

Basics of Clinical Trial Design

James P. Smith, MD, MS

Director, Office of New Drug Policy

Office of New Drugs

CDER | US FDA

CITC – 2024



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.”

21 CFR 314.126

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

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

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

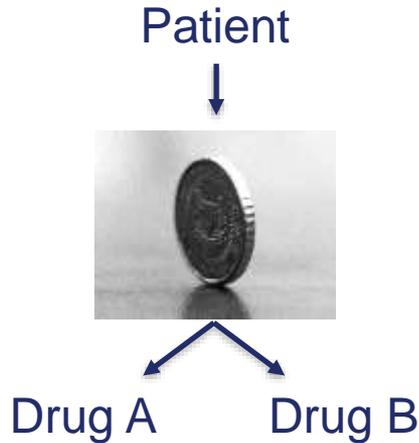


- Should minimize bias & assure comparability of the groups with respect to pertinent variables
- Typically, in a concurrently controlled study, assignment is by randomization

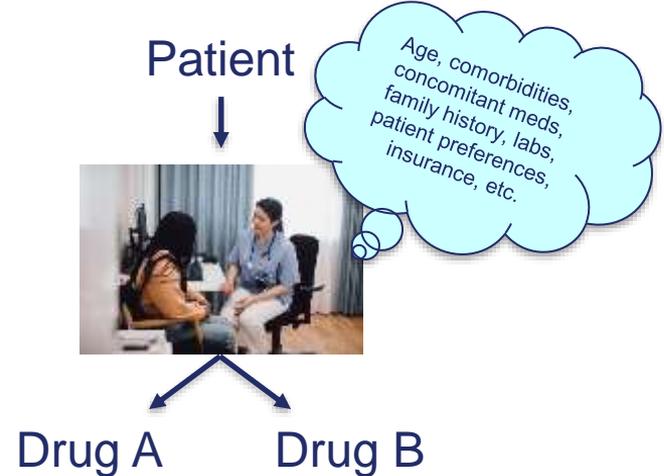
Randomized vs. Observational Studies



Randomized Study



Observational Study



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

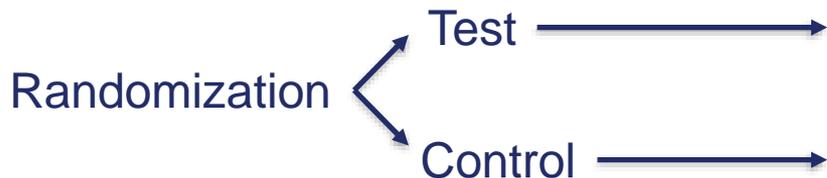
Intercurrent Events

- 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



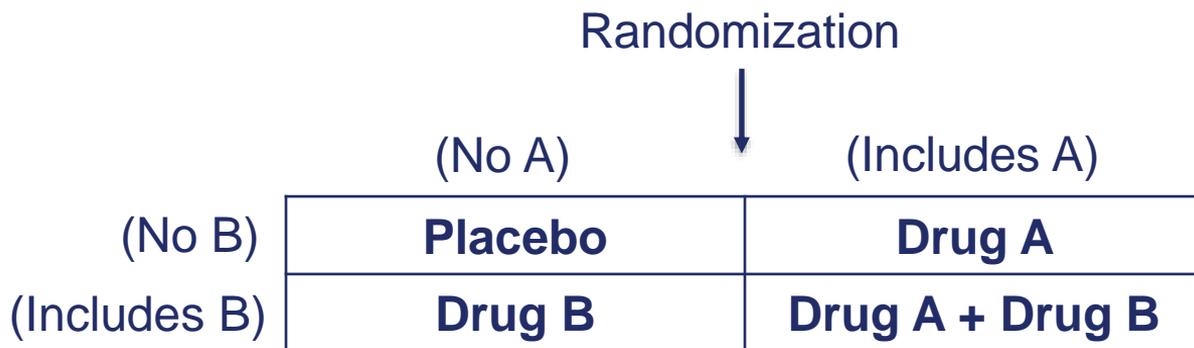
Crossover



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