Basics of Clinical Trial Design

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Learning Objectives

- Describe the characteristics of adequate & well-controlled studies
- Describe the purpose of control groups & various types of controls
- Describe methods to reduce bias in clinical investigations

Adequate & Well-Controlled Studies

"The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."

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Adequate & Well-Controlled Studies

- Clear objectives, summary of methods of analysis in protocol
- Design permits a valid comparison with a control
- Adequate selection of patients
- Assigning patients to treatment/control groups to minimize bias
- Adequate measures to minimize biases on subjects, observers, and analysts
- Well-defined and reliable assessment of subjects' responses
- Adequate analyses to assess the effects of the drug

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What are the Scientific Questions?

- The scientific questions to be answered & trial objectives need to align
- Inform choices about trial design, data collection, and analysis
  - E.g., superiority vs. non-inferiority? How to handle events that might occur after randomization (use of rescue drug, etc.)? Is objective to understand effect of drug when added to a specific background treatment?

Purpose of Control Group

- Control groups allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors.
- What would have happened to patients…
  - if they had not received the test treatment, or
  - if they had received a different treatment known to be effective?

Examples of Control Groups

- Placebo
- No treatment
- Different dose(s) or regimen(s) of same drug
- A different active treatment
- Historical or other external control

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Study Population

- Typically, eligibility criteria should identify participants with, or at risk for, the disease or condition being studied
- May be narrowly or more broadly defined, depending on objectives
- Avoid unnecessary exclusion criteria
- Proactively set enrollment goals designed to ensure that the study population is representative of the intended use population (e.g., age, sex, race, etc.)

Enrichment

- Selection of a study population in which detection of a drug effect (if one is present) is more likely than it would be in an unselected population
- Broad categories of strategies:
  - Strategies to decrease variability (e.g., placebo lead-in period to exclude participants with large “responses” or who demonstrate poor adherence *before* randomization)
  - Prognostic enrichment (who is most likely to progress or have an outcome of interest?)
  - Predictive enrichment (who is most likely to respond?)
    - Example: randomized withdrawal study

Methods of Assignment to Study Arms

- Should minimize bias & assure comparability of the groups with respect to pertinent variables
- Typically, in a concurrently controlled study, assignment is by randomization

Randomized vs. Observational Studies

Randomized Study

Patient

Drug A Drug B

Observational Study

Patient

Age, comorbidities, concomitant meds, family history, labs, patient preferences, insurance, etc.

Drug A Drug B

Similarity of Groups

- Similarity at baseline
  - Randomization
- Similarity after baseline
  - Adherence to assigned treatment
  - Use of rescue therapy, if applicable
  - Completeness of data & follow-up
  - Outcome assessment

Measures to Reduce Bias

- Concealing treatment assignments (blinding)
- Biases may be conscious or unconscious
- Aim is to ensure that study groups are treated and observed similarly during the trial (except for the intervention of interest)

Examples of Potential Impacts from Knowledge of Treatment Assignment

- Healthcare providers may treat the trial participant differently (in ways that could affect the outcome of interest)
- Those on active drug might report more favorable outcomes
- Observers may be less likely to identify & report apparent treatment responses in a no-treatment group
- Those on active drug may be more (or less) likely to report adverse events
- Knowledge may affect rigor of attempts to obtain follow-up data
- Knowledge could impact decisions related to analysis (e.g., look for reasons to exclude “poorly performing” study site)

Measures to Reduce Bias

- Even with blinding, patients or investigators may be able to detect (or guess) treatment assignment.
- If open-label, consider prespecified decision rules, blinded outcome assessment, etc.
- Maintain confidentiality of interim results (whether individual or treatment group level).
- Statistical analysis plans should be finalized before treatment assignments revealed.

Assessing Response / Endpoints

- Primary endpoint: should provide relevant evidence related to the primary objective
- Secondary endpoints: either supportive measurements related to the primary objective, or measurements related to secondary objectives
- Exploratory: further explain/support study findings or to explore new hypotheses for later research

Endpoints

- Precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question
  - Assessment itself (e.g., lab value, patient-reported outcome, physiologic test, clinical event)
  - May incorporate other information that occurs during the trial (e.g., treatment discontinuation = treatment failure)
  - Timing of the assessment
  - If relevant, how assessments in each participant are formulated or combined (e.g., composite endpoint; average, maximum, or minimum score over a pre-defined period)

Endpoints

- Clinical outcome: an outcome that describes or reflects how an individual feels, functions, or survives
- Surrogate endpoint: an endpoint used as a *substitute* for a direct measure of how a patient feels, functions, or survives
  - Level of evidence that an effect on the surrogate predicts clinical benefit can vary; if strong, it is called a "validated surrogate endpoint" (e.g., HbA1c in diabetes mellitus, blood pressure in hypertension)

Intercurrent Events

- Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
  - E.g., treatment discontinuation (and why), beginning or switching to other treatments, death
  - Do NOT lead to a problem of missing data
  - Should be considered & incorporated into design

Intercurrent Events

- Consider possible intercurrent events when defining the clinical question of interest.
  - In a trial for a drug of type 2 diabetes mellitus, suppose the primary endpoint is the change in HbA1c from baseline to week 24.
  - Trial allows rescue medication if thresholds are met.
  - Examples of possible treatment effects of interest:
    - Effect if rescue medication is not available
    - Effect regardless of whether rescue medication is used

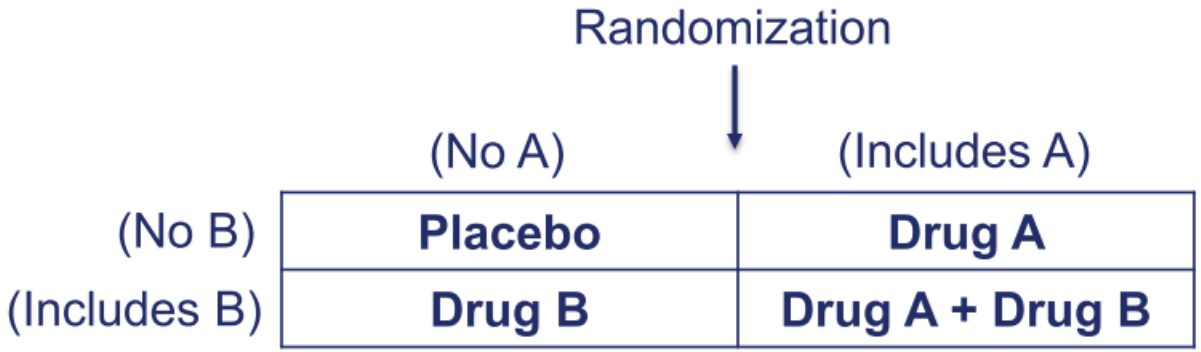
Strategies of Comparison

Parallel Group

Crossover

Strategies of Comparison

Factorial Design



Superiority vs. Non-inferiority

- In a trial of Drug A vs. Drug B…
  - Superiority: Drug A is better than Drug B
  - Non-inferiority: Drug A is not meaningfully worse than Drug B. The “NI margin” quantifies “meaningfully worse.”
- If no difference is detected between groups, are both drugs effective or ineffective?
- There is no confirmation, in this trial, that Drug B is effective: This is an *assumption*.

NI Trials & Assay Sensitivity

- Assay sensitivity is the ability of the trial to have detected a difference between treatments of a specified size.
- Not directly assessed within an NI trial, so consider:
  - Historically, have consistent findings been observed with the active control (vs. placebo)?
  - Similarity of the new trial to the historical trials? (“Constancy assumption”)
  - Quality of the new trial (poor conduct can minimize differences between treatments)

Other Design Considerations

- Focus on activities essential to the study
  - Consider eliminating nonessential activities & data collection to focus available resources on critical areas
- Engage interested parties in study design
  - Patients / patient organizations
  - Study coordinators & site staff
  - Clinical investigators

Challenge Question #1

Which of the following is NOT an example of enrichment:

A. Enroll patients with a lab value that indicates they are at greater risk for the outcome of interest during the trial

B. Limit enrollment to patients with a certain genetic variant that is specifically targeted by the investigational drug

C. Ask trial participants who demonstrate poor adherence after randomization to withdraw from the trial

D. Require patients to have 3 consistent values during a screening period for the assessment of primary interest in the trial.

Challenge Question #2

The choice of a control group affects which of the following:

A. The inferences that can be drawn from the trial

B. The ethical acceptability of the trial

C. The degree to which bias in conducting and analyzing the trial can be minimized

D. The scientific credibility and impact of the results

E. All of the above

Summary

- Design clinical investigations to distinguish the effects of an intervention from other influences
- Always start with the clinical question(s) of interest
- Key design aspects include study population, an appropriate control, well-defined endpoints, measures to minimize bias (including assignment of treatment), and the analytical plan