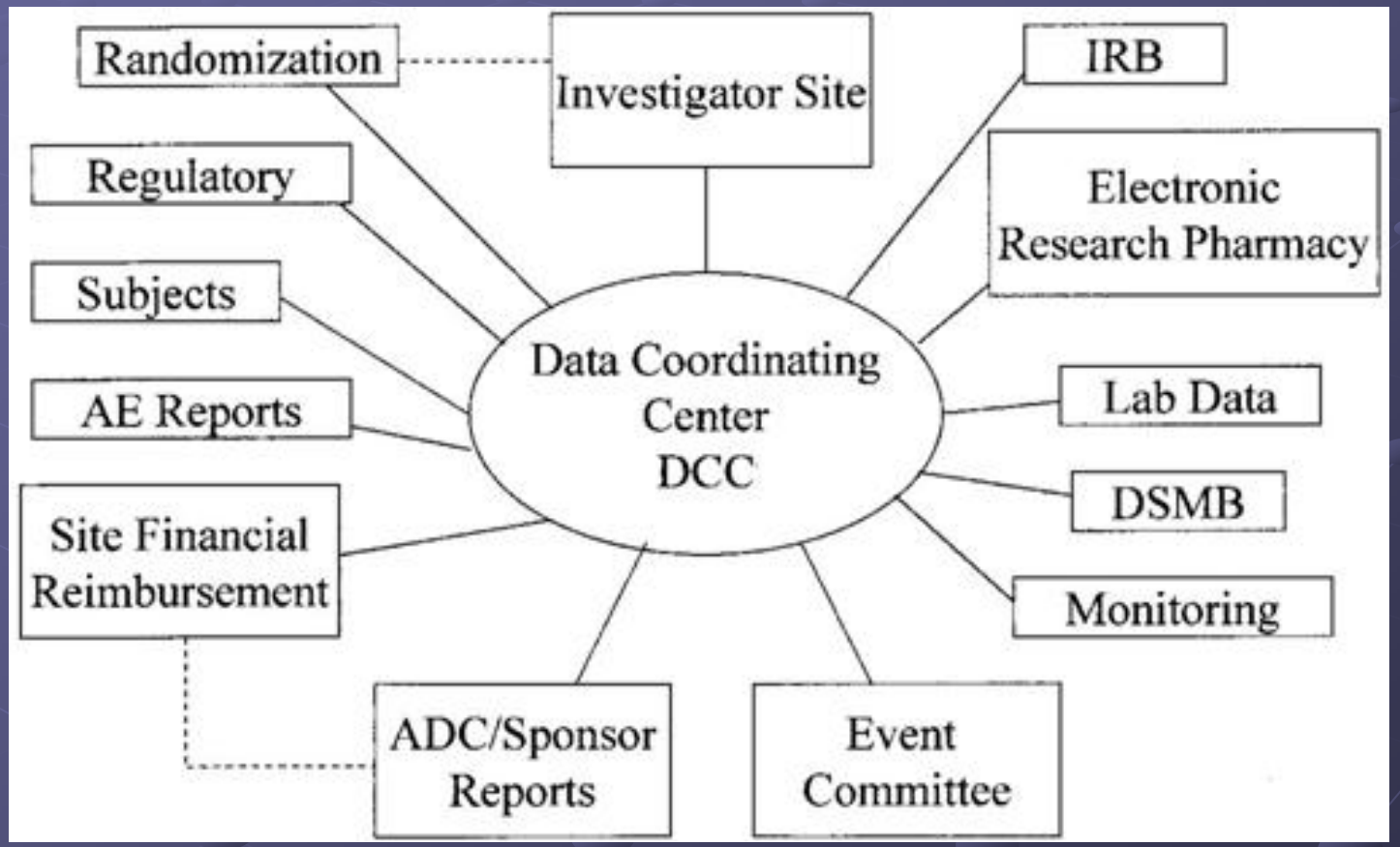
Nuts & Bolts of Clinical Trials, DSMBs, Event Committees, Core Labs and Data Standards

Ron Waksman, MD
Professor of Medicine,
Georgetown University
Associate Chief of Cardiology,
Washington Hospital Center

A quick Amazon search revealed > 1,000 books on the topic!

Study Management Structure



Clinical Trials

- What is a Clinical Trial?
  - “A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings.”
- Clinical Equipoise
  - “Equipoise is the concept that a clinical trial (especially a randomized trial) is motivated by collective uncertainty about the superiority [or equivalence] of one treatment versus its alternative.”
  - "....at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way s to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed."

Friedman, Furberg, DeMets. Fundamentals of Clinical Trials. 3rd Ed. Pg 2 1998
Piantadosi. Clinical Trials; A Methodologic Prospective. 2nd Ed. Pg 31 2005
Freedman, B., "Equipoise and the Ethics of Clinical Research", New England Journal of Medicine. 1987, 317: 141–143.

Clinical Trials

- What is the Research Question?
  - Should be of clinical relevance
  - Have established clinical equipoise
  - Have the capacity to be adequately answered for which a sample size can be generated
  - The outcome of the study could have beneficial action: saving life, ameliorate illness, improve quality of life, etc.

How to Answer the Research Question?

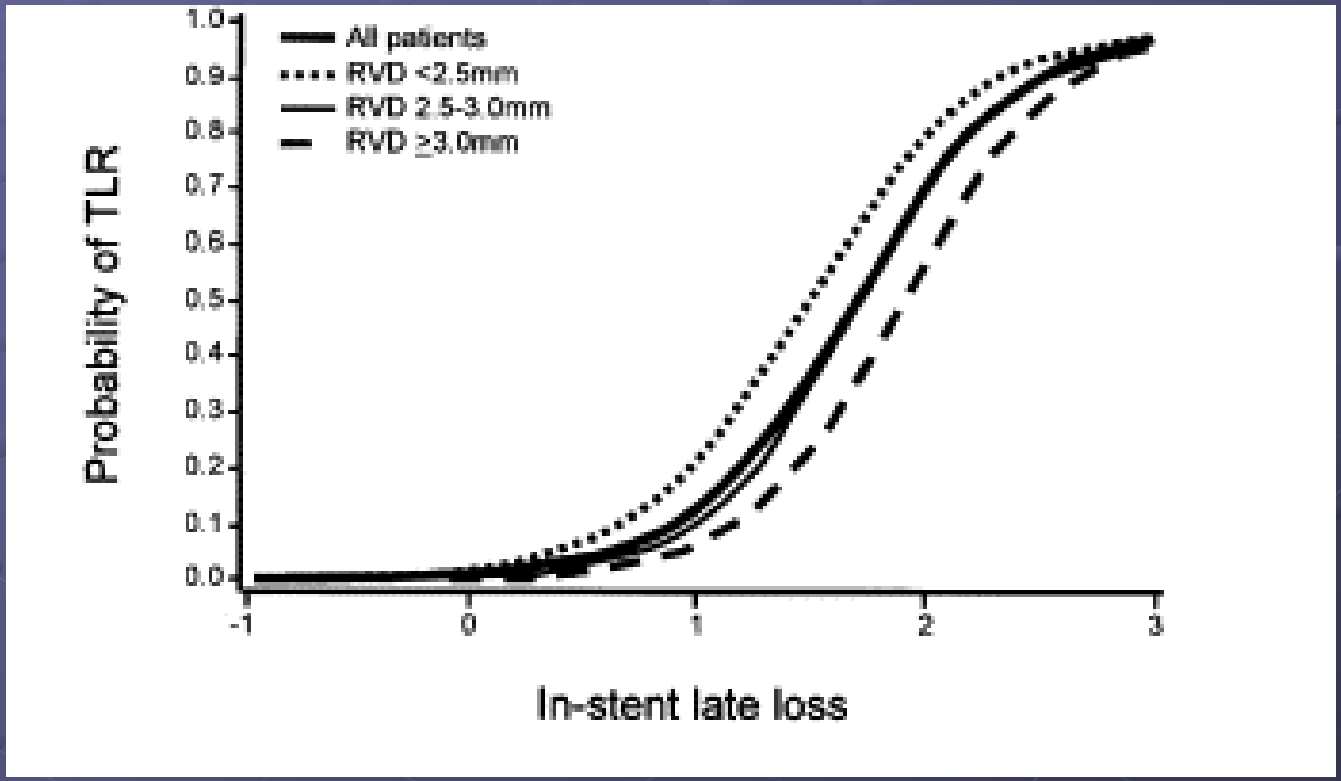
- Primary Endpoint
  - Efficacy/Effectiveness vs. Safety
    - One Variable vs. Composites
      - Examples: MACE (Major Adverse Cardiac Events); TVF (Target Vessel Failure)
      - Can/should these be combined?
- Secondary Endpoint(s)
  - Addresses subgroup study questions, exploratory variables. etc.

Response Variables

- What is a Response Variables
  - An outcome measure that defines and answers the study question.
    - Example: Death, Amputation, etc
  - Surrogate Endpoints
    - Due to the cost and length of some studies, surrogate variables are used.
      - Example: TLR, Late Loss, Restenosis
    - Criticism – how do the surrogates correlate to the true response variable – e.g. death?

Surrogate Endpoint

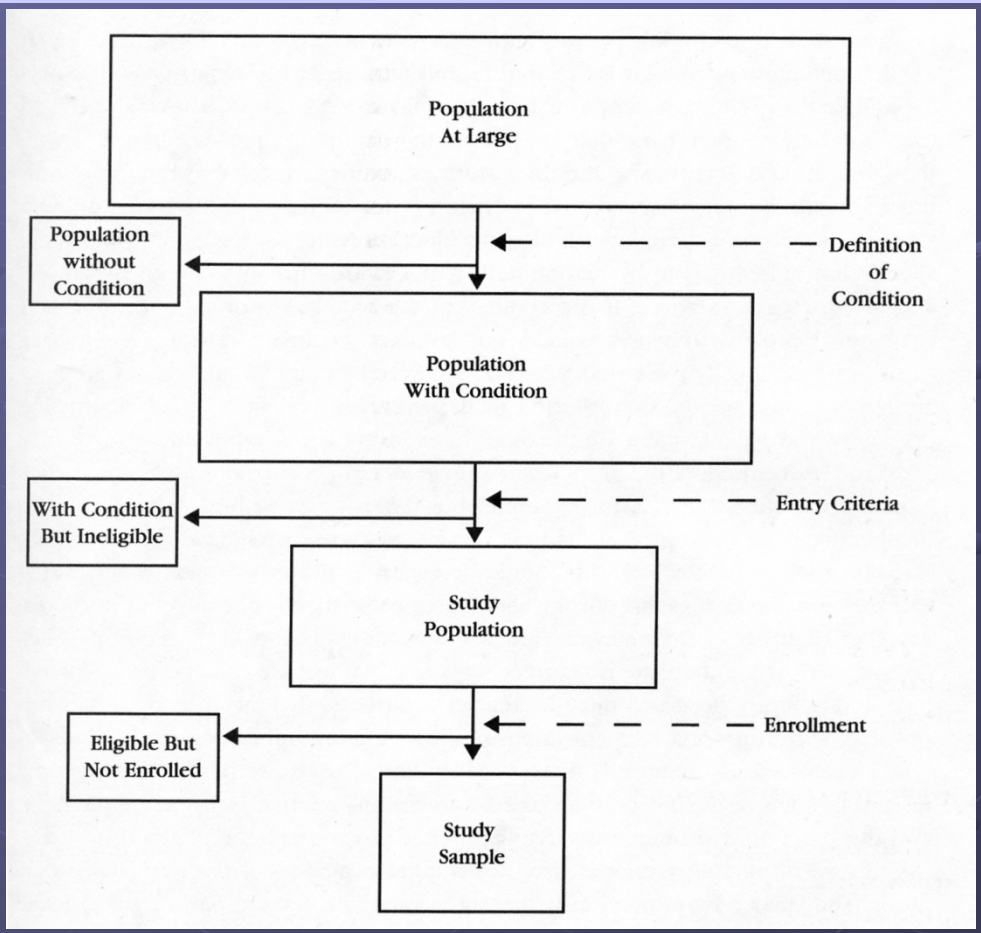
Two commonly used Surrogate Endpoints for Stent Trials



Do either of these variables correlated to improvement in life expectancy?

Pocock SJ *et al*. *J Am Coll Cardiol*. 2008 Jan 1;51(1):23-32.

Study Population



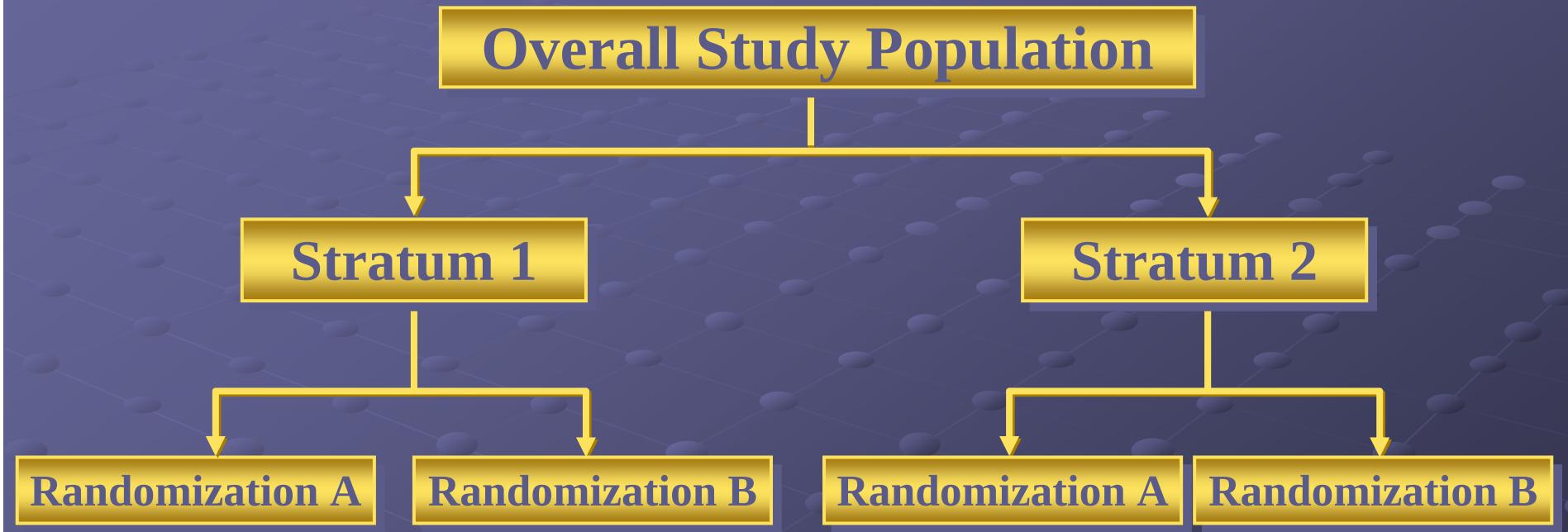
The study population should be well defined by unambiguous criteria (inclusion/exclusion criteria), however the key is to effectively answer the study question while addressing the 'generalizability' of the study conclusions to the target population.

Friedman, Furberg, DeMets. Fundamentals of Clinical Trials. 3rd Ed. Pg 31 1998

Trial Designs

- **Randomized Controlled Trials**
- Nonrandomized Concurrent Control Studies
- Historical Controls/Data Bases
- Cross-over Design
- Withdrawal Studies
- Factorial Design
- Group Allocation Design
- Hybrid Design
- Studies of Equivalency (Trial with positive controls)
- Large Simple Clinical Trials

Randomized Controlled Trials



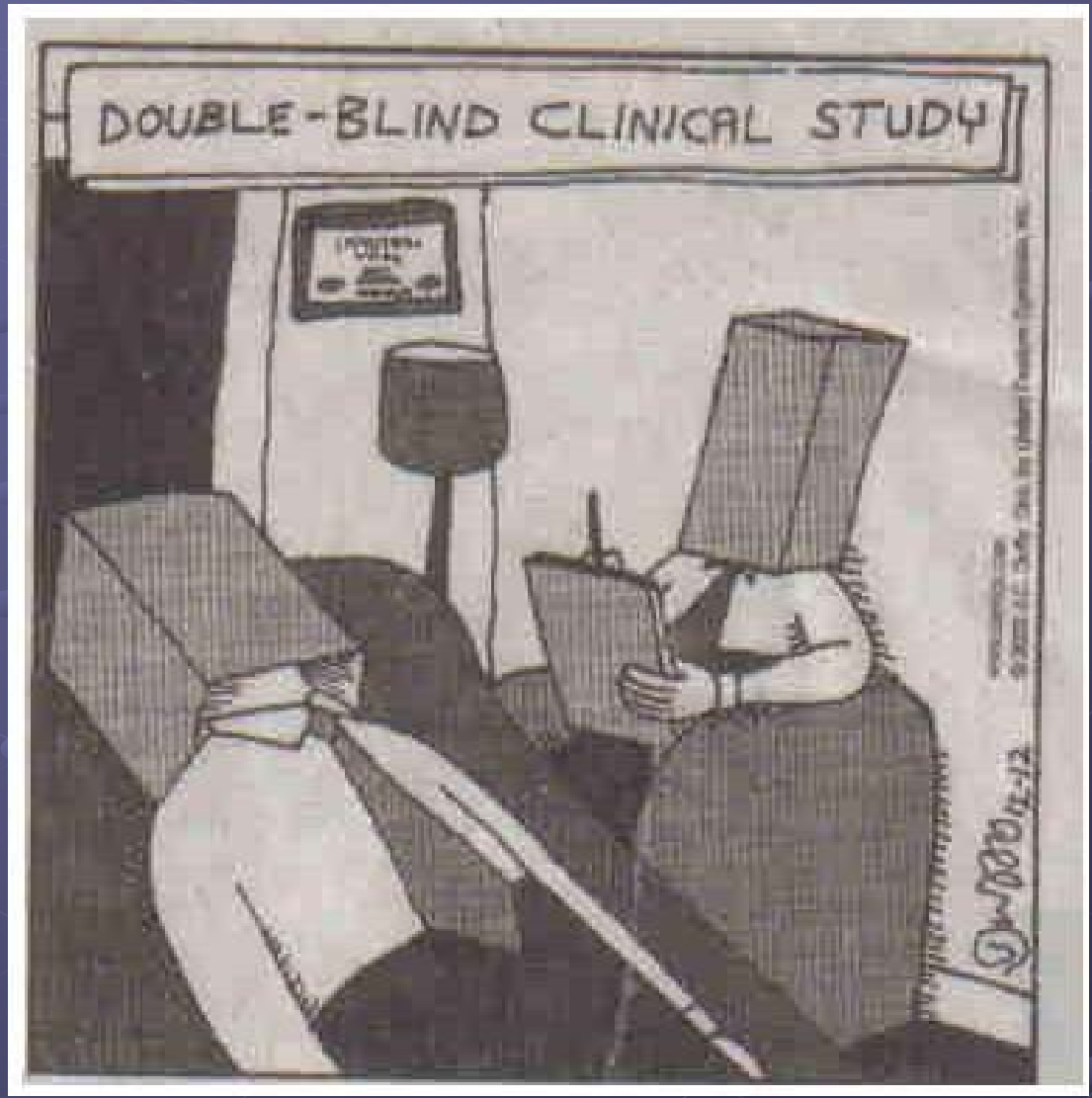
Advantages to Randomization

- Removes potential bias in the allocation of subjects the each rand. assignment
- Produces comparable groups with respect to known and unknown risk factors
- Guarantees statistical test will have valid significance levels

Study Design and Methods

- Study population
- eligibility, inclusion/exclusion criteria
- enrollment plan, feasibility
- primary and secondary endpoints
- methods of randomization
- important considerations for sample size and power calculations
- methods and frequency of data collection and entry
- monitoring accuracy of data collection
- quality control procedures including training of study personnel
- plans for statistical analysis

Double-Blind Clinical Trials



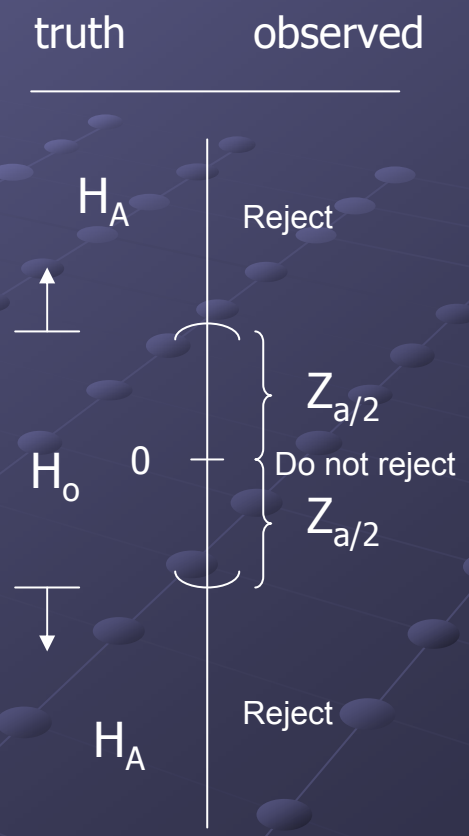
Trial Designs

- One-Sided Superiority
- **Two-Sided Superiority**
- Futility (One-Sided Non-Superiority)
- Equivalence
- **Non-inferiority**
- Etc.

Two-sided Superiority

H_o: $\mu_1 = \mu_2$
(treatment 1 is not different than treatment 2)

H_A: $\mu_1 \neq \mu_2$
(treatment 1 is different than treatment 2)



Usual Suspects:

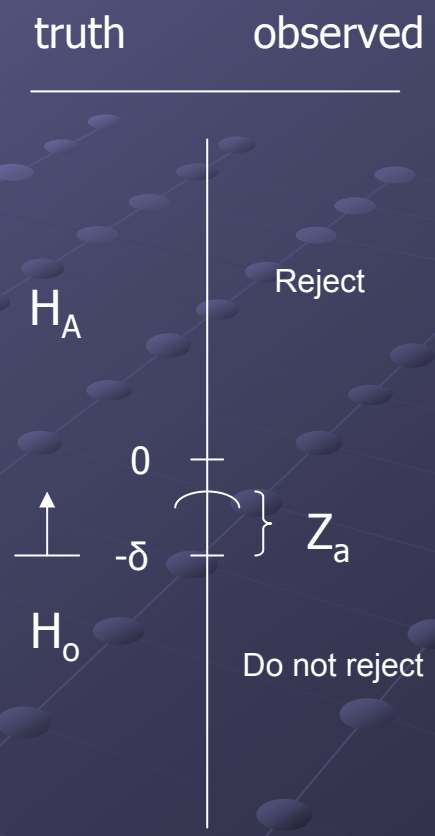
$\alpha \leq 0.05$ $\quad Z_{\alpha/2} \leq 1.96$

$\beta \leq 0.2$ $\quad$ Power ≥ 0.8

Non-Inferiority

H_o: $\mu_1 - \mu_2 < -\delta$
(treatment 1 is inferior to treatment 2)

H_A: $\mu_1 - \mu_2 \geq -\delta$
(treatment 1 is non-inferior/ superior to treatment 2)



Usual Suspects:

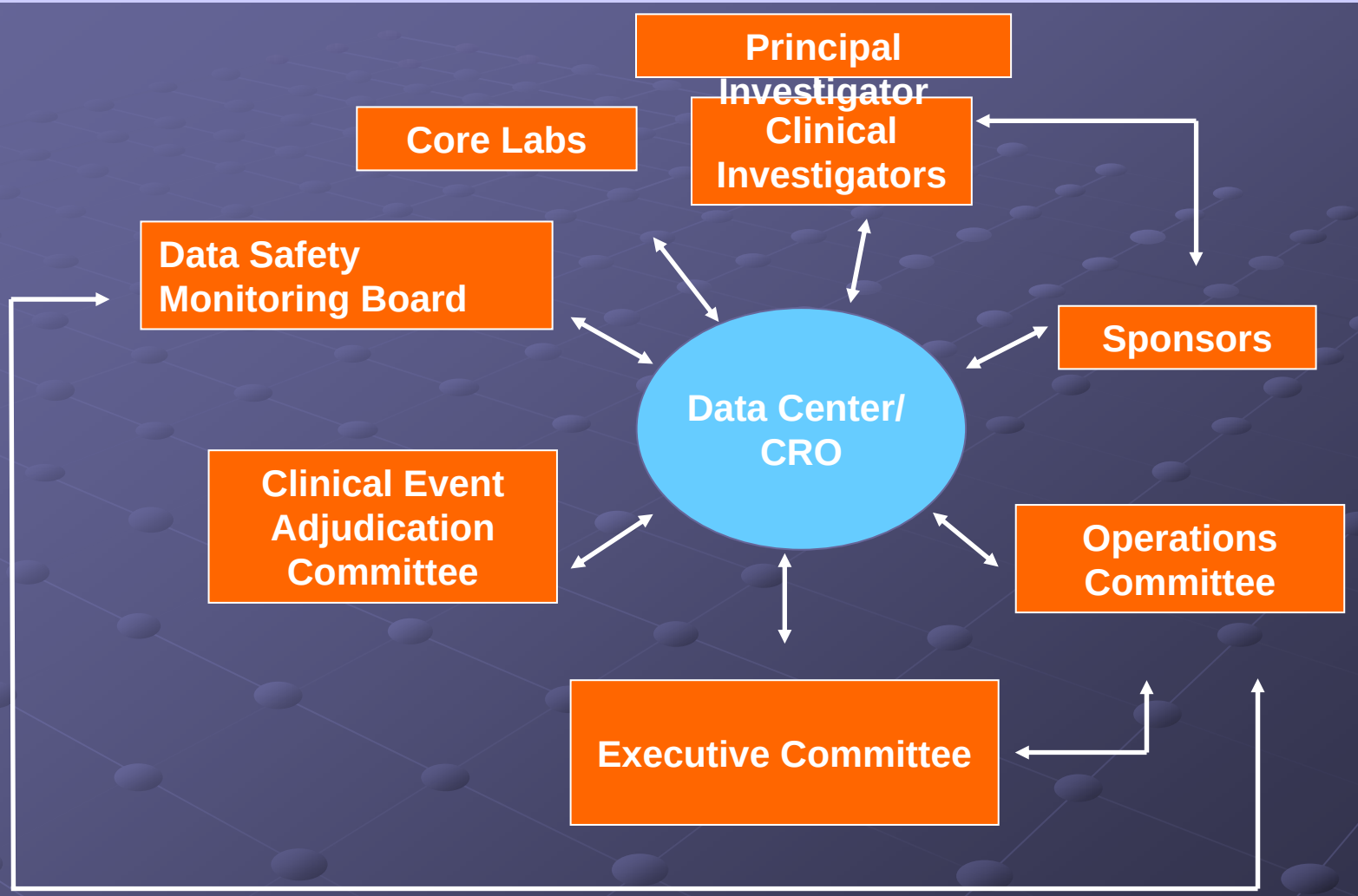
$\alpha \leq 0.1$ $Z_\alpha \leq 1.282$

$\beta \leq 0.1$ Power ≥ 0.9 δ = ???

Type I and II Error

	Type I Error	Type II Error
Superiority	Declare treatment 1 different than treatment 2 when in fact no difference	Declare treatment 1 NOT different than treatment 2 when in fact they are different
Non-Inferiority equivalence	Declare treatment 2 non-inferior to treatment 2 when in fact treatment 1 is different than treatment 2	Declare treatment 1 NOT non-inferior (equivalent) to treatment 2 when in fact treatment 1 is non-inferior (equivalent to treatment 2

Charisma Study Organization



1. Adapted from Bhatt DL et al. *Am Heart J* 2004; 148: 263–268.

The Role of PI

- For multi-center trials there will be a designated Principal Investigator (PI) or lead Clinician.
- Prior to commencement of a trial, the Principal Investigator is responsible for preparation and final approval of the protocol.
- During the conduct of the study he/she is in charge of medical monitoring (particularly toxicity/safety) or designate a party when a trial is blinded.
- On completion of the study he/she is responsible for liaison with statistician over analysis, and finally for reporting the results.

DSMB
Data Safety Monitoring Board

- Monitoring Board is an independent advisory group to the sponsor with the responsibility of providing recommendations concerning starting, continuing, and/or stopping the clinical research study under review

- The Monitoring Board's recommendations are based on:
  - Safeguarding the interests of study participants
  - Assessing the safety and efficacy of study procedures (both clinically and statistically evaluated)
  - Monitoring the overall conduct of the study

Responsibilities of DSMB's

The Monitoring Board is asked to make recommendations regarding:

- **Participant Safety (No. 1)**
- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Data and Statistical Integrity
- Adequacy of measured and collected data
- Recommendation regarding amendments to the study protocol and consent forms, only if cannot be influenced by knowledge of interim outcomes data
- Performance of individual centers and core labs

Power of DSMB's


The New York Times
nytimes.com

December 4, 2006

End of Drug Trial Is a Big Loss for Pfizer

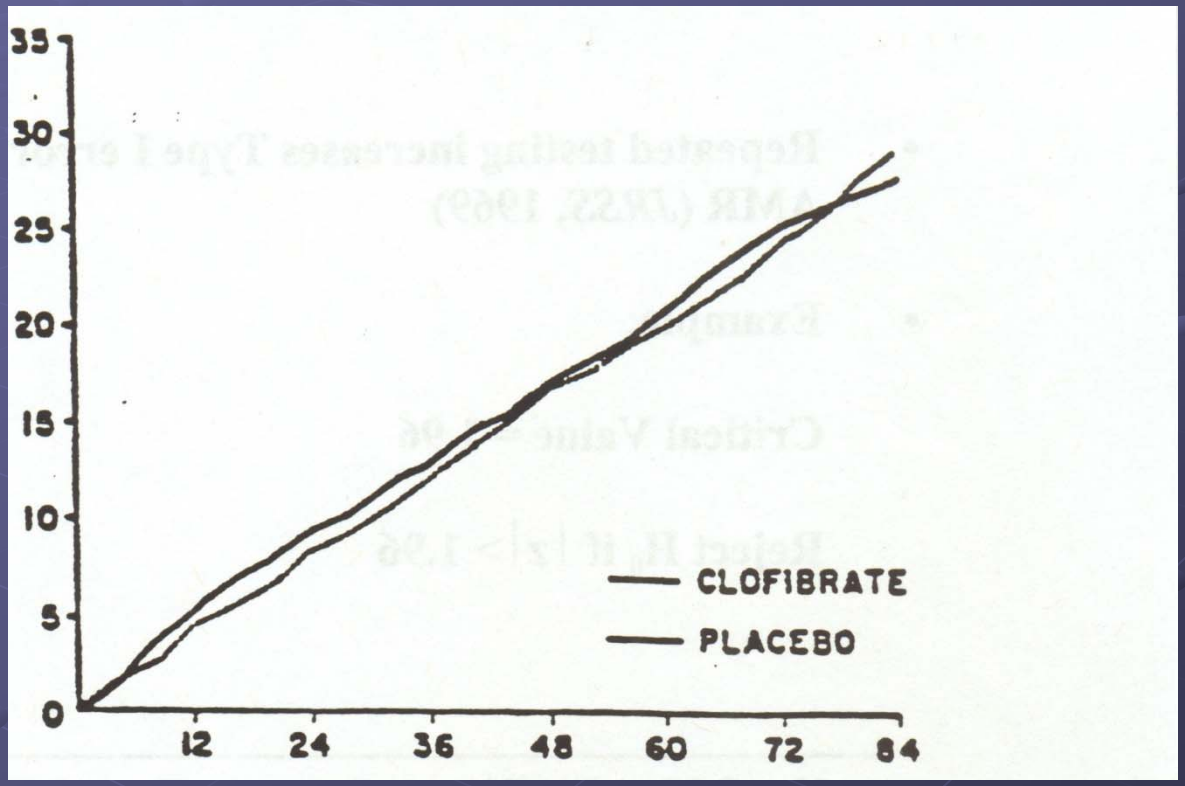
- The JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial was stopped early based on a recommendation from an independent Data and Safety Monitoring Board because there is unequivocal evidence of a reduction in cardiovascular morbidity and mortality in patients treated with rosuvastatin compared with placebo

- Ultimately patient safety comes first – both stopped as one group was receiving a more "harmful" treatment

Reasons for Early Termination

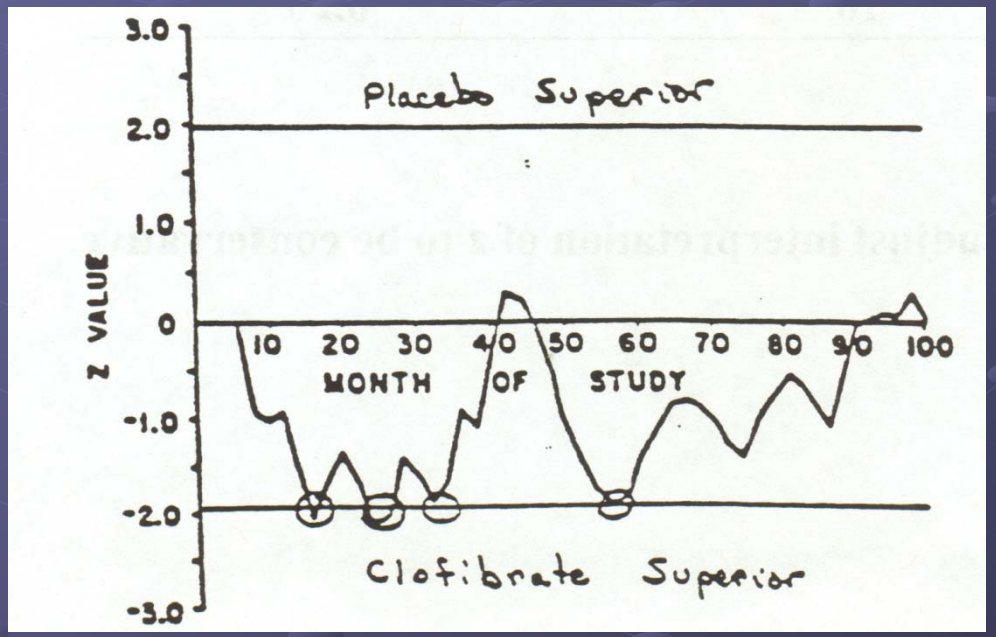
1. **Serious toxicity**
2. **Established benefit**
3. **Futility or no trend of interest**
4. **Design, logistical issues too serious to fix**

Coronary Drug Project



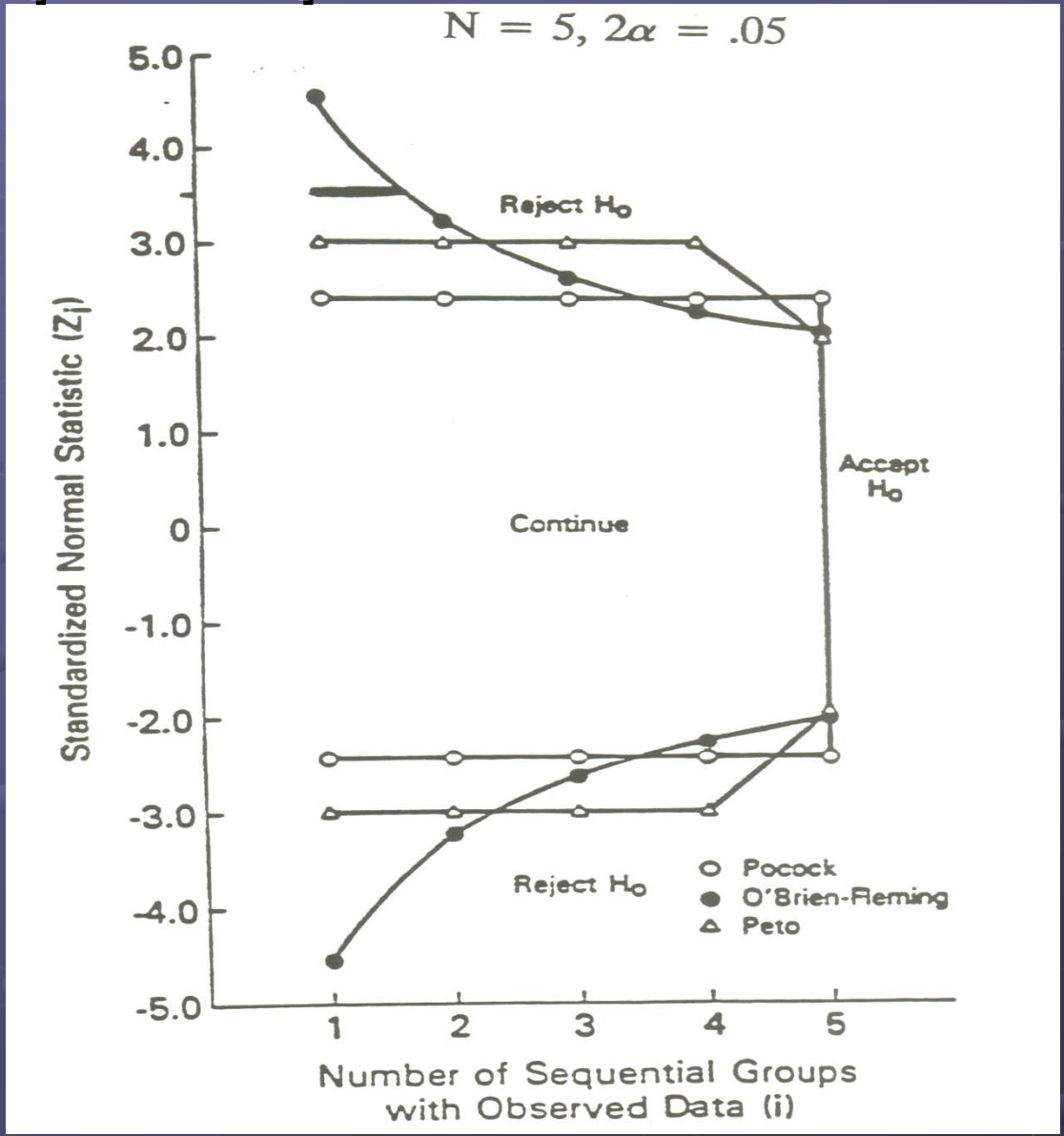
Life-table cumulative mortality rates, Coronary Drug Research Project Group

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)

Group Sequential Boundaries



DMCs and Patient Safety

- At best, can only evaluate relatively short term exposure
- Due to sample size and power, can only detect major safety issues / dramatic increases in risk
- Small numbers problem
- Granularity problem
- Must ultimately rely on a somewhat “unreliable” surveilance system

Adverse Events

- **Adverse Event (AE)**: any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

- **Serious adverse event (SAE):**
  - Results in death
  - Is life threatening, or places the subject at immediate risk of death from the event as it occurred
  - Requires or prolongs hospitalization
  - Causes persistent or significant disability or incapacity
  - Results in congenital anomalies or birth defects
  - Is another condition which investigators judge to represent significant hazards

- **Unanticipated Adverse Device Effect (UADE):**
  - a serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the protocol.

Clinical Event Committee

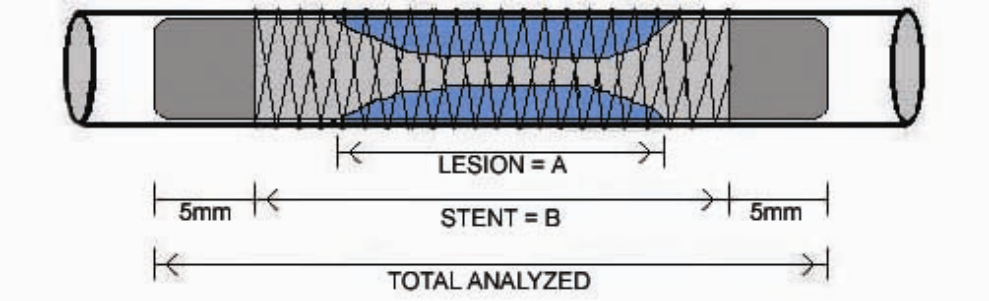
- These committees are developed as independent bodies to review each event in micro-detail with respect to the pre-specified protocol definitions and adjudicate to relation to the investigational products.
- This committee differs from a DSMB as they review on the micro-level whereas the DSMB review on the macro-level

Core Laboratories

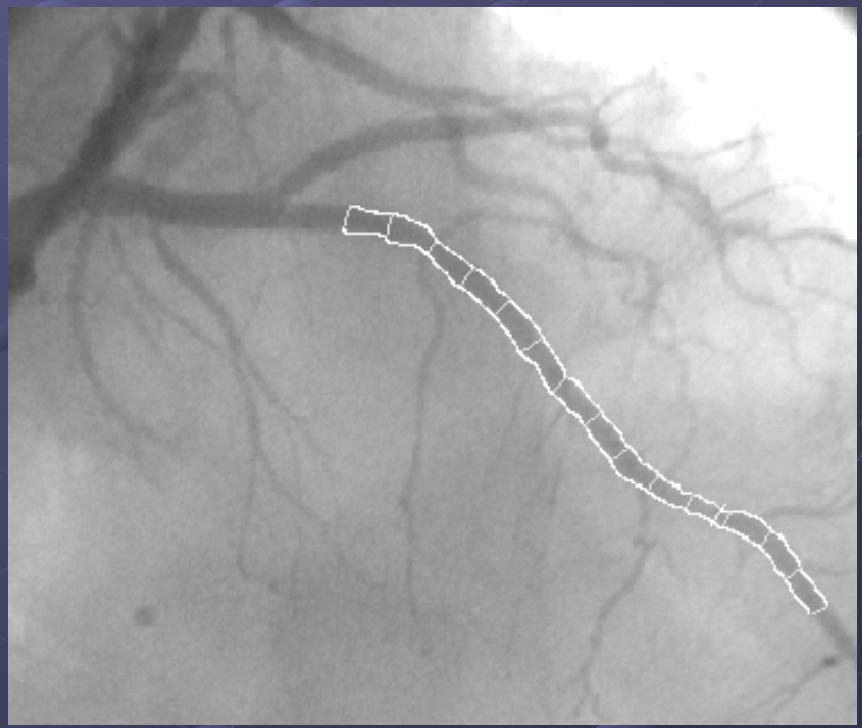
- Standardize testing
  - Examples:
    - Specimen laboratory assays
    - Quantitative Coronary Angiographic Analysis
    - IVUS Analysis
    - ECG Readings
    - Echo Readings
    - Etc.

Core Laboratories

QCA Core Lab:



Reviews and calculates through exact, reproducible, measurements the diseased areas



Data Coordinating Center (1)

- The DCC organizes the central research activities for the Network, including maintaining a secure data entry system, preparing data collection forms and manuals of operations for each study, participating in the development of study protocols,
- monitoring recruitment and adverse events,
- conducting statistical planning and analyses,
- organizing meetings and conference calls, training study coordinators,
- overseeing core laboratories for central interpretation of study data, and managing randomization schemes.

Data Coordinating Center (2)

- The DCC also develops procedures for quality control, training and certification, and data management.
- The DCC monitors the quality and quantity of data received from the Clinical Centers and prepares specific statistical analyses and other reports for the CCs, SC and DCC;
- prepares protocols for submission to the DSMB; and assists manuscript preparation through data analysis, statistical consultation, editorial support, and meeting coordination.

Data Coordinating Center (3)

- Development of standard CRF at the beginning trial
- Development of security within the database (eg e-Crf's have difference levels of security for difference activity levels (PI, clinical monitor, CRC, etc.))
- Development of quality control measure at the beginning of the trial to enable quality/edit checks throughout the trial and not just at the end!
- This allows for cleaner data for interim analyses

Conclusions

Elements of a Good Clinical Trial

- Clear study population – defined by specific inclusion/exclusion criteria
- Feasible enrollment plan
- Clear primary and secondary endpoints
- Clear methods of randomization – as balanced as possible
- Sufficient POWER to evaluate primary endpoint/ question (Ideally > 80%); sufficient sample size accounting for possible missing data up front
- methods and frequency of data collection and entry
- monitoring accuracy of data collection
- quality control procedures including training of study personnel
- plans for statistical analysis
- Proper Data Safety Monitior both with DSMBs and CECs
- Core Labs for independent comparable results