

Bioengineering and World Health

Lecture Twenty: Clinical Trials

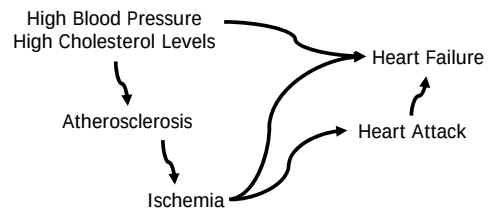


Overview of Today

- 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

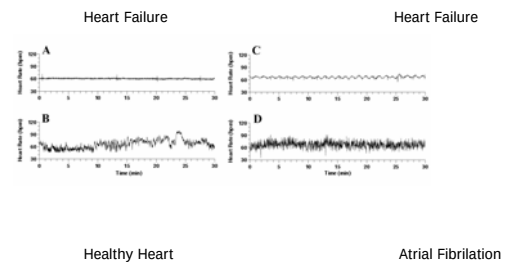
Progression of Heart Disease

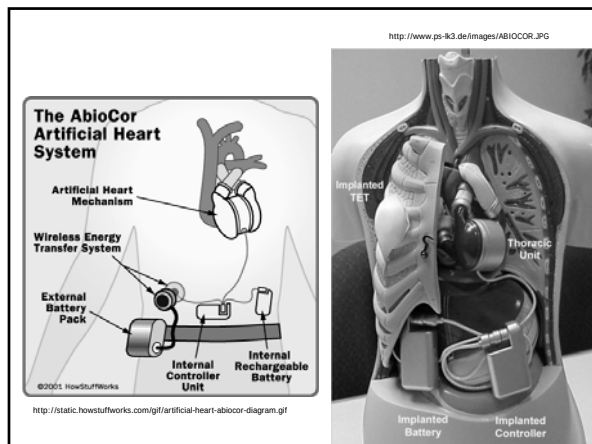


Heart Failure Review

- 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/dilcardiomyopss.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?

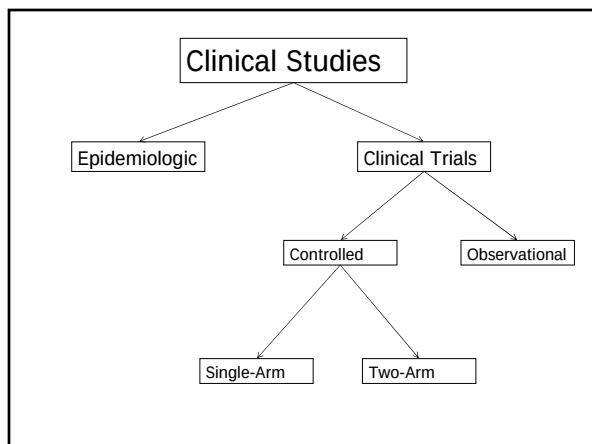
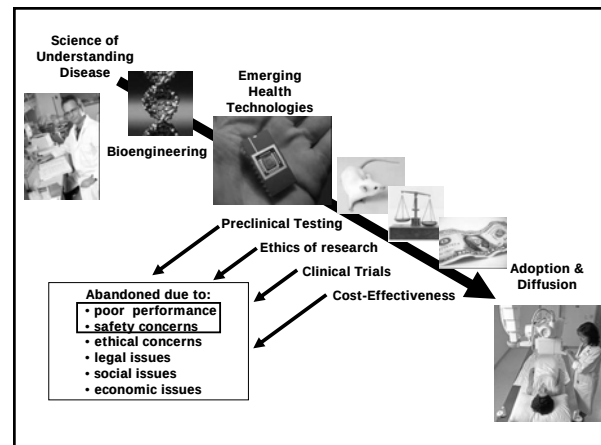




CLINICAL TRIALS

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

- 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.

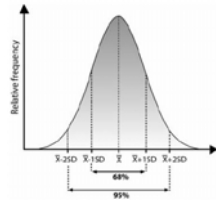
Descriptive Statistics

- Mode
 - Most common value
- Mean

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

- Standard Deviation

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



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

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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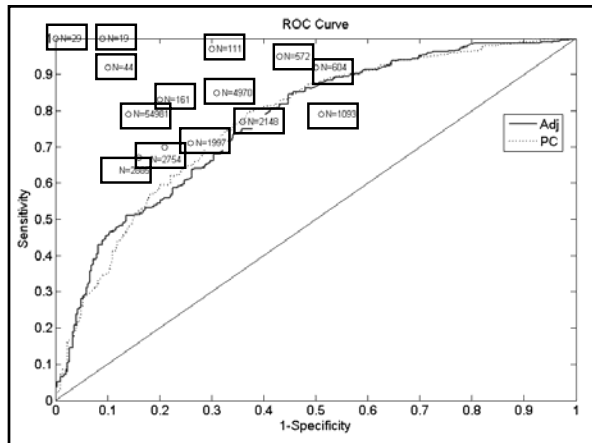
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PLANNING A CLINICAL TRIAL



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 $\ll$ 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

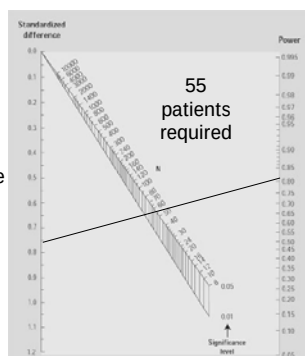
- Type I Error:
 - We mistakenly conclude that there IS a difference between the two groups
 - p-value – probability of making a Type I error
 - Usually set $p = 1\% - 5\%$
- Type II Error:
 - We mistakenly conclude that there IS NOT a difference between the two
 - Beta – probability of making a Type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

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:
 - $p = .05$
 - $\text{Beta} = 0.2$



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