# New Investigator Clinical Trial
# Section 2: Statistics for Clinical Trials
# Part 1: Basics of Phase III Trial Design

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## Outlines

- Randomized Clinical Trials (Phase III)
- Blindness
- Endpoints
- Sample Size
- Non-inferiority Trials
- Summary

## 1. Randomized Clinical Trial

- Objectives
  - Study efficacy of an intervention in a given ***study population***
  - Need an intervention group and a control group
  - Method of selection: Randomization
- Randomized Clinical Trials
  - Cross-over design
  - Factorial design
  - Large simple clinical trial
  - Non-inferiority trial (Study of equivalency)

## Trial Design – II

- Cross-over design
  - Each participant to serve as his or her own control
    - Receives either intervention or control in the first period and the alternative in the succeeding period
    - The order is randomized
  - Assumption: no carry over effect, which is inappropriate in many clinical trials
    - e.g. cured patients may not return to the initial state

## Trial Design – III

- Factorial design
  - Evaluate two or more interventions compared with control in a single trial, e.g. 2x2 design:

| | Intervention A | Control |
|---|---|---|
| Intervention B | A and B | B only |
| Control | A only | Control |

  - It is possible to leave some of the cells empty
  - Sample size depends on the *interaction*
  - Impact on recruitment and compliance

## Trial Design – IV

- Large simple design
  - Uncover modest benefits of intervention
    - Short term
    - Easily to implement in a large population
  - Unbiased allocation of participants
  - Unbiased assessment of the outcomes
  - No for trials with
    - Complex interventions
    - Complex Outcomes

## Randomization - I

- Randomized Clinical Trials (RCT)
  - Assign participants to control or treatment group using formal randomization procedure
- Advantages of RCT
  - Ensure balance for all baseline factors
  - Remove potential ***bias***
  - Produce comparable groups
  - Guarantee validity of statistical tests

## Randomization - II

- Method of Randomization
  - Simple Randomization
    - Toss a coin or use a computer-based algorithm
    - Not guarantee for balance of important factors
  - Block Randomization
    - e.g. block size 4: AABB, ABAB, ABBA, BBAA BABA BAAB
    - Balance between treatment groups
    - Not guarantee for balance of important factors
  - Stratified Block Randomization
  - Dynamic randomization/minimization

## Randomization - III

- Stratified Block Randomization
  - Identify important stratification factors
    - eg. Age, Gender, Centre, etc
  - Ensure treatments are balanced for a few pre-selected stratification factors
  - Randomly assign treatment group (Block Randomization) within each combination (cell) of stratification factors
  - Risk of not balanced if the number of cell is large

## Randomization - IV

- Dynamic Randomization / Minimization
  - Large number of cells
    - Age (3 levels), Gender (2 levels), smoking history (3 levels), centre (5 levels), node status (3 levels): 270 cells
  - For a new subject in a give cell, total number of patients allocated in each treatment group is counted. The subject will be allocated to group with smallest number (coin tossing if tied)
  - Guarantee balance but treatment allocation may be predictable

## 2. Blindness

- Objective
  - Reduce ***bias***
- Type of Trials
  - Un-blinded trials (open trials)
    - Both the participant and the investigator are aware of the intervention assignment. e. g. lifestyle intervention
  - Single-blind trials
    - Only the investigators are aware of the intervention assignment
  - Double-blind trials

## Blindness - II

- Double-blind trials
  - Neither the participants nor the investigators know the intervention assignment.
  - Usually restrict to trials of drug efficacy
  - ***Bias*** is reduced (but can't be completely eliminated)
  - An outside body to monitor the data for toxicity and benefit (e.g. DSMC)

## Blindness - III

- Special problems in double-blind trials
  - Participants and investigators may try to unblind the medication
    - Consciously
    - Unconsciously
  - Matching of drugs: Tablets or capsules closely resembled one another
  - Coding of drugs: Labeling of individual drug bottles or vials so that the identity of the drug is not disclosed

## Blindness - IV

- Ideally, a clinical trial should have double-blind design to avoid potential bias
- If a double-blind design is impossible, use a single-blind approach or other measures to reduce potential bias

## 3. Endpoints

- Primary Endpoints
  - Most clinically relevant and direct related to primary objective of the trial
  - Base for sample size calculation
  - Analysis to be adjusted for Type I error if there are multiple primary endpoints
- Secondary Endpoints
  - Supportive measurements of effects related to the secondary objective
  - Hypothesis generation
  - No need to adjust trial results for secondary endpoints

## Endpoints - II

- Examples of Endpoints
  - Time to event endpoints
    - Overall survival
    - Event free survival
    - Progression free survival
    - Recurrent free survival
  - Binary endpoints
    - Overall response rate
    - Complete response rate
  - Continuous endpoints
    - Quality of life scores
    - Incremental cost-effectiveness ratios

## 4. Sample Size

- Objectives
  - Provide an estimate of the needed size of a study
  - Ensure sufficient statistical power to detect clinical meaningful difference between groups
  - Provide adequate levels of significance
  - Parameters for sample size estimation shall be as conservative as possible while still being realistic

## Sample Size - II

- Parameters for Sample Size Calculations
  - Specify Type I error (or Significant level)
  - Specify Type II error (or Power)
  - Determine the minimum difference to be detected or of clinical interest (defined by $\delta$)
- Sample size calculations for
  - Continuous endpoint
  - Binary endpoint
  - Time to event endpoint
- Details will be covered in this afternoon's Workshop.

## 5. Non-inferiority Trials

- Objectives
  - Study of equivalency
  - Test whether a new intervention is as good as an established one
  - Trials with positive control
- Requirements
  - Control or standard treatment must have been shown to be effective (i.e. better than placebo)
  - Similar populations, concomitant therapy and dosage
  - Trials that demonstrated efficacy of the standard shall be recent and properly designed and conducted

## Non-inferiority Trials - II

- Other important factors to be considered
  - Frequency and severity of adverse effects
  - Changes in Quality of Life (QoL)
  - Ease of applying the new intervention
  - Cost of the new intervention

## Non-inferiority Trials - III

- What is meant by equivalence?
  - Two therapies are identical? – Require infinity sample size to test $\delta = 0$
  - New intervention falls sufficiently close to the standard as defined by reasonable boundaries
  - Non-inferiority margin
    - Specify some value, $\delta$, such that interventions with differences that are less than this might be considered equally effective or equivalent

## Non-inferiority Trials - IV

- Example
  - A recent trial shows that drug A has response rate of 60%, compared with 30% of the placebo
  - Drug B is less expensive and has fewer side effects
  - Drugs A and B are considered to be equivalent if the difference in response rate is less than δ=10%
    - Null hypothesis $H_0$: $P_A - P_B > \delta$ vs $H_a$: $P_A - P_B < \delta$
  - Calculate sample size such that one can reject $H_0$ with power 80% if the upper 5% confidence interval for the difference of the response rate does not exceed δ (e.g. $\alpha = 0.05$, power = 80%: N = 594)

## Summary

- Define the term randomized clinical trials
- Randomization methods used in clinical trials
- The importance of blindness in clinical trials
- Different endpoints used in clinical trials
- Necessary parameters for sample size calculation
- Difference between superiority and non-inferiority trials

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