BIOE 301

Lecture Twenty: Clinical Trials

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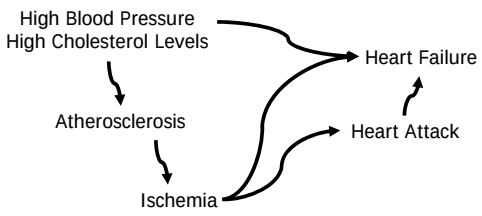
Overview of Today

- 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

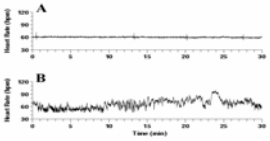


Heart Failure Review

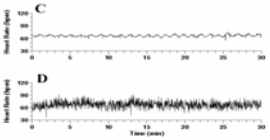
- What is heart failure?
  - Occurs when left or right ventricle loses the ability to keep up with amount of blood flow
  - http://www.kumc.edu/kumcpeds/cardiology/movies/ssmovies/dilcardiomyopsss.html
- How do we treat heart failure?
  - Heart transplant
    - Rejection, inadequate supply of donor hearts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

Which one is a healthy heart?

Heart Failure

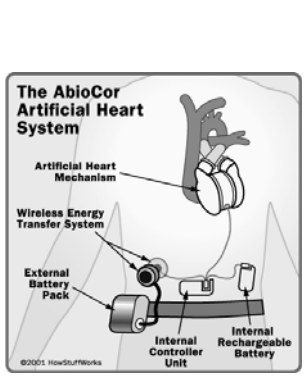


Heart Failure



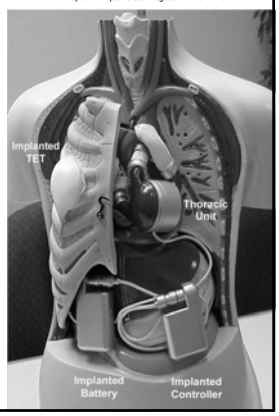
Healthy Heart

Atrial Fibrilation



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

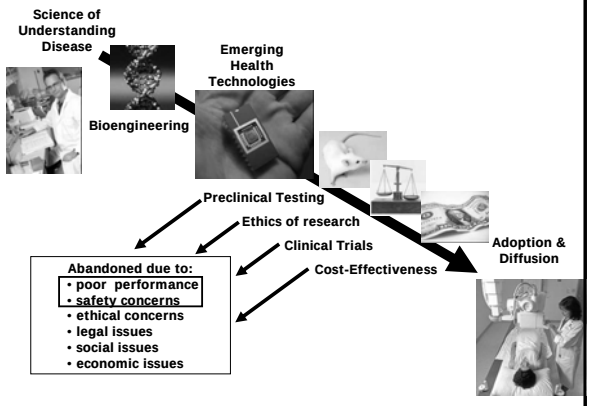
http://www.ps-lk3.de/images/ABIOCOR.JPG

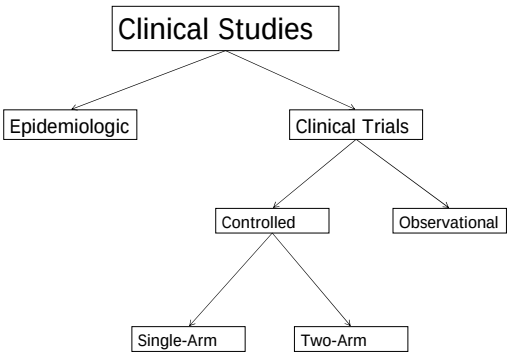


CLINICAL TRIALS

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**





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 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.

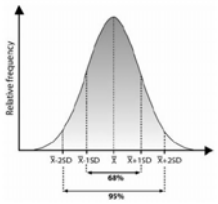
Descriptive Statistics

- Mode
  - Most common value
- Mean

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

- Standard Deviation

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



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

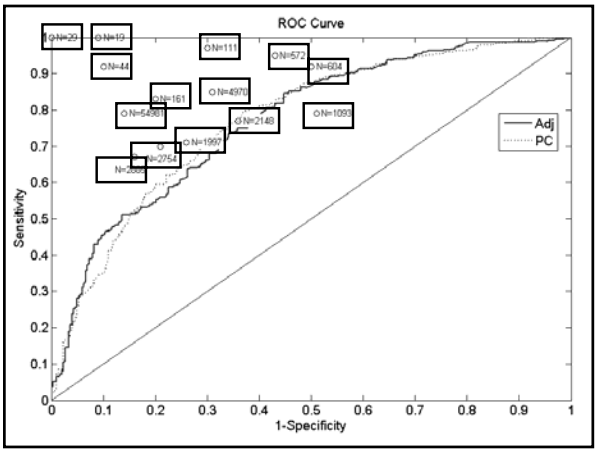
The Study

- 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



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

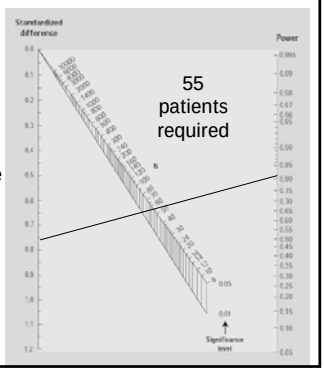
- Type I Error:
  - We mistakenly conclude that there IS a difference between the two groups
  - p-value – probability of making a Type I error
  - Usually set p = 1% - 5%
- Type II Error:
  - We mistakenly conclude that there IS NOT a difference between the two
  - Beta – probability of making a Type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



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