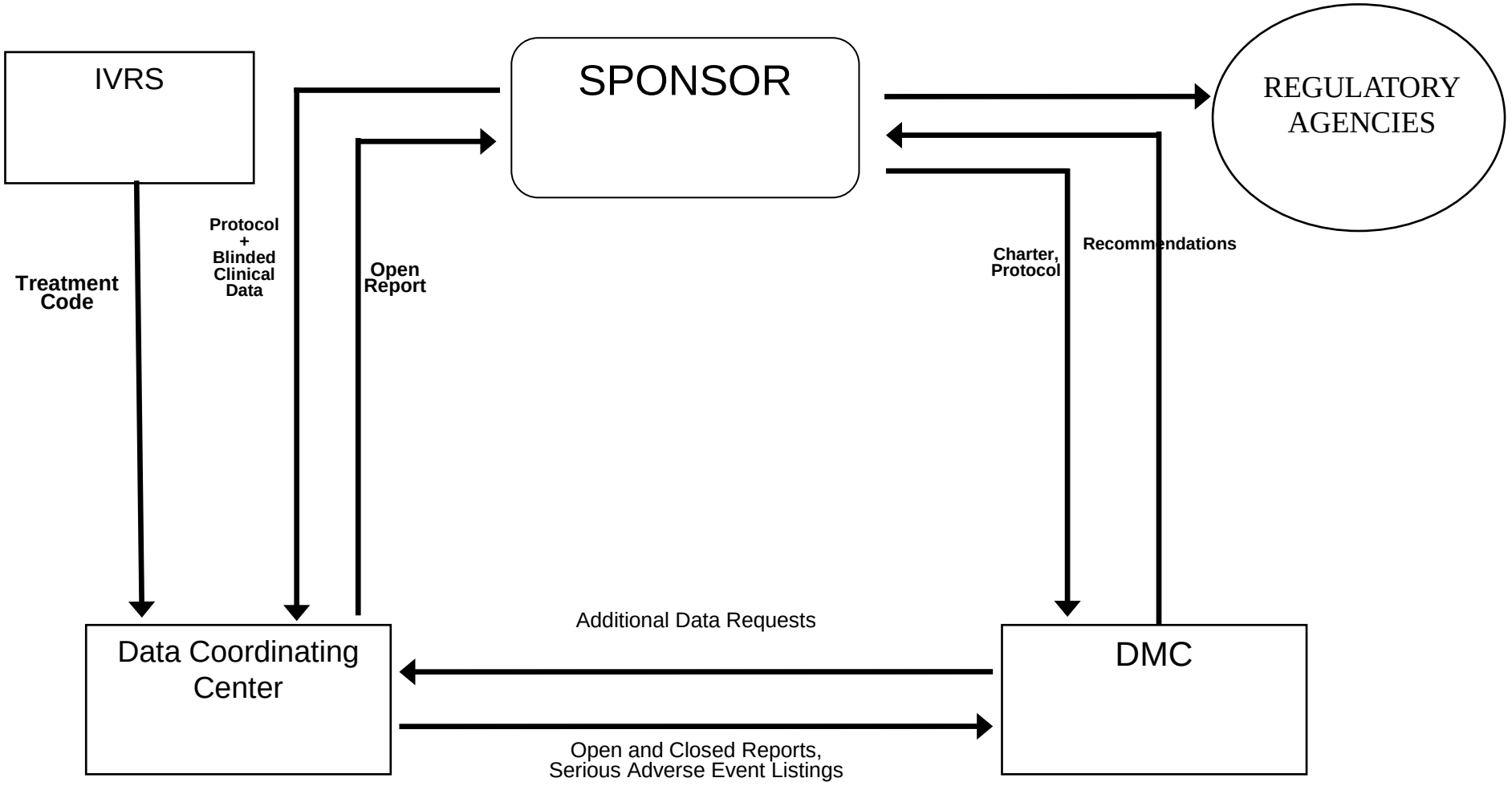
- Some of the most important contributions of the DMC are design recommendations
  - Appropriate control group
  - Appropriate analysis plan

- You will be monitor the study for safety and efficacy
- Thus is it reasonable that you believe the study is appropriately designed so that you can accomplish this task

Organizational Flow: Example



Organization Flow: Example



DMC Roles

- Advisory
  - Only make recommendations
- DMCs do not alleviate sponsor responsibilities
  - But DMC decisions can have significant implications for sponsors
    - Future of trial
    - Future of product
    - Regulatory activities
    - Investors and stock pricing

DMCs Can Recommend

- Protocol modification
- Early termination
- Temporary hold until issues are resolved
- Continue as scheduled
  - This is the most common case

DMC Roles: Safety Assessment

- Stop development of toxic treatments
- Drop unsafe arms
- Make dose adjustments
- Assess safety at several levels
  - Individual patient
  - Aggregate (and subgroups)

DMC Roles: Assess Efficacy/Futility

- Stop early for benefit
  - Accelerate development of treatments for a life-threatening disease when efficacy > expected
  - Caution: over zealous assessment of efficacy without adequate attention to safety
- Stop early for futility
  - Stop development of ineffective treatments

Themes

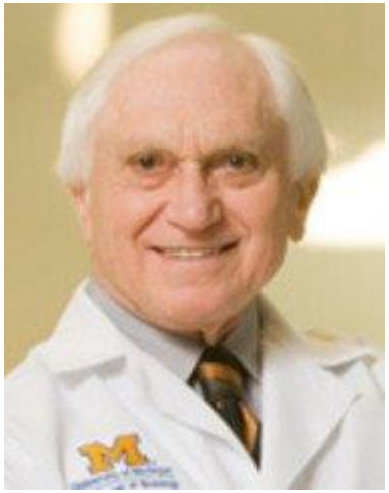
- DSMB must have tools for good decision-making
  - Members should assess competence of reporting statistician
  - You must be comfortable with their role
- Role of the DSMB must be clear
- Complexity of communication
- DSMBs have different sociologies
- Necessity of trust

Suggested guidelines

Members are free of apparent conflicts of interest involving financial, scientific, or regulatory matters. In case of any question of conflict of interest, standards used by the FDA in determining COI for advisory committee members shall apply.

J Herson

What not to do if you chair a DSMB: Michigan Professor Tied to Insider Trading Case Resigns



As you may have heard, earlier today, Mathew Martoma, a former portfolio manager in SAC Capital's CR Intrinsic unit, was charged with allegedly running "the most lucrative insider trading scheme ever," netting $276 million for the fund. He did so based on information that was given to him by Sid Gilman, a University of Michigan neurologist and chair of a safety-monitoring committee that oversaw a clinical trial by Wyeth LLC and Elan Corp. into whether the drug bapineuzumab, or bapi, was safe for patients with mild-to-moderate Alzheimer's disease.

Who looks at safety

- Investigators
- Steering Committee
- Pharmacovigilance
- IRBs
- FDA
- DSMB – what is your unique role?

Who looks at efficacy

- Only the DSMB
- Tea leaves
  - Sponsor
  - Investigators
  - Investors

What should members do

- Respond to questions about your availability
- Don’t lose your reports
- Don’t keep them open at open session meetings
- Don’t blurt out results!
- Come to meetings – don’t cancel!
- In general, take the job seriously

Special jobs of the chair

- Make sure everyone understands what they need to
  - MDs should explain biology to the statisticians
  - Statisticians should explain methods to MDs
- Elicit comments from all members
- Be prepared to write (or edit) minutes quickly!
- Forge consensus

What you need

- Indemnification
- Ability to meet with the Sponsor's knowledge
- Ability to receive materials
  - Timely data
  - With enough time and clarity for you to review

What if….

- DMC begins after recruitment has started
  - You can't change protocol
  - Has a safety concern arisen already
- The report to you is a mess (or unclear)
  - Complain!
- The reporting group refuses to do an analysis
  - "We aren't being paid for that"
- Remember your responsibility

Evaluating study conduct

- NIH/VA trials – role is often explicit
- Industry – role is often defined by DMC

Who looks at recruitment & progress?

- Sponsor
- Steering Committee

Quality of data

- Data management team (CRO or inhouse)
- Sponsor
- BUT, they are thinking “end of the trial”

Who should prepare data for DMC?

- Sponsor?
- CRO?
- Independent statistical group?
- Statistician on the Board?

Interim analysis and trial integrity

- Interim analyses can threaten the integrity of a trial
  - If investigators/subjects see interim results
  - If multiplicity is not accounted for prospectively
  - If trial managers/planners/sponsors know or meet with those who know interim results

Problems knowing interim results

- Medicine, science, and financial circumstances change, frequently prompting desire to change an ongoing clinical trials, e.g.,
  - in the primary endpoint
  - in entry criteria, evaluable population
  - in concomitant medications
  - in size of the trial
- This may be quite appropriate and acceptable but NOT if the change is proposed by individuals with knowledge of interim results

Often the DSMB has clout

- You are the policemen
- Centers will listen to you more than the sponsor
- You report to the IRBs

NIH DSMB Charters

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National Heart, Lung, and Blood Institute

Issues that DSMB charters address

- Purpose and Composition of DSMB
- Conflicts of interest
- Other players
- Differences between NIH and Industry
  - Executive Secretary
- How are meetings structured?
- Who is blinded?
- Logistics
- Indemnification of DSMB members
- Regulatory Issues
- Stopping a trial
- Channels of communication

Purpose of an External DSMB

- To protect welfare of study participants while preserving scientific integrity of trial
  - These goals are sometimes at odds.
  - Separating monitoring from operations mitigates this inherent conflict

Composition of DSMB

- Chair
- Subject Matter Experts
  - Disease experts (cardiology, rheumatology, hypertension)
  - Technology experts (laboratory, imaging, etc.)
- Biostatistician
- Bioethicist

Conflicts of Interest (COI)

- DSMB members must disclose potential COI annually and at the start of every meeting.
- Examples of Potential COI
  - Salary, consultancy, or stock in an affected company
    - A company whose product is being tested
    - A competitor of that company
  - Employee of CCC/DCC grantee or contractor
  - Professional relationship with study investigator(s)
  - Public positions indicating lack of equipoise
- Some COI can be managed, rather than disqualifying prospective DSMB member.

Other Players

- Sponsor:
  - DSMBs are appointed by and advisory to sponsor.
  - NHLBI Project team is blinded, DCC prepares and presents reports. Executive Secretary and statistician are unblinded. Senior staff may be unblinded on need-to-know basis.
    - Industry sponsors are blinded. CRO prepares and presents reports.
- Study Statisticians:
  - Unblinded: Prepare, review, and present reports to DSMB
  - Blinded: Statistical advice for study operations, limited role in DSMB
- Investigators (Blinded):
  - Present operational data to DSMB
  - Receive operational recommendations at the end of the meeting

NIH versus Industry Sponsors

Issue	Industry	NHLBI
Purpose of Trial	Regulatory approval of a specific product	Compare strategies using established regimens
Vested Interest in Trial	Financial and professional	Professional only
Vested Interest in Direction of Outcome	Positive outcome = success.	None. Many big-impact NHLBI trials are “negative”.
Regulatory	Designed to gain FDA approval of a product	Designed to compare strategies; often no IND/IDE.
Sponsor role in decision to stop or continue a trial	Rigid preset stopping **rules**. No real input during trial.	Flexible preset stopping **guidelines**. Sponsor may reject DSMB recommendation.

Executive Secretary

- NIH Staff member with no role in project team or study publications.
  - For some DSMBs, this function is handled by an external contractor.
- Responsibilities:
  - Prepares minutes of DSMB meetings and calls
  - Interface for DSMB communications with project team, investigators, and NHLBI Director.
- Executive secretary and NHLBI statistician are only NHLBI staff with routine access to unblinded outcome data.

How are meetings structured?

- Sessions
  - Open (sponsor, investigators, study statisticians, executive secretary)
    - Operations, site activation, recruitment, protocol deviations, completeness of data, treatment compliance, dropout, crossovers, lost to follow-up, baseline data, aggregate post-randomization data
  - Closed (unblinded study statisticians, executive secretary)
    - Post-randomization outcome data broken out by treatment group, case reviews of adverse events
  - Executive (executive secretary)

NHLBI DSMBs
Who is Blinded to Outcome Data by Group?

Unblinded:

- DSMB
- Statisticians who prepare and review data reports
- NIH Executive Secretary

Blinded:

- Everyone else

Note: This is a separate issue from blinding investigators and participants to individual treatment assignment.

Blinding of DSMBs

- Some DSMBs choose to see treatment groups identified only as Group A, B, C, etc., without knowing which is which. This is not generally recommended:
  - Efficacy and safety monitoring are not symmetrical; quicker trigger for an adverse than a beneficial trend.
  - Blinding may compromise ability to interpret data
    - Treatment groups of unequal sizes
    - Fragmented coding for specific biomarkers affected by treatment
  - Blinded DSMBs often try to guess treatment assignment. When they act on incorrect guesses, patients may be endangered.
- **Protecting participant welfare is paramount!**

Logistical Issues

- Frequency of Meetings
  - Teleconference versus in-person
- What constitutes a quorum?
- Interim contacts
  - Email polls
  - Ad hoc meetings

Indemnification

- The government may only directly indemnify government “special employees”, such as those on formally constituted advisory committees, which are limited in number.
- Since we have too many DSMBs to convert to formal advisory committees, NHLBI has handled this through a special CRO contract.
- Since NHLBI DSMBs are truly advisory and entail participation by staff as executive secretaries, an NHLBI DSMB member is unlikely to be successfully sued – and none ever has been.
- Although industry DSMBs are technically advisory, they are far more vulnerable to a lawsuit; since the industry sponsor (unlike NIH) has no access to outcome data during the trial, their DSMBs de facto “own” the decision to continue a trial.

Regulatory Issues

- Apply to studies performed under an IND or IDE
- Focus on unexpected SAEs with possible relationship to study intervention
  - May include delivery method – example: cardiac catheterization for cell product (or placebo) delivery in a cell therapy trial
  - May occur in control as well as active treatment group
- Timeliness of notification – usually stipulated by FDA regulations
- Expedited DSMB Review of SAE
  - Does DSMB want to review SAE before they go to FDA?
  - Entire DSMB or just the Chair or a small subcommittee?

Stopping a Trial

- The most critical and difficult decision a DSMB makes is whether and when to stop a study before its scheduled completion:
  - Efficacy
  - Safety
  - Futility
    - Statistical: Sufficient evidence that null hypothesis will not be rejected if trial is carried to completion
    - Unfeasibility: Insufficient power to test the study hypothesis
- Statistical stopping boundaries may be included or referenced in the charter.
- Rules versus Guidelines
  - NIH trials: Guidelines with leeway for interpretation.
  - Industry trials: Prescriptive rules, especially under IND/IDE
    - Prescriptive stopping rules enable industry sponsors to limit DSMB's leeway for *ad hoc* judgments that may jeopardize regulatory approval.

Stopping a trial for lack of feasibilty

Examples:

- Major cost overruns
- Low patient accrual
- Low power due to low event rates
- Poor compliance: Low pill counts, high dropouts, high crossovers, etc.

DSMB has a limited role in making this decision:

- It is largely a financial decision, since the alternatives to stopping include extending enrollment and/or follow-up.
- Other alternatives, such as modifying the endpoint to include more components, ought not be left to an unblinded group (like a DSMB).

➢ **NHLBI can no longer afford its traditional habit of supplementing the budgets of struggling trials.**

NHLBI Trials
Communication of DSMB Recommendations

- Summary minutes are co-signed by the DSMB Chair and Executive Secretary and forwarded to the Director, NHLBI within 15 days of the meeting.
- Notification of Investigators and NHLBI Program Staff
  - Routine operational recommendations: DSMB Chair reports out at the end of the DSMB meeting.
  - Recommendation to stop or suspend a trial: Withheld from the investigators until the NHLBI director has concurred.
    - In urgent cases, an expedited decision is sought.
- A summary with appropriate excerpts of the signed minutes is later provided to IRBs by the study investigators.

Safety

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Safety Monitoring – 2 Kinds of Questions

- Are trial participants being harmed by the procedures and requirements of participation?
  - Comparison of trial patients to external standard of care
  - FDA, IRB, Blinded Safety Officer at NIH or CC
- In a trial comparing a new treatment or paradigm with a standard treatment or placebo, is there evidence that the new treatment is harmful.
  - Comparison of treatment groups within trial
  - Unblinded DSMB

Individual Case Reports for SAE

- Serious, unexpected, possibly related to treatment
- No identifying information
- Blinded
- Routinely provided to:
  - IRBs
  - FDA in regulated trials
  - DSMB
    - Chair in real time
    - Committee at pre-set intervals (q6 months)
- Most useful for identifying rare adverse effects

Aggregate Event Tables

- Doesn't matter whether they are expected or thought *a priori* to be related to treatment
- Unblinded (DSMB only)
  - Compare frequencies of common events among treatment groups
    - Example: Are patients receiving the active drug suffering more strokes than those receiving the control regimen?
- Blinded (may be shared with sponsor, Investigators):
  - Trial patients versus external standard
    - Example: Are complications of cardiac cath performed in the trial more frequent than in standard practice?
  - Trial subgroups
    - Example: In an international PCI trial, does the frequency of stent thrombosis differ among countries?

What reports can blinded investigators see?

- Blinded individual case reports for their own site
  - Site staff generally prepare
- Blinded SAE frequency data for their own site
- Blinded study-wide SAE frequency data
  - May include site-specific data with sites de-identified

Evaluating Safety Data
What is important and what is spurious?

- Multiple comparisons:
  - P-values may flag potential problems but are not definitive
- Biomarkers versus clinical harm
  - Example: increased ALT versus liver failure
- Consistency
  - Internal -- similar effects on related outcomes
  - External-- reports in literature for the same or similar treatments
- Did patients suffering the adverse events actually receive the active treatment?
  - Be careful; intention to treat principle still applies
- Plausible Mechanism
  - Beware of your biases
- First, do no harm.
  - Less evidence is required to stop for safety than for efficacy.

Quality of Safety Reports

- Clarity
  - Tables should be self-explanatory.
  - A picture is worth a thousand words (or numbers).
  - No “data dumps”!
- Completeness
  - Are all relevant outcomes reported?
    - Not all safety outcomes are SAEs
  - Is reporting up to date?
- Are additional analyses needed?
  - Patient subgroups
  - Composites of related events
  - Breaking down overly broad categories of SAE
- ➢ A DSMB is responsible for asking for the analyses it needs.
  - ➢ If the study statistician(s) cannot or will not provide them, that may itself be grounds for stopping a study.

Now you monitor a very complicated study

- DG will describe the study and set you to the task of monitoring it.

Monitoring for efficacy

Problem with looking at data more than once

- Multiple interim analyses, each at a nominal level of 0.05, inflates the Type I error rate

- Assuming independence

# Analyses	Type I error
2	.0831
3	.1073
4	.1262
5	.1417
.....	
10	.1934

- Actual effect smaller in clinical trials because successive analyses not independent

Methods of monitoring for efficacy

- Deal with the inflation of the Type I error rate created by multiple testing
- If there is no statistical testing or no possibility of changes in trial conduct (e.g., stopping trial), then theoretically no adjustments are needed.
  - But operational bias can still be induced with interim looks
  - FDA may still claim that if you perform IA, then there is a possibility of stopping (e.g., when evidence is overwhelming)…even if you claim there is no such possibility.

Controlling Error Rates

- Statistical methods can control errors (α) created by multiple testing using a plan for error spending and appropriate sample size adjustment

- Aside: If decision rules are binding, do we really need a DMC?

Operational Issues

- Confidentiality

- Data management and cleaning
  - Database is still open
  - Time lag between data in report and date of DMC meeting
  - Cleaning and logical checks

- Commercial software: EAST, S+SeqTrial, PEST, PASS
- Free software: www.medsch.wisc.edu/landemets/

Operational Bias

- Interim results being announced (or not being announced) could affect how patients/investigators react during the remaining part of the trial
  - Patients selectively drop out
  - Slower accrual (investigators choose not to enroll patients; patients choose not to enroll)
  - Adherence decreases
  - Subjective or self-report data could be influenced

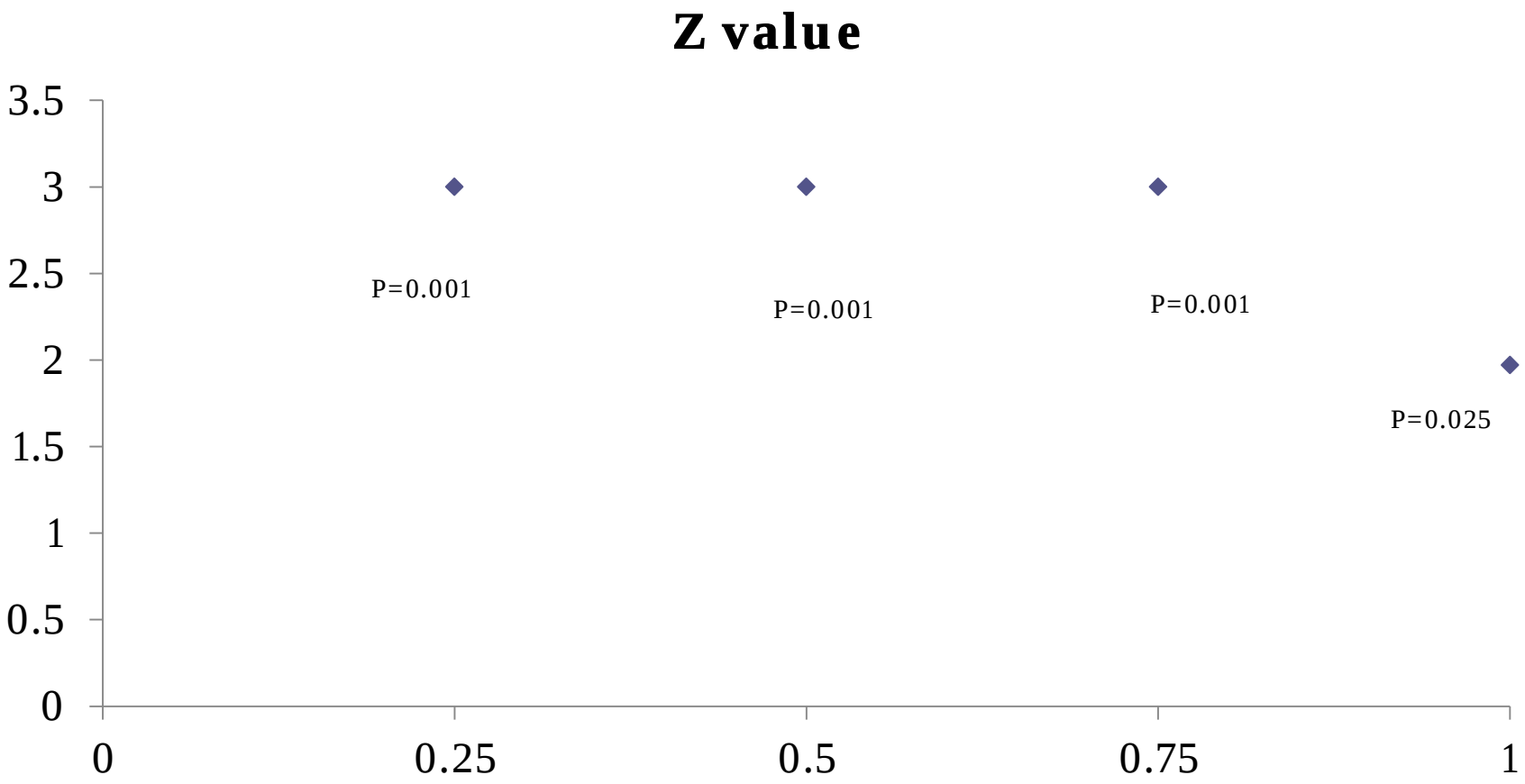
Stopping for efficacy: Haybittle-Peto

- Stop at 3 sds (p=0.0005) or at the end of the trial (p=0.025)

- Haybittle JL (1971). "Repeated assessments of results in clinical trials of cancer treatment". *Brit. J. Radiol* **44** (526): 793–797

- Yusuf uses even more extreme – 4 sds for the 1st half; 3 for second. Or two successives 3's.

Haybittle-Peto boundary



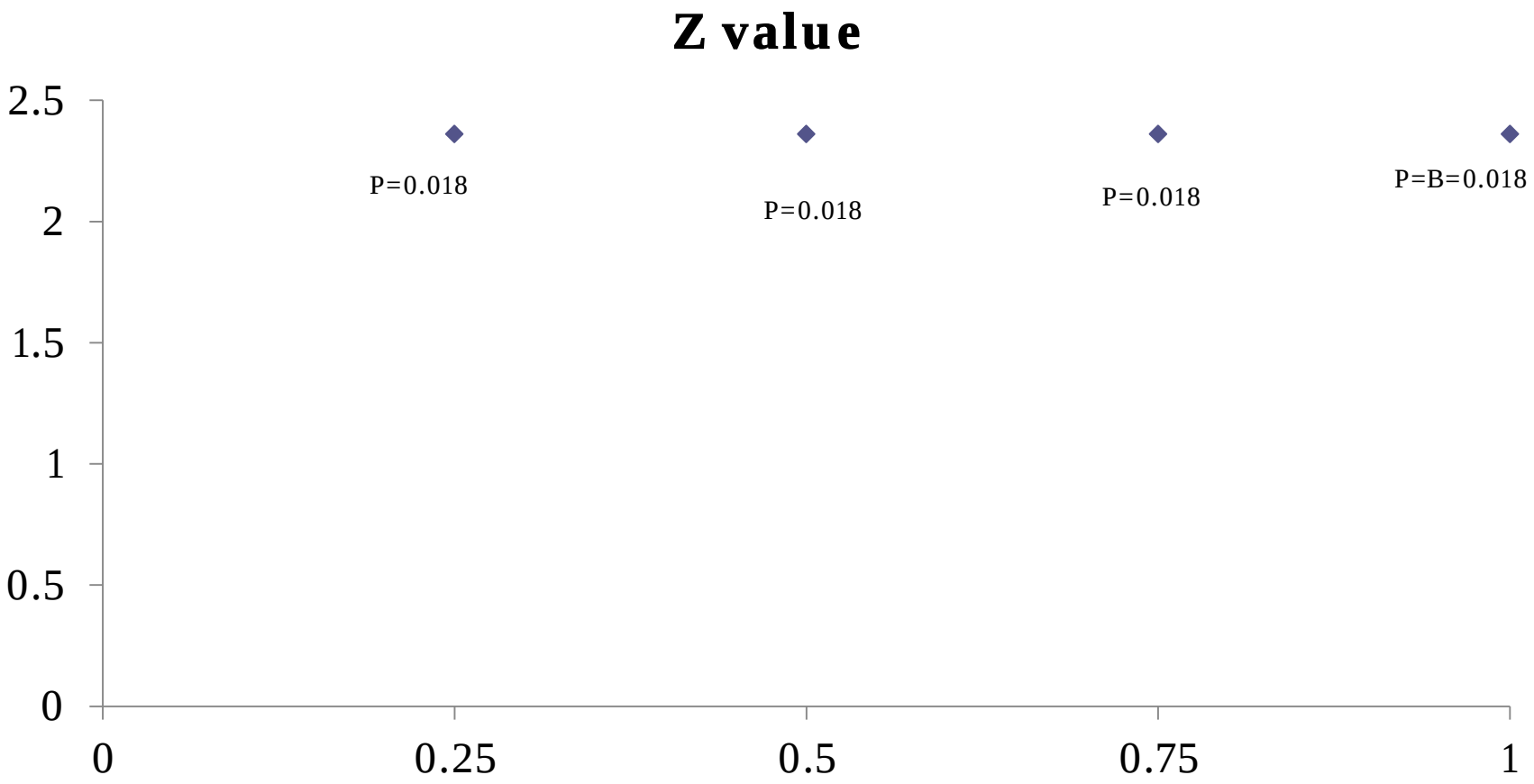
Stopping early for efficacy

Pocock (Biometrika, 1977)

- Test interim and final analyses at a fixed (constant) nominal α level
- More aggressive early, less aggressive later

# Analyses	Type I error
2	.0294
3	.0221
.....	
5	.0158
.....	
10	.0106

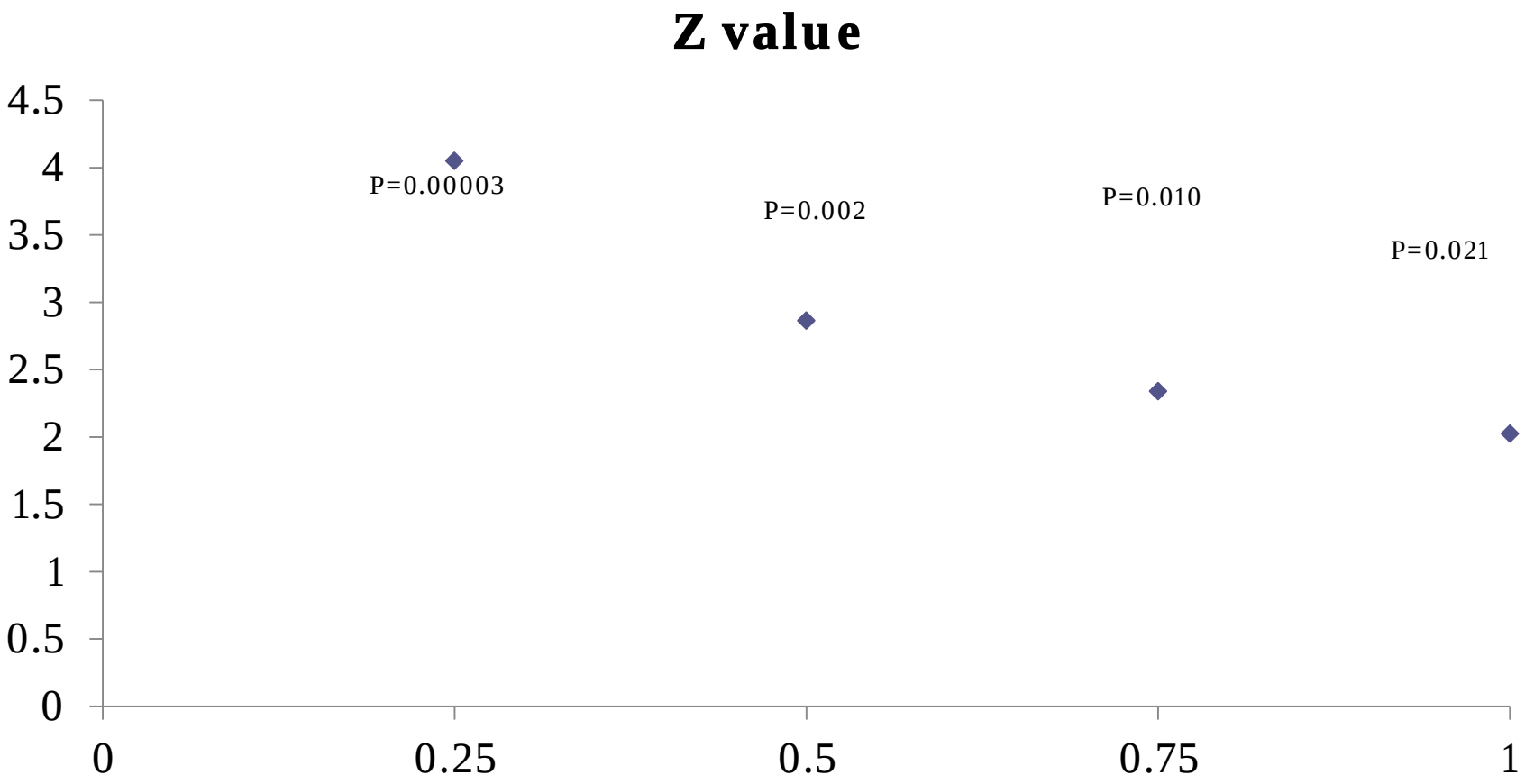
Pocock boundary



O'Brien-Fleming (Biometrics, 1979)

- Test early interims at small nominal α levels, increasing slowly so final nominal alpha is close to α
- Conservative early, aggressive at the final.
- Good for efficacy, as one needs significance at the end of the trial. (Saves most of the α for the final look.)

O’Brien-Fleming boundary



Limitations of These Methods

- Little information regarding the reasons for:
  - High p-values:
    - Negligible effect vs. insufficient data
  - Low p-values:
    - Large effect vs. lots of data

Limitations of Methods

- Inflexible: real decisions based on many factors
  - Results of other trials
  - Safety data
  - Balance of benefit to risk
  - Secondary endpoints
  - Development of new treatments
    - Changing market
  - Political/economic considerations
    - Cost:benefit
  - Company dynamics

Choosing a Method

- Depends on objectives of the interim analysis
- Members should understand the method
  - Ask: what effect size corresponds to p-value?

Now you monitor a trial

- JW will lead you through a trial (much simpler than DG's that you already struggled with)

Statistical Futility (Lack of Efficacy)

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What do we mean by statistical futility?

- We can determine based on the data in hand that there is a very low probability that the trial will reject the null hypothesis if carried to its planned conclusion.

The “data in hand”

- Ascertainment of Events
  - Missing visits, dropouts, losses to follow-up
  - Submission of forms
- Adjudication of Events
  - Turnaround time of adjudication process
  - Probability that a reported event will be confirmed.
- Secondary Endpoints of Interest

“Very low probability”

- Metrics for low probability
  - Conditional power < 10-20%
    - If there is truly an underlying treatment benefit that will apply to future events, what is the probability of ultimately rejecting the null hypothesis? But what benefit should be assumed?
      - Alternative hypothesis assumed in study design?
      - Trend based on observed effect to date? This may be null or negative.
      - “Optimistic” boundary of 95% CI of observed treatment benefit to date?
  - Sequential boundary to reject H0 of “non-equivalence”.
    - Example: Asymmetric monitoring boundary requiring HR > 1.02 and P < 0.001 to reject H0 at the mid-point of follow-up.

“Planned conclusion”

- Accrual of the aggregate number of primary endpoints upon which the study’s power and sample size were originally predicated.
  - Even if the study was designed to be of fixed duration rather than event-driven, the term “statistical futility” is reserved for lack of efficacy, not trials that simply run out of time.

Other General Comments about Futility

- Although the term futility connotes a waste of time and effort, statistical futility is not tantamount to failure. Lack of efficacy is a more fitting term.
- Stopping for futility is rarely urgent
  - No harm to patients if a neutral study goes too long.
  - DSMBs should be, and generally are, very conservative.
- Before stopping a trial:
  - How much incomplete or outstanding data?
  - Continue to get key secondary endpoints?
- When a DSMB stops a study for futility, look for a safety concern under the surface.

Another trial to monitor

- DG will lead you through Trial #3

Monitoring a complex trial -Janet

- And, for your last trial….