Clinical Trials: An Overview

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Randomized Clinical Trial

- A TEST comparing two or more therapies
  - Drugs
  - Procedures
  - Behavioral treatments
- Usually has a "best conventional therapy" arm
- Best conventional therapy MAY BE a placebo
- PARALLEL CONTROLS: separate groups of subjects are treated with different therapies at the same time
The Controlled Randomized Double-Blind Multi-Center Clinical Trial
Randomized Clinical Trial

• The essential feature: Randomization of subjects to treatment

• Logic is clear, first treat, then observe outcome

• In theory, this is the best way to assess a treatment effect
Cross-over design

- Each subject gets all treatments, usually with a wash-out in between
- Randomization between treatment orders
- Much more common in comparative experiments
- Leads to comparison within a subject rather than comparison between groups of subjects
Example?
Cross-Over Design

- **Advantages:**
  - Controls for many confounding variables
  - Usually requires fewer subjects and tests for the same power

- **Disadvantages**
  - Requires more from each subject
  - If a subject does not complete the study, then all or most of his data is not useful
  - Not always feasible
Target Population
Target Population

• Who do you want the results to apply to
• Needs to be framed both globally
  – All patients with the diseases
• And concretely
  – Age, ethnicity, gender
  – Method of diagnosis
  – Time since diagnosis
  – Prior-current treatment
  – Likelihood of compliance
There are two extremes ("poles") which can be used to determine who will be in the target population:

- An assessment in a tightly defined group vs
- An assessment in the general population
Validity

• The conclusions of the study are true for the population studied

• Critical to any study: what use is a study in which the conclusion isn’t true

• Precondition to any use of the results
Generalizability

• The conclusions of the study are true in general for population with the disease

• The results of the study can be used by other care givers to guide their practice
Techniques to Increase Validity

• Rigorously defined population

• Restrictive treatment protocol

• Rigorous assessment procedures
Techniques to Enhance Generalizability

• Very expansive population definition

• Very broad study, e.g. multi-center with different types of centers

• Very practical, easy to use treatment plans

• Very basic (and clear cut) treatment assessment
The Dilemma

- If the study is too general, differences within population groups may hide or confound the results of the study or make them difficult to interpret.

- If the study is too narrowly defined, the results may not have much application in the general population.
Example

• A study of the use of Gorillamycin® for the treatment of urinary tract infections with gram negative bacteria

• The target might be: All patients with infection with that bacteria
But what about

• Age
• Ethnicity
• Gender
• Method of diagnosis
• Time since onset of infection/symptoms
• Prior Treatment
• Other conditions
• Contraindications to therapy
• Current medications
• Probability of compliance
A Possible Resolution

- Aged 18-65 year
- Male or female, pregnant women excluded
- Onset of symptoms within 3 days
- No other treatments
- Persons with diabetes, urinary tract abnormalities excluded
Study Population

Is the group of patients actually studied. At best, this is all eligible patients, but usually it will be a subset of the eligible patients because:

- Not all eligible patients will be able or willing to participate
- Not all physicians will allow their patients to participate
- Recruitment stops when the specified sample size has been achieved
Study Population

• All patients must be able to understand and willing to give an informed consent

• In some circumstances a surrogate may be allowed to give consent for the patient

• A patient may not be enrolled in a clinical trial without giving informed consent except in very rare circumstances
Example

Study Pool: All patients reporting to the clinics at 10 participating centers with urinary tract infections caused gram negative bacteria

Eligible Population: Patients who meet the criteria

Study Population: Patients from this center who agreed to participate during the recruitment period
Bias

• The results observed reflect other factors in addition to (or even instead of) the effect of the treatment

• Different from random variation because results are influenced in one direction
Bias

• There are multiple POTENTIAL sources of bias
  – Selection bias
  – Performance bias
  – Detection Bias
  – Reporting bias

• It is impossible to completely eliminate the POSSIBILITY of bias

• It is possible to minimize some of the major biases with careful planning
Bias

The **ACCUSATION** that a bias may exist is often sufficient to cause the validity of a study to be questioned.
Why randomization is important:

Avoids a major potential bias, selection bias, when recruiting patients into a study
What randomization means:

• A method to randomly assign subjects to groups after they have been identified and enrolled into the study

• The assignment to a group is not known prior to the time the assignment is made

• The assignment to a group is not based on patient characteristics or preference
What randomization implies:

- Groups are comparable on all measured factors
- Groups are comparable on all unmeasured (unknown) factors

Together this implies

- That groups are comparable in prognosis
Implications

• If prognostic factors are equal, and the only difference is study treatments, then any difference in outcome is attributable to difference in treatment

• This provides the intellectual justification for tests of statistical significance
Randomization

- Randomization does not guarantee that prognostic factors are equal
- In fact, 5% of all the variables measured should be statistically significant different between groups (at P < 0.05) by chance alone
- The issue is not whether there are differences between groups, but rather whether the differences between groups affect prognosis
Randomization

Usually patients are randomized as they are accepted into the study according to a predetermined assignment plan maintained by someone not involved in patient recruitment or assessment.
Randomization

- Assigning patients alternately to treatment group is NOT random assignment
- Assigning the first half of the population to one group is NOT random assignment
- Knowing which treatment a patient will receive if recruited into the study is NOT random assignment
To control for very important prognostic factors, subjects may be grouped in some ways while still maintaining randomization within these groups.

Two common methods of grouping are:

- Stratification
- Blocking
Patients are classified into strata by one or more personal characteristics. Characteristics are usually thought to be prognostic of outcome. Within each strata patients are randomized separately. Example: stratification might be by age group, gender and recurrent infection.
Patients are grouped into blocks by time of recruitment

Within blocks randomization is completely balanced

Example: Two Groups, block size 4

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Stratification/Blocking

Advantages

• Stratification ensures that patients are reasonably well balanced across treatment groups based on the stratification factors used

• Blocking ensures that patients are reasonably well balanced with respect to treatment groups over time
Blinding (also called MASKING) is intended to avoid biases due to knowledge of treatment.
Blinding

I'm in the control group
Hierarchy of Blinding

- OPEN LABEL: no blinding
- SINGLE BLIND: patient or assessor blinded to treatment but not both
- DOUBLE BLIND: patient and assessors blinded to treatment
- COMPLETE BLIND: everyone involved in study blinded to treatment
Open Label Studies

These may be useful for

• pilot studies
• dose ranging studies
• compassionate use protocol
• “Placebo” impossible

However, this may introduce bias by knowledge of the treatment given

• toxicity over (or under) reported
• efficacy overestimated
Single Blind Studies

- Assessors may not know the treatment even when it can’t be concealed from the patient
  - e.g. exercise studies

- Patient blind to the treatment but not the assessors
  - E.g., because of need to adjust medication, etc.
Double Blind Studies

- The standard by which all studies are judged since it minimizes both potential patient and assessor biases.
- Should be used whenever possible, which is whenever it is ethically permissible and feasible.
Examples when it would not be possible or permissible to do a double blind study:

- Surgical vs medical treatment
- Comparison of utility of different invasive procedures
- Study in which one treatment is exercise or behavior modification
Techniques needed for double blind studies:

For each possible treatment

- Tablets identical in physical appearance and with similar taste and smell
- Same number of tablets (mix placebo/control and study drug for different dose studies)
- IV infusions using the same carrier
- Simulated dose changes for all subjects at given time
Blinding

Blinding is not simple, it often causes extra work and expense, but eliminates many potential biases.

The existence of a potential bias casts doubt on the validity of a study, potentially reducing its impact on general practice.
“I’m part of a double-blind study to see how weight loss supplements help people lose weight. I’m guessing I received the sugar pill placebos.”
Endpoints

• A primary measure of efficacy must be defined
• It must specifically answer the question: Has the treatment been shown to be effective in treating the condition?
• Secondary outcome variables may include other changes, both good and bad
Example

• Endpoint - within a given time
  – Disappearance of symptoms
  – Bacteria count below a given minimum

• Alternative endpoint: Time until
  – Disappearance of symptoms
  – Bacteria count below a given minimum

• Secondary endpoints could be side effects, white blood cell count, subjective measures of wellbeing, etc.
Clinical Trial Designs

• Non-inferiority

• Superiority

• Equivalence
Non-Inferiority

- Null hypothesis: 2 treatments differ more than $\Delta\%$
  - Aim is to reject the null hypothesis
- Even if things are amazing for one treatment, you can only claim non-inferiority
- Typically used for a “me too” drug
Superiority (Inferiority)

- Null hypothesis: two treatments are the same
  - First step is usual to try to disprove the null hypothesis, hence prove one treatment is superior (inferior)
- Needs many more subjects than non-inferiority design
- FDA prefers this but Pharmaceutical Industry less enthusiastic
Equivalence

• Uncommonly used
• Null hypothesis is treatments differ
  – study designed to prove treatments are equal
• Used for bioequivalence
  – E.g., 2 active drugs or vaccines, if neither treatment can be considered standard of accepted
Summary

Time spent to develop a carefully thought out study design in the beginning of a study is essential for the validity of results.
Clinical Trials Phases

• Preclinical studies
  – Laboratory studies in living systems or models

• Phase I
  – Primarily examine the acute, dose-related pharmacological toxicities of new drugs
  – Often conducted in healthy subjects

• Phase II
  – Primarily examine the short-term pharmacological toxicities
  – To a lesser extent, examines efficacy
  – Conducted in populations with specific diseases
Clinical Trials Phases

• Phase III
  – Primarily examine the pharmacological efficacy
  – To a lesser extent, examine short-term toxicities
  – Designed to increase the survival, improve outcomes or the quality of life of subjects suffering from a specific disease or condition
  – Required by FDA for review for drug approval (typically ≥ 2 clinical trials)

• Phase IV
  – Also known as post-marketing surveillance studies
  – Primarily examine the long-term efficacy and toxicity of already marketed drugs
Study Design Exercise

• You are hired to study Chocoderm™, a new medication for the treatment of chocoholism.
Chocoholism: Background

• Epidemiology:
  – Affects appx. 10 million Americans (1 in 30)
  – prevalence unrelated to age, gender, race, education, and income
  – highly prevalent in persons living < 1 mile from a chocolate factory (1 out of 5 affected)
  – 1 out of 25 people live < 1 mile from a chocolate factory in Los Angeles County
Chocoholism: Background (2)

• Symptoms:
  – uncontrollable desire to eat chocolate
    set out for general consumption
    (e.g. office, parties, holidays)
  – excessive chocolate consumption
Chocoholism: Background (3)

- Sequela of disease:
  - weight gain
  - exacerbation of chronic disease (e.g. diabetes)
  - missed days from work

- Treatment:
  - nose plugs
    - work only in patients living < 1 mile chocolate factory
  - otherwise no known treatment
A new pharmaceutical company has developed Chocoderm™

- effective in the animal model of chocoholism
- transdermal patch developed
- phase I & II trials in non-pregnant adults completed
- available in Mexico over the counter
Study Design Exercise

• Devise a Clinical Study of Chocoderm™ to be conducted at UCLA/Harbor-UCLA/Cedars-Sinai

• In your study design address:
  – Objectives
  – Hypothesis
  – Subject (patient) selection
  – Randomization and controls (be specific)
  – Outcome measures