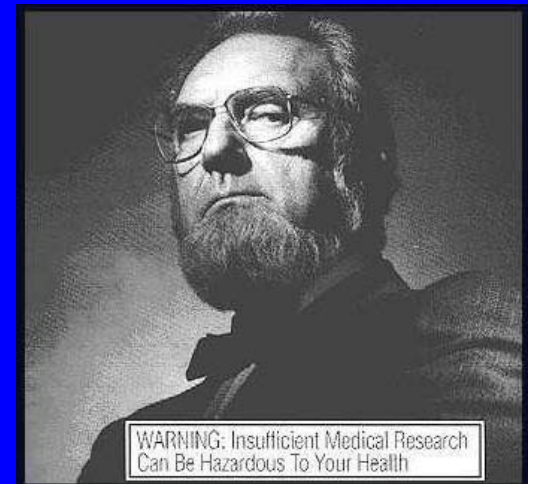


BIOE 301

Lecture Twenty: Clinical Trials

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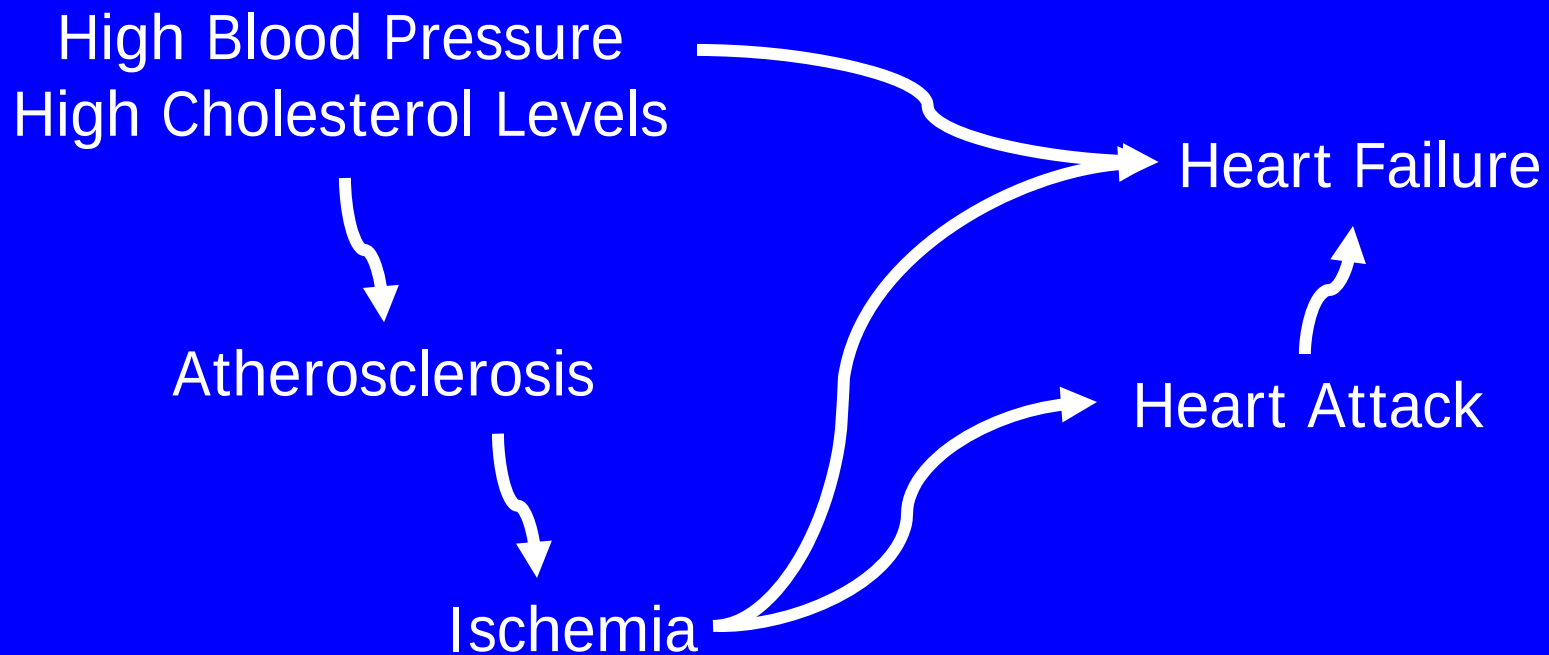


Overview of Today

- 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?

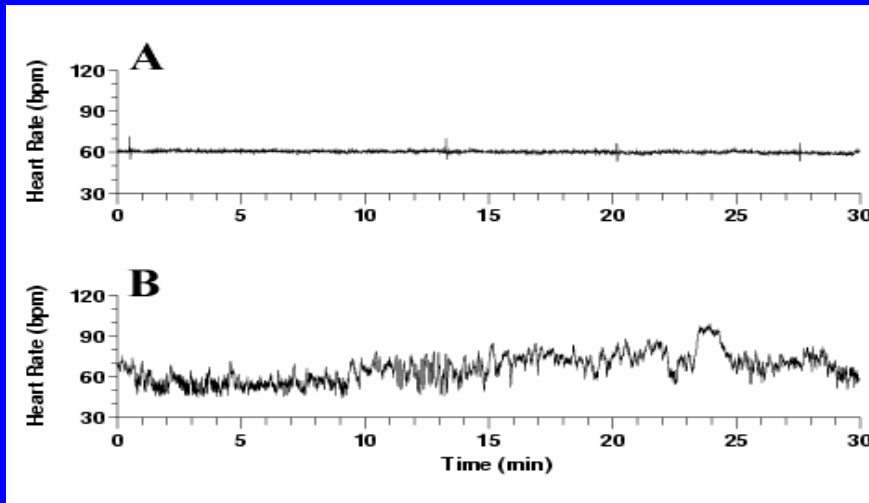
- Occurs when left or right ventricle loses the ability to keep up with amount of blood flow
- <http://www.kumc.edu/kumcpeds/cardiology/movies/ssmovies/dilcardiomyopsss.html>

■ How do we treat heart failure?

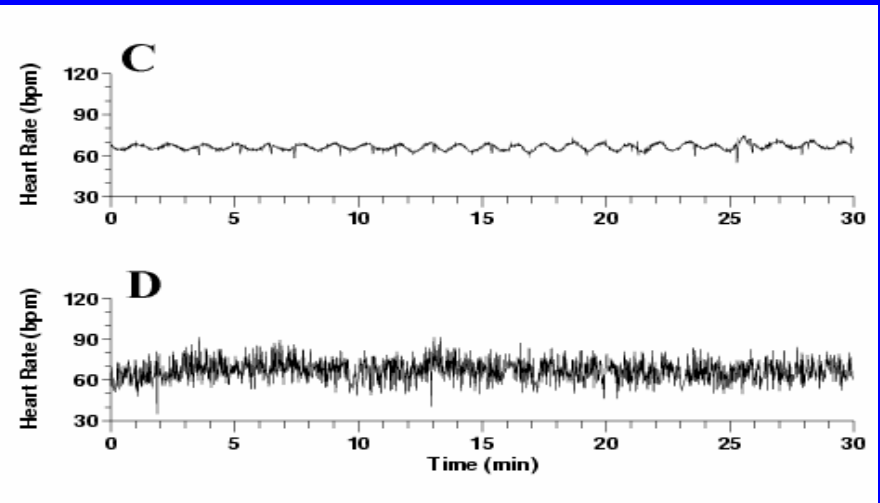
- Heart transplant
 - Rejection, inadequate supply of donor hearts
- LVAD
 - Can delay progression of heart failure
- Artificial heart

Which one is a healthy heart?

Heart Failure

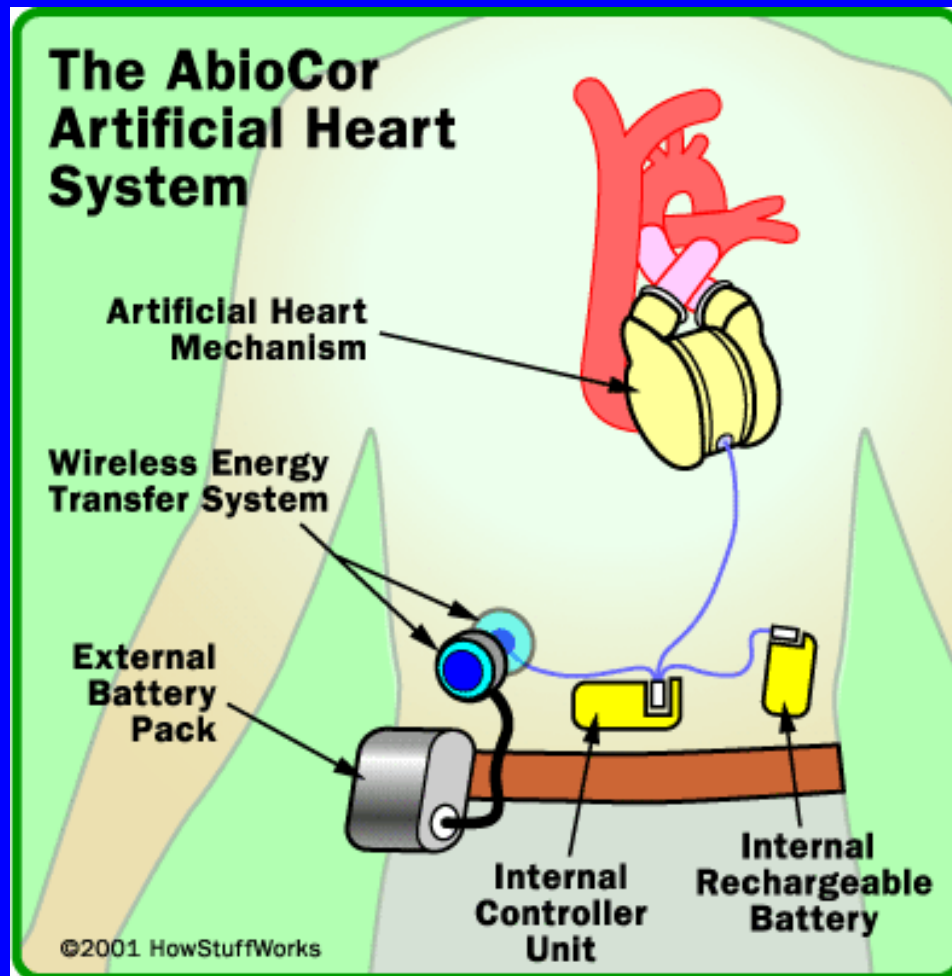


Heart Failure

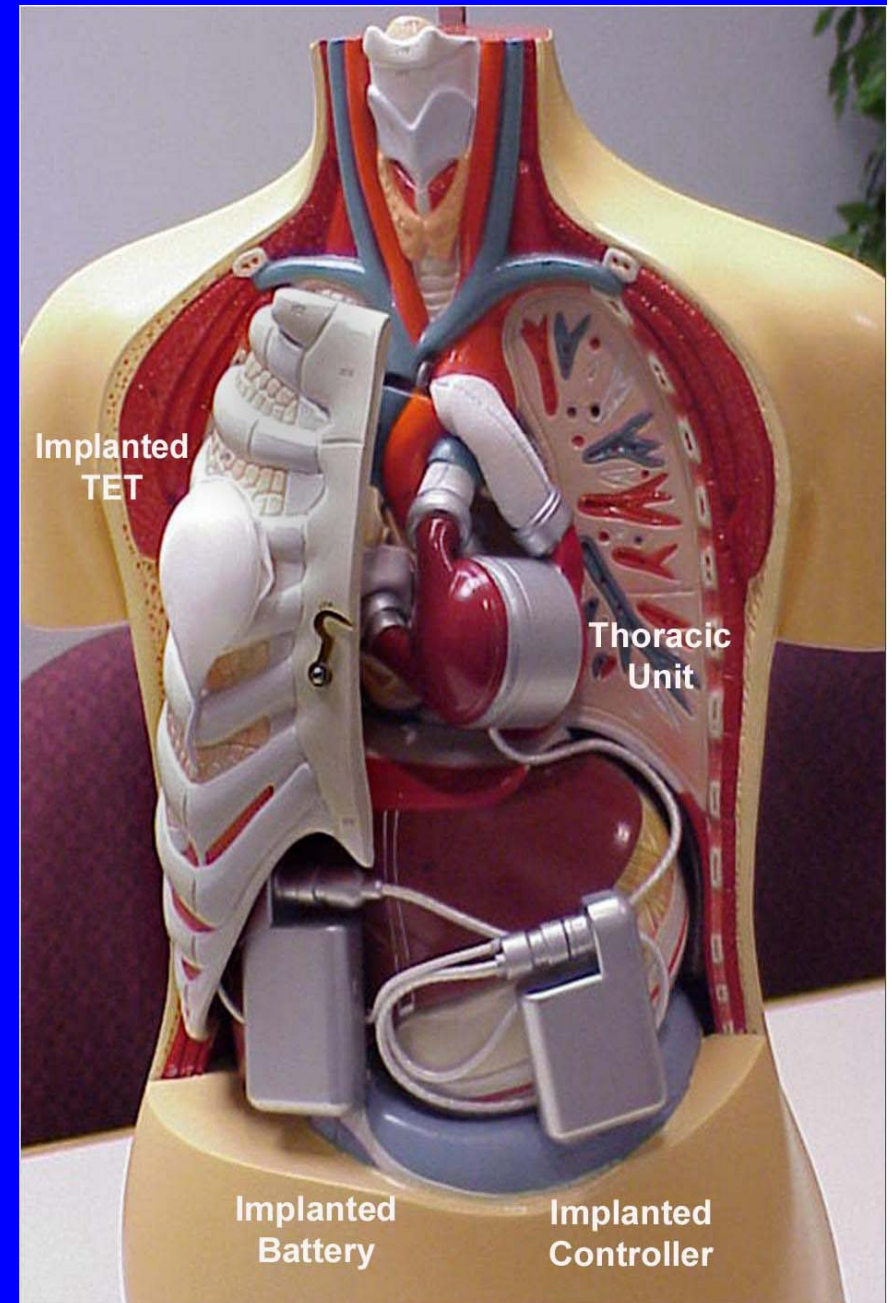


Healthy Heart

Atrial Fibrillation



<http://static.howstuffworks.com/gif/artificial-heart-abiocor-diagram.gif>



CLINICAL TRIALS

Take-Home Message

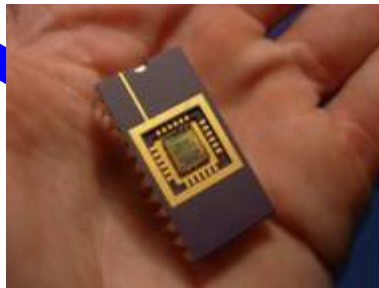
- Clinical trials allow us to measure the difference between two groups of human subjects
- There will always be some difference between selected groups
- By using statistics and a well designed study, we can know if that difference is meaningful or not

Science of
Understanding
Disease



Bioengineering

Emerging
Health
Technologies



Preclinical Testing

Ethics of research

Clinical Trials

Cost-Effectiveness

Adoption &
Diffusion

Abandoned due to:

- poor performance
- safety concerns
- ethical concerns
- legal issues
- social issues
- economic issues



Clinical Studies

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graph TD; A[Clinical Studies] --> B[Epidemiologic]; A --> C[Clinical Trials]; C --> D[Controlled]; C --> E[Observational]; D --> F[Single-Arm]; D --> G[Two-Arm];
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Epidemiologic

Clinical Trials

Controlled

Observational

Single-Arm

Two-Arm

Types of Clinical Studies

■ Epidemiologic - Hypothesis Generation

- Observe a group of patients and look for common factors
- AIDS in the 1980s
- Dr. Snow and the Broad St. Pump

■ Clinical Trial - Hypothesis Testing

- Determine the difference, if any, between two groups of patients

Types of Clinical Trials

■ Observational Studies

- Observe two groups already existing, and review data to determine differing factors between groups
 - Ex. What behaviors are prevalent in lung cancer patients but not in those without the disease
- Problems – Bias, and lack of control

■ Controlled Study

- Introduce difference between two selected groups

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 effects as well as effectiveness versus standard treatments

■ Phase IV (Post-Market Surveillance)

- Searches for additional drug effects 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

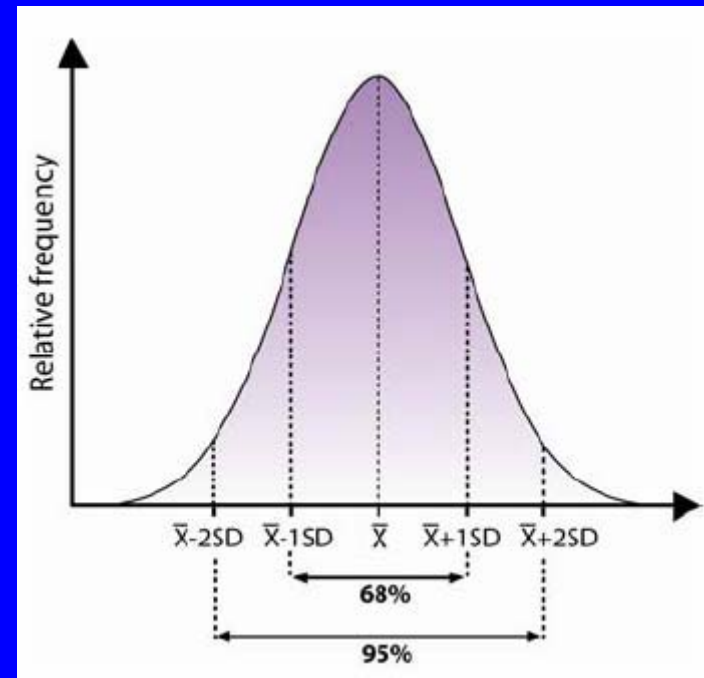
- Most common value

■ Mean

$$\bar{X} = \sum_{i=1}^n \frac{X_i}{n}$$

■ Standard Deviation

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



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

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>

EXAMPLE: VITAMIN E

The Study

■ Pilot Study

- In the early 1990's, small study done which showed taking vitamin E reduced risk of heart disease
- Regularly taking high doses shown to reduce risk by up to 40%

■ Media Coverage

- These studies received huge amounts of coverage in the media

Follow-Up

■ 1996

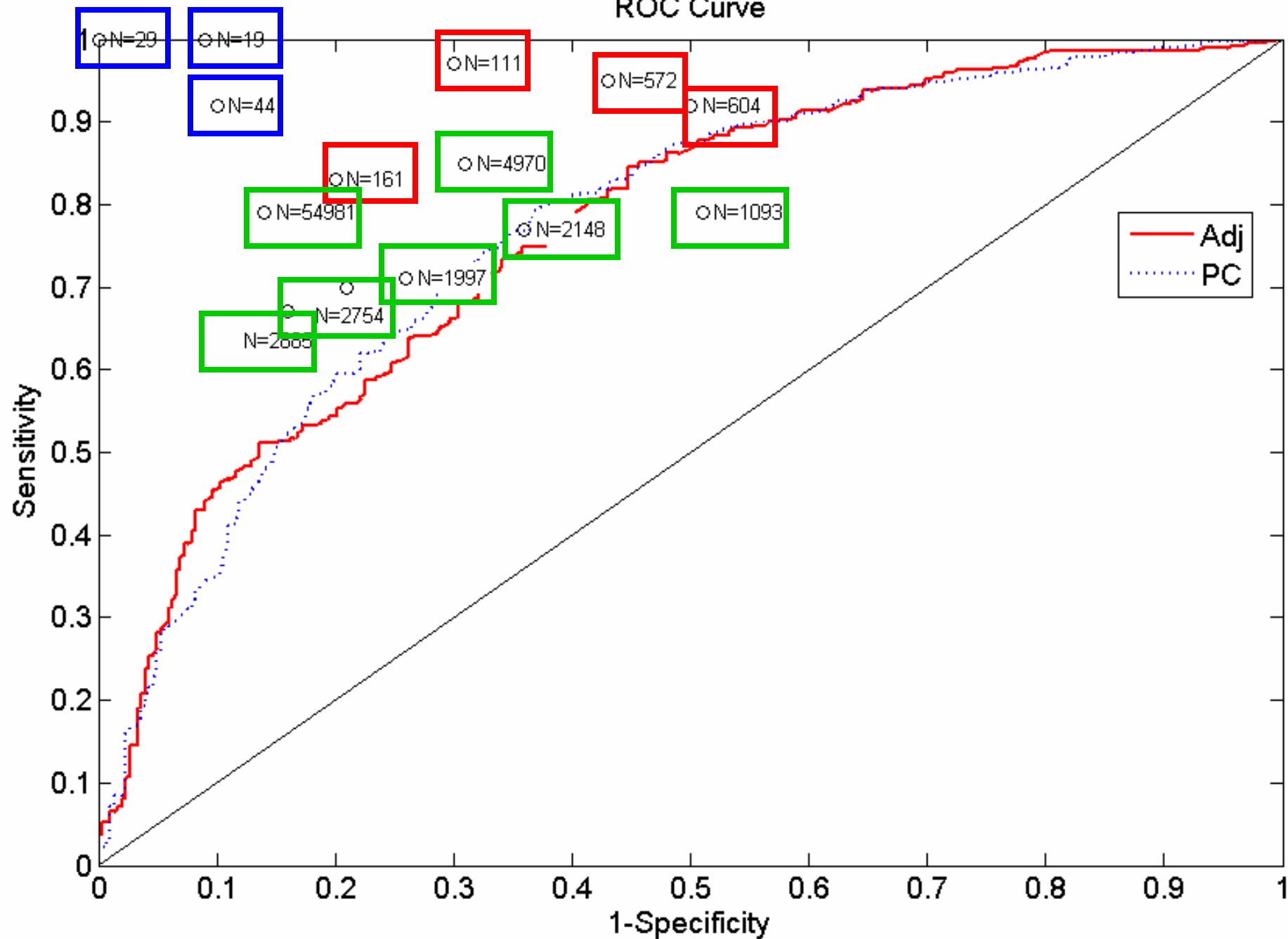
- Study compared 1,035 patients on vitamin E and 967 on placebo
- Demonstrated a positive effect of the vitamin

■ 2000

- Very large study (9,541 patients) shows vitamin E has no effect
- Study tracked patients for 7 years and found evidence that vitamin E in large doses might actually be harmful

PLANNING A CLINICAL TRIAL

ROC Curve



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 $\ll$ 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:

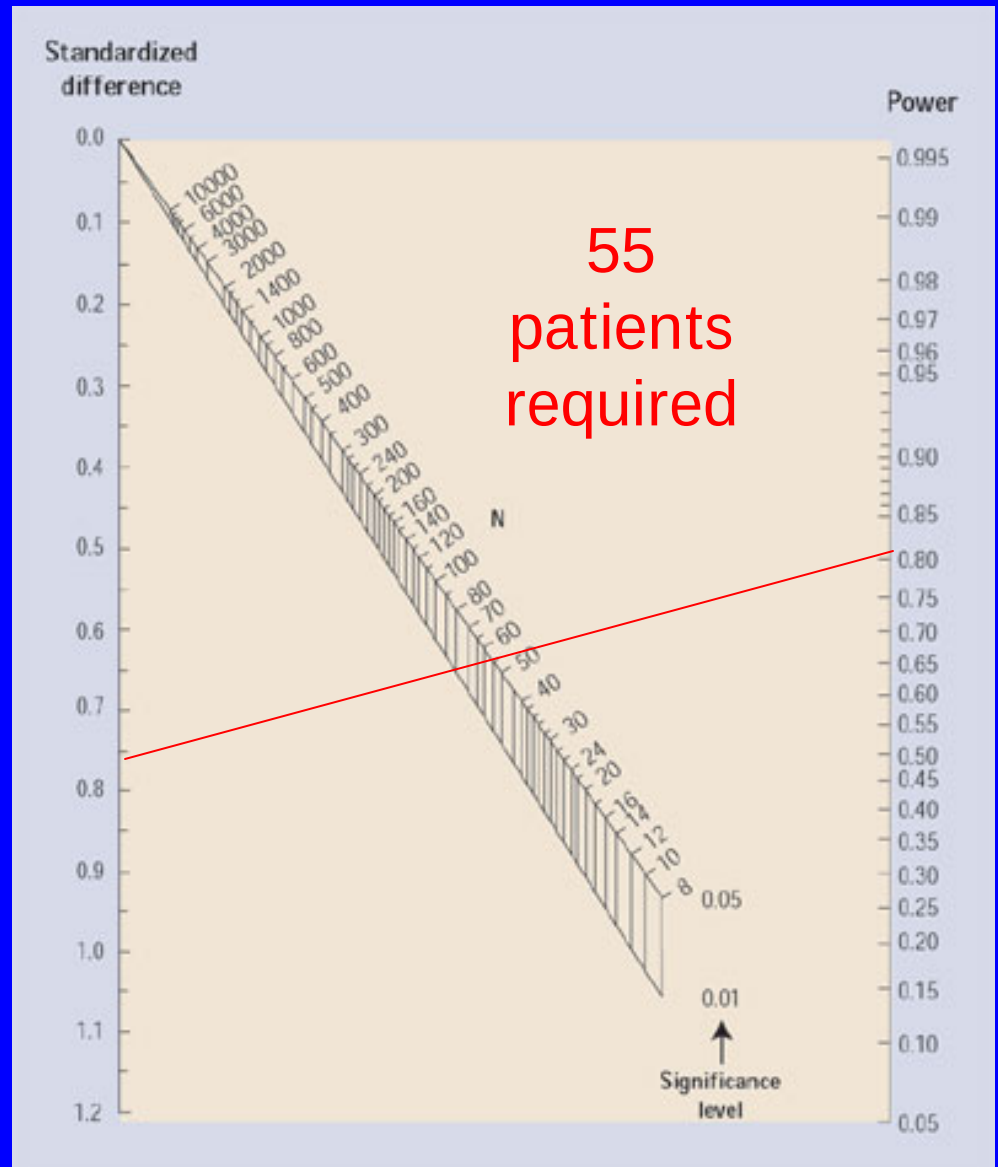
- We mistakenly conclude that there **IS NOT** a difference between the two
- **Beta** – probability of making a Type II error
- Power
 - **= 1 – beta**
 - **= 1 – probability of making a Type II error**
- Usually set **beta = 10 - 20%**

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



How to Get Involved

- Government Database of Trials
 - www.clinicaltrials.gov

Assignments Due Next Time

- HW14
- Project 6
- Exam Three:
 - April 11th
 - Take Home Exam