Introduction to Clinical Trials - Day 2

Session 1 - Introduction

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Goals of Clinical Trial Design

Clinical trials

- Experimentation in human volunteers
- Investigation of a new treatment or preventive agent
  - *Safety* : Are there adverse effects that clearly outweigh any potential benefit?
  - *Efficacy* : Can the treatment alter the disease process in a beneficial way?
  - *Effectiveness* : Would adoption of the treatment as a standard effect morbidity in the population?

Goals of Clinical Trial Design

A trial must meet minimum scientific standards

- It must address a meaningful question
  - Discriminate between viable hypotheses (Science)
- Trial results must be credible to the scientific community
  - Valid materials, methods (Science, Statistics)
  - Valid measurement of experimental outcome (Science, Clinical, Statistics)
  - Valid quantification of uncertainty in experimental procedure (Statistics)

Goals of Clinical Trial Design

Individual Ethics

- Conducted in human volunteers, the clinical trial must be ethical for participants on the trial
  - Minimize harm and maximize benefit for participants in clinical trial
  - Avoid giving trial participants a harmful treatment
  - Do not unnecessarily give trial participants a less effective treatment

Goals of Clinical Trial Design

Group Ethics

- The clinical trial must ethically address the needs of the greater population of potential recipients of the treatment
  - Approve new beneficial treatments as rapidly as possible
  - Avoid approving ineffective or (even worse) harmful treatments
  - Do not unnecessarily delay the new treatment discovery process

Goals of Clinical Trial Design

Optimality criteria

- A good procedure will

1. Minimize “false positives"
   - Any treatment recommended for adoption will have a high probability of being a truly effective therapy
2. Minimize “false negatives"
   - Any truly effective therapy will have a high probability of being recommended for adoption
3. Be highly safe and ethical
   - Minimize the number of patients exposed to inferior treatments while investigations proceed
4. Be efficient
   - Minimize costs (patients, calendar time, money)

Goals of Clinical Trial Design

Common statistical approach

- Optimality criteria (1) and (2) speak directly to the need for achieving high PPV and low NPV
- Design an RCT to answer relevant question
  - Treatment, patient population, intervention, comparator, outcome
    - There is an underlying probability of our hypotheses being correct: “Prevalence of effective therapies"
- Fix probability of making wrong decisions
  - Erroneously decide against status quo < 2.5%
  - But: erroneously decide against status quo 2.5%
- Design trial to fix sensitivity of study
  - Power: High probability to detect beneficial treatment

Goals of Clinical Trial Design

Positive predictive value in research

- Positive predictive value: probability that a statistically significant trial indicates a truly effective treatment.
- Negative predictive value: probability that a non-significant trial indicates a truly non-effective treatment.
- Relationship to type I error, power, and prevalence of truly effective therapies

$$PPV = \frac{\text{Power} \times \text{Prev}}{\text{Power} \times \text{Prev} + (\text{Type I Error}) \times (\text{1-Prev})}$$

$$NPV = \frac{(\text{1-Type I Error}) \times (\text{1-Prev})}{(\text{1-Type I Error}) \times (\text{1-Prev}) + (\text{1-Power}) \times \text{Prev}}$$

Goals of Clinical Trial Design

Predictive value of statistically significant result depends on

1. Probability hypothesis is true to begin with (start with “good ideas")
   - Fixed when hypothesis is formulated
2. Type I error (Specificity)
   - Fixed by level of significance
3. Power (Sensitivity)
   - Statistical power made as high as possible by design

Goals of Clinical Trial Design

The later two elements are improved by

1. Minimizing bias
   - Remove confounding and account for effect modification
2. Decreasing variability of measurements
   - Homogeneity of population, appropriate endpoints, appropriate sampling strategy, more precise measuring device

Goals of Clinical Trial Design

Common pitfalls of studies

- Common pitfalls of experimentation are:
  - Data driven hypotheses (↑ Type I error)
  - Multiple comparisons (↑ Type I error)
  - Poor selection of subjects (↓ Power)
  - Over-fitting of data (↑ Type I error, (↓ Power)
  - Poor selection of subjects, outcomes (↓ Power)
  - Noncomparability of treatment groups (↑ Type I error)
- Each of these pitfalls leads to increases in variability and/or bias in clinical trials...

Course roadmap

Where are we going?

- Module 1: Design
  - Background
    - Phases of clinical trials
    - Interplay between science and statistics
    - Ethics and varying roles of oversight committees
  - Role screening studies in trial design
  - Fundamental design elements
    - Variability and bias
    - Identification of target population
    - Definition of intervention(s)
    - Choice of outcomes
    - Choice of comparison groups
    - Blinding
    - Brief introduction to randomization
  - Statistical tasks in trial design
    - Refinement of hypotheses
    - Probability models and summary measures
    - Determination of sample size
  - Focus on elements of a clinical trial protocol

Course roadmap

Where are we going?

- Module 2: Primarily implementation
  - Choice of outcome (surrogate outcomes vs. clinical outcomes)
  - Methods of randomization
  - Monitoring for quality and missing data
  - Role and function of IDMCs
  - Group sequential monitoring
  - Data management
  - Review of key elements of a clinical trial protocol
  - (Extra?) Further discussion on common endpoints: survival and change from baseline

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