Biomedical Engineering for Global Health

Lecture Twenty:

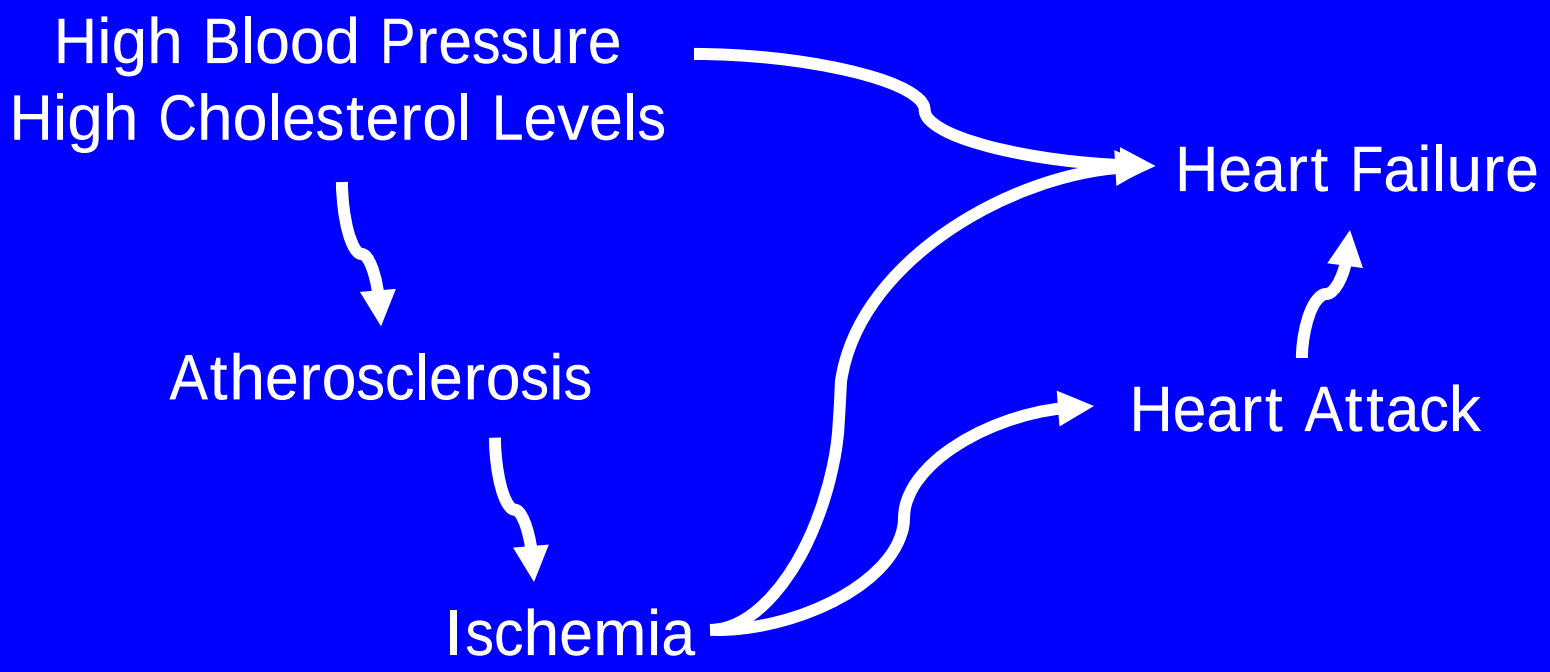
Clinical Trials

Overview of Today

- Review of Last Time (Heart Disease)
- What is a Clinical Trial?
- Clinical Trial Data and Reporting
- Clinical Trial Example: Artificial Heart
- Clinical Trial Example: Vitamin E
- Planning a Clinical Trial

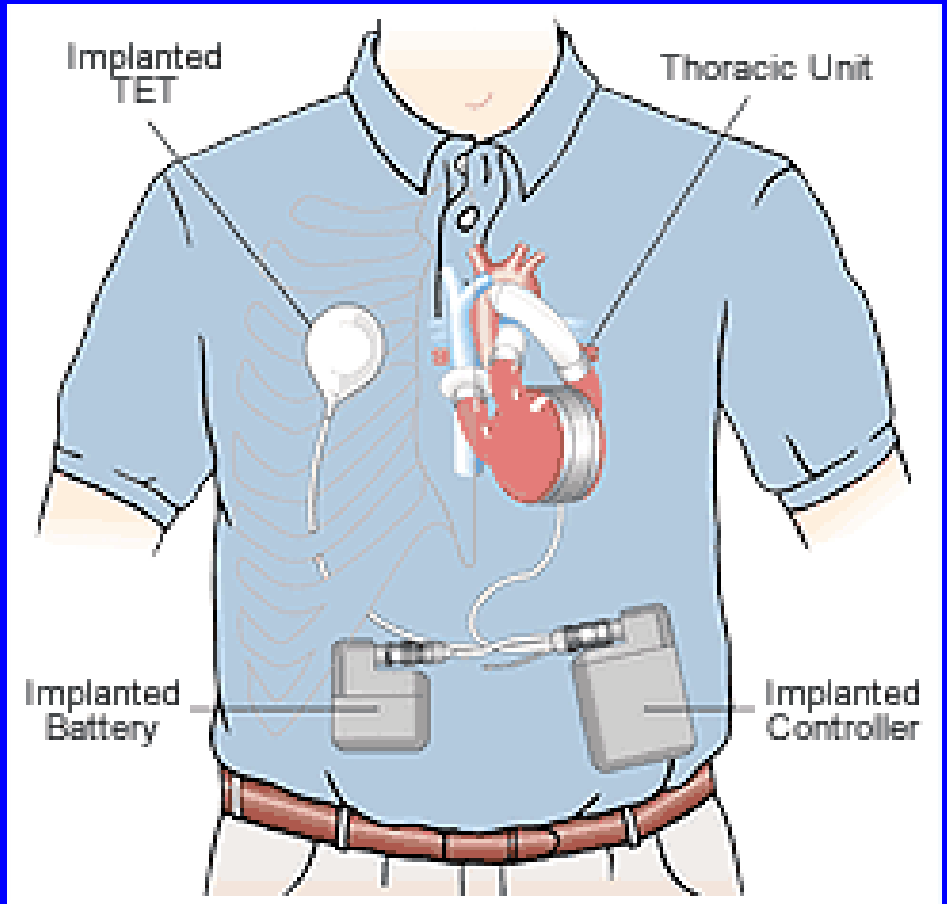
REVIEW OF LAST TIME

Progression of Heart Disease



Heart Failure Review

- What is heart failure?
  - Occurs when left or right ventricle loses the ability to keep up with amount of blood flow
  - http://www.kumc.edu/kumcpeds/cardiology/movies/ssmovies/dilcardiomyopsss.html
- How do we treat heart failure?
  - Heart transplant
    - Rejection, inadequate supply of donor hearts
  - LVAD
    - Can delay progression of heart failure
  - Artificial heart



The AbioCor System has four main parts that are implanted inside the body.

CLINICAL TRIALS

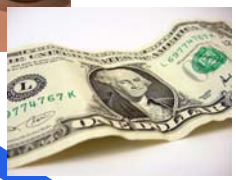
Take-Home Message

- **Clinical trials allow us to measure the difference between two groups of human subjects**
- **There will always be some difference between selected groups**
- **By using statistics and a well designed study, we can know if that difference is meaningful or not**

Science of Understanding Disease

Bioengineering

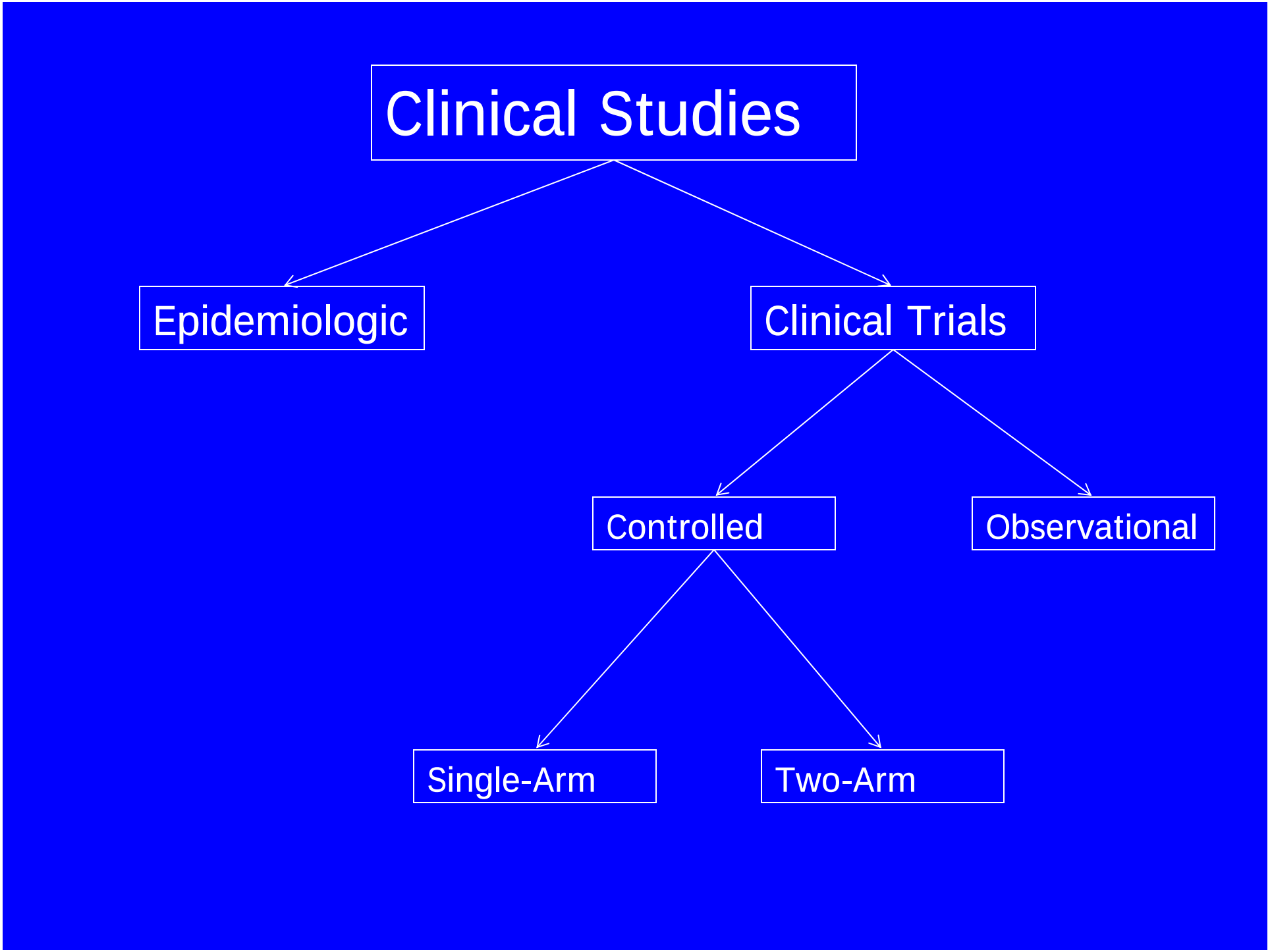
Emerging Health Technologies



Adoption & Diffusion

Abandoned due to:

- Poor performance
- Safety concerns
- Ethical concerns
- Legal issues
- Social issues
- Economic issues


Clinical Studies
Epidemiologic
Clinical Trials
Controlled
Observational
Single-Arm
Two-Arm

Types of Clinical Studies

- Hypothesis Generation
  - Case study, case series: examine patient or group of patients with similar illness

- Hypothesis Testing:
  - Observational:
    - Identify group of patients with and without disease. Collect data. Use to test our hypothesis.
    - Advantage: Easy, cheap.
    - Disadvantage: Bias. Can't control the interventional to decisively show cause and effect.

Types of Clinical Studies

- Hypothesis Testing:
  - Experimental:
    - Clinical trial: Research study to evaluate effect of an intervention on patients.
    - Isolate all but a single variable and measure the effect of the variable.
    - Done prospectively: Plan, then execute.
    - Single arm study: Take patients, give intervention, compare to baseline. Can suffer from placebo effect.
    - Randomized clinical trials: Different subjects are randomly assigned to get the treatment or the control.

Single and Two Arm Studies

- Single-Arm Study
  - Give treatment to all patients
  - Compare outcome before and after treatment for each patient
  - Can also compare against literature value
- Two Arm Study
  - Split patients in trial into a control group and an experimental group
  - Can blind study to prevent the placebo affect

Phases of Clinical Trials

- Phase I
  - Assess safety of drug on 20-80 healthy volunteers
- Phase II
  - Drug given to larger group of patients (100-300) and both safety and efficacy are monitored
- Phase III
  - Very large study monitoring side affects as well as effectiveness versus standard treatments
- Phase IV (Post-Market Surveillance)
  - Searches for additional drug affects after drug has gone to market

CLINICAL TRIAL DATA AND REPORTING

Examples of Biological Data

- Continuously variable
  - Core body temperature, height, weight, blood pressure, age
- Discrete
  - Mortality, gender, blood type, genotype, pain level

Biological Variability

- Variability
  - Most biological measurement vary greatly from person to person, or even within the same person at different times
- The Challenge
  - We need some way of knowing that the differences we're seeing are due to the factors we want to test and not some other effect or random chance.

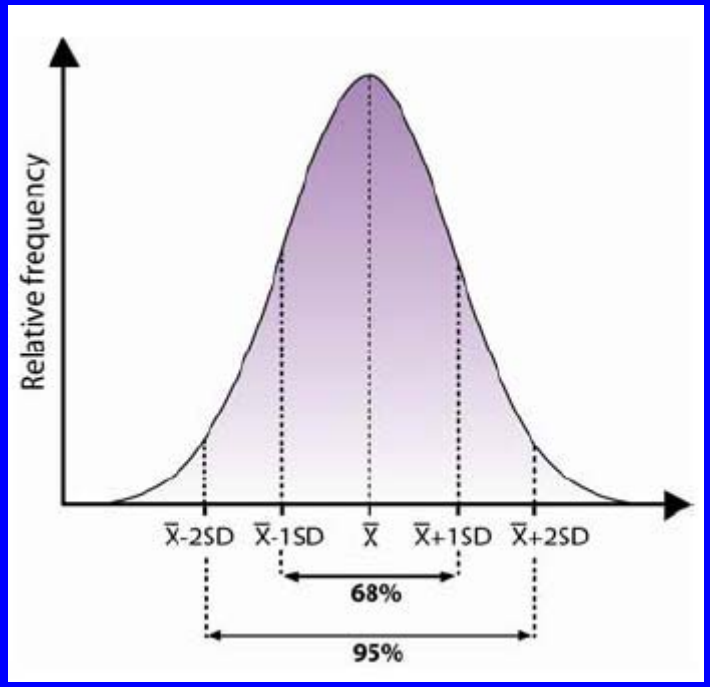
Descriptive Statistics

- Mode
  - Most common value
- Mean

$$\bar{x} = \sum_{i=1}^{n} \frac{x_i}{n}$$

- Standard Deviation

$$\sigma = \sqrt{\sum_{i=1}^{n} \frac{(x - \bar{x})^2}{n}}$$



Normal Distribution. Gore and Altman, BMA London.

Example: Blood Pressure

- Measurement
  - Get into groups of 4 and take each others blood pressure for the next 5-10min
- Reporting
  - In those same groups, calculate the mean, mode and standard deviation of the class
- Analysis
  - Is the data normally distributed?
  - Is there a difference between sides of the classroom?
  - Does it mean anything?

EXAMPLE: ABIOCOR TRIAL

Clinical Trial of AbioCor

- Goals of Initial Clinical Trial
  - Determine whether AbioCor™ can extend life with acceptable quality for patients with less than 30 days to live and no other therapeutic alternative
  - To learn what we need to know to deliver the next generation of AbioCor, to treat a broader patient population for longer life and improving quality of life.

Clinical Trial of AbioCor

- Patient Inclusion Criteria (highlights)
  - Bi-ventricular heart failure
  - Greater than eighteen years old
  - High likelihood of dying within the next thirty days
  - Unresponsive to maximum existing therapies
  - Ineligible for cardiac transplantation
  - Successful AbioFit™ analysis
- Patient Exclusion Criteria (highlights)
  - Heart failure with significant potential for reversibility
  - Life expectancy >30 days
  - Serious non-cardiac disease
  - Pregnancy
  - Psychiatric illness (including drug or alcohol abuse)
  - Inadequate social support system

Prevention of Heart Disease

- 1990s:
  - Small series of trials suggested that high doses of Vitamin E might reduce risk of developing heart disease by 40%
- 1996: Randomized clinical trial:
  - 1035 patients taking vitamin E
  - 967 patients taking placebo
  - Vitamin E provides a protective effect

Prevention of Heart Disease

- 2000: pivotal clinical trial
  - 9,541 patients
  - No benefit to Vitamin E
  - Followed for 7 years: may increase risk of heart disease
- What happened?

Challenges: Clinical Research

- Early studies, small # patients:
  - Generate hypotheses
- Larger studies
  - Rigorously test hypotheses
- Due to biological variability:
  - Larger studies often contradict early studies
- Recent study:
  - 1/3 of highly cited studies - later contradicted!
  - More frequent if patients aren't randomized

Clinical Trial of AbioCor

- Clinical Trial Endpoints
  - All-cause mortality through sixty days
  - Quality of Life measurements
  - Repeat QOL assessments at 30-day intervals until death
- Number of patients
  - Initial authorization for five (5) implants
  - Expands to fifteen (15) patients in increments of five (5) if 60-day experience is satisfactory to FDA

Consent Form

- Link to Consent Form:
  - http://www.sskrplaw.com/gene/quinn/informedconsent.pdf
- Link to other Documents about lawsuit
  - http://www.sskrplaw.com/gene/quinn/index.html

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PLANNING A CLINICAL TRIAL

Planning a Clinical Trial

- Two arms:
  - Treatment group
  - Control group
- Outcome:
  - Primary outcome
  - Secondary outcomes
- Sample size:
  - Want to ensure that any differences between treatment and control group are real
  - Must consider $$ available

Example – Planning a Clinical Trial

- New drug eluting stent
- Treatment group:
- Control group:
- Primary Outcome:
- Secondary Outcomes:

Design Constraints

- Constraints
  - Cost, time, logistics
  - The more people involved in the study, the more certain we can be of the results, but the more all of these factors will increase
- Statistics
  - Using statistics, we can calculate how many subjects we need in each arm to be certain of the results

Sample Size Calculation

- There will be some statistical uncertainty associated with the measured restenosis rate
- Goal:
  - Uncertainty << Difference in primary outcome between control & treatment group
  - Choose our sample size so that this is true

Types of Errors in Clinical Trial

- Type I Error:
  - We mistakenly conclude that there is a difference between the two groups, when in reality there is no difference
- Type II Error:
  - We mistakenly conclude that there is not a difference between the two, when in reality there is a difference
- Choose our sample size:
  - Acceptable likelihood of Type I or II error
  - Enough $$ to carry out the trial

Types of Errors in Clinical Trial

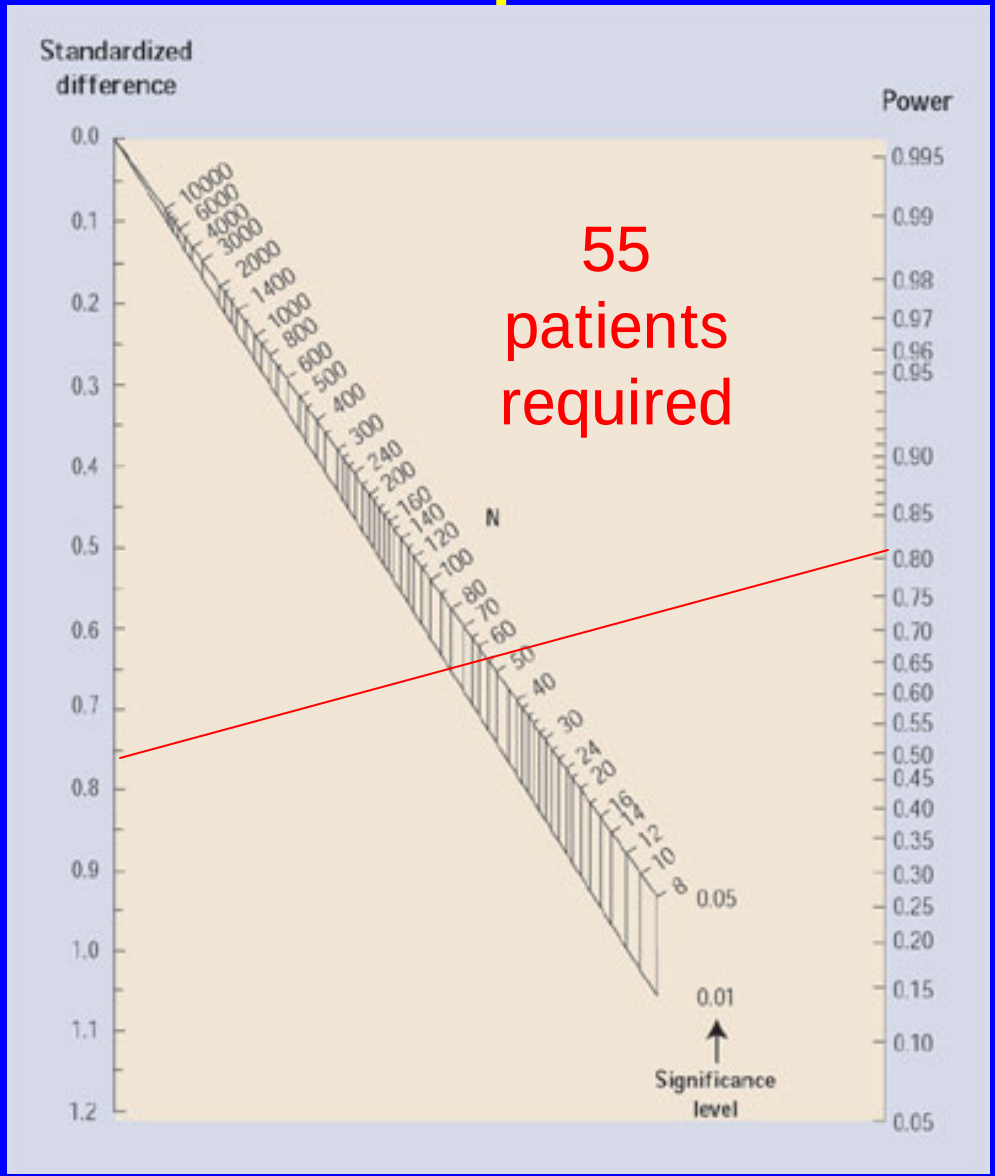
- Type I Error:
  - We mistakenly conclude that there IS a difference between the two groups
  - p-value – probability of making a Type I error
  - Usually set p = 1% - 5%
- Type II Error:
  - We mistakenly conclude that there IS NOT a difference between the two
  - Beta – probability of making a Type II error
  - Power
    - = 1 – beta
    - = 1 – probability of making a Type II error
  - Usually set beta = 10 - 20%

How do we calculate n?

- Select primary outcome
- Estimate expected rate of primary outcome in:
  - Treatment group
  - Control group
- Set acceptable levels of Type I and II error
  - Choose p-value
  - Choose beta
- Use sample size calculator
  - HW14

Drug Eluting Stent – Sample Size

- Treatment group:
  - Receive stent
- Control group:
  - Get angioplasty
- Primary Outcome:
  - 1 year restenosis rate
- Expected Outcomes:
  - Stent: 10%
  - Angioplasty: 45%
- Error rates:
  - p = .05
  - Beta = 0.2



Altman (1982). How Large a Sample? In Statistics in Practice. Eds S. M. Gore and D. G. Altman.

Data & Safety Monitoring Boards

- DSMB:
  - Special committees to monitor interim results in clinical trials.
  - Federal rules require all phase III trials be monitored by DSMBs.
  - Can stop trial early:
    - New treatment offered to both groups.
    - Prevent additional harm.

DSMBs

- New treatment for sepsis:
  - New drug
  - Placebo
  - n = 1500
- Interim analysis after 722 patients:
  - Mortality in placebo group: 38.9%
  - Mortality in treatment group: 29.1%
  - Significant at the p = 0.006 level!
- Should the study be stopped?

DSMBs

- Decision:
  - No
  - Neither researchers nor subjects were informed
- Outcome:
  - Mortality in placebo group: 33.9%
  - Mortality in treatment group: 34.2%
  - Difference was neither clinically nor statistically significant!
- Informed consents should be modified to indicate if a trial is monitored by a DSMB.

How to Get Involved

- Government Database of Trials
  - www.clinicaltrials.gov