

Clinical Trials

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Objectives - I

- Describe the “Phases” of Drug Development
- Introduce the various types of randomized, controlled trials (RCTs)
- Describe the architecture of a “parallel group design” study
- Describe the effect of sampling on the generalizability of the findings of clinical trials
- Describe how an intervention should be judged in a clinical trial
- Describe how comparison groups should be chosen in an ethical fashion

Objectives - II

- Define various randomization options
- Describe how certain events arising after randomization can affect the validity of the study
- Describe how the assessment of outcomes can affect the validity of the study
- Describe various methods of assessing the effect of the treatment on the outcome of a clinical trial

Objectives - III

- Distinguish management from explanatory trials
- Distinguish efficacy from effectiveness
- Briefly discuss
 - Crossover Design
 - Factorial Design
 - Effect estimation (as opposed to hypothesis testing)
 - Noninferiority trials
 - Equivalence trials

Phases of Drug Development Research

- Describes stages of research involving drugs or devices in human subjects that are being evaluated for a new (unlicensed) indication
- Part of an approved Investigational New Drug (IND) application or Investigational Device Exemption (IDE) application under FDA guidelines, which provides permission for experimental testing of new drug/device or a new indication for an old drug/device

Drug Development Phases

- Phase I (find maximum tolerated dose)
- Phase II (initial effectiveness trial)
- Phase III (efficacy trial)
- Phase IV (post-marketing surveillance for toxicity)

Phase I

- To determine the dosage of the drug that can be given without serious side effects (maximal tolerable dose: MTD)
- Generally conducted on a small number (tens) of healthy adults
- Occasionally used on patients who have exhausted other available treatments
- Usually uncontrolled
- Three subjects at a time approach (if no toxicity in first three, increase dose for the next 3; if toxicity, reduce dose)
- Short follow-up period (days to months)

Phase II

- To determine if a new drug is effective enough to warrant further study
- Preliminary data on efficacy (often used surrogate endpoints)
- Supplements safety data
- Larger population of patients (20-hundreds)
- Short follow-up period (months)
- More exclusions than in Phase III
- **Could be a clinical trial**

Phase III

- Estimates efficacy
- Supplements safety data
- Larger population of patients (thousands)
- **Almost always a clinical trial** (placebo or standard treatment)
- Longer follow-up (months to years)
- Required prior to application for licensure
- In chronic disease trials, follow-up duration may be short relative to the time the intervention might be used in clinical practice. Therefore the assessment of long-term beneficial and/or adverse effect may be inadequate.

Phase IV

- Post-marketing research after NDA has been submitted and approved by the FDA
- Long-term safety and efficacy
- Very large, population-based
- Generally in the form of a survey
- **Could be a clinical trial**

Types of Clinical Trials Designs

- Parallel group
- Crossover
- Factorial
- Non-traditional (use of effect estimation as opposed to hypothesis testing)
 - Noninferiority trials
 - Equivalence trials

RCT: Parallel group design

- A special kind of cohort study
- Risk factor or exposure is randomly distributed to the “experimental” and “control” groups
- Advantage: Best design for dealing with selection bias due to known and unknown confounders
- However, there are disadvantages and pitfalls of experimental designs as well

Problem: Who gets into clinical trials?

- Volunteers
- Why might a person not be eligible for a clinical trial?
 - Do not meet specific entry criteria
 - Exclusion criteria
 - To control for possible confounding
 - Contraindications for treatment in either group
 - Subject already has the outcome of interest
 - Factors associated with non-adherence of protocol
 - Refuse to participate
 - Not cooperative with the conduct of the trial
- **Result is a highly selected, biased sample of all patients with the condition of interest**

Problem: What was the intervention compared to?

- No intervention
- Observation only
- Placebo
- Usual treatment
- **Scientific and ethical imperatives may not coincide**

Problem: How was the treatment allocated?

- True randomization?
- Stratified randomization
- Block randomization
- **Despite the use of modern, computer-aided techniques, randomization may still not be successful.**

Problem: What can go wrong after successful randomization?

- Subjects don't have the disease
- Compliance
- Cointerventions
- Dropouts
- **Bias can still occur even after successful randomization.**

Problem: Were the outcomes assessed precisely and accurately and without measurement bias?

- Less precise (reliable) outcome measures reduce the power of the study
- Objective vs. subjective measures
- **Blinding is a major tool to reduce measurement bias**

When is blinding feasible?

- Ethics: Blinding procedures should not result in any harm or undue risk to a patient.
- Practicality: For some treatments it would be impossible to arrange a double-blind trial.
- Avoidance of Bias: One needs to assess just how serious the bias might be without blinding.
- Compromise: Sometime partial blinding (e.g., independent blinded evaluators) can be sufficient to reduce bias in treatment comparison.

Classification of Blinded Trials

- Unblinded
- Single-blinded
- Double-blinded

Recommendations for Unblinded Trials

- Use objective measures as outcome measures, preferably those most likely to be free of detection bias, e.g., total mortality, laboratory measurements, continuous measure for smoking cessation (# cigs).
- Use independent evaluators who are blinded to the treatment groups to assess the study outcomes. (Particularly important for life-style intervention trials.)
- Persons performing laboratory measurements also should not know which treatment the patient is receiving. If there are several measurements taken on the same participant that are expected to change as a result of the intervention, consideration should be given to randomizing the order of specimens (for those that can be stored), or blinding the specimens so that specimen codes are different from participant ID codes.

Single-Blind Trials

- Only the investigators are aware of which treatment each subject is receiving. The participant is not aware of the treatment assignment.
- *While this is the typical meaning, single-blind can also mean that only the subject is aware of which treatment they received and the investigator is blinded.*
- *Because there are different interpretations, the intent of "single-blind" should always be explicitly stated.*

Single-Blind Trials - II

- Advantages
 - Double-blind trial may not be possible.
 - It may be easier to implement than double-blind trials.
 - Investigators may feel more comfortable.
 - Potential participant biases are eliminated.
- Disadvantages
 - Potential biases due to investigator behavior
- Recommendations – see unblinded trials

Double-Blinded Trials

- Neither the participants nor the investigators know the identity of the treatment assignment.
- Advantages: Both participant and investigator biases are minimized.
- Disadvantages: Trial may be more difficult to design and implement.
- Recommendations: If feasible, double-blind design should be used. Most drug trials are double-blinded.

Evaluation of Maintenance of the Double-Blind

- Periodic reports on the use of concomitant medications or alternative treatments and chemical test to detect the drugs (if possible) should be performed throughout the trial.
- After the study is complete, it is a good idea to ask participants and investigators (clinic staff) what they think the treatment was for each participant.
- How would you know if the blinding was successful?

Problem: How was the effect of the intervention on the outcome expressed?

- Relative risk (hazard rate) reduction
 - $(1 - RR) = 1 - (I_E / I_C)$
- Absolute risk reduction
 - $I_C - I_E$
- Number needed to treat
 - $1 / \text{Absolute risk reduction}$

Problem: Was the analysis according to the treatment to which subjects were randomized or to the one they actually received?

- Intention to treat or “management” trial analysis
- As treated or “explanatory” trial analysis
 - Subject to bias of a cohort study since randomization did not allocate treatment
- **Intention to treat analysis is the “gold standard” analysis for RCTs**

Problem: What are the ethical and safety monitoring challenges of RCTs

- Selection of control treatment
- Particular ethical challenges of RCTs in pediatric populations
- “Remuneration” vs. “coercion”
- IRBs and “local control” – challenges of multi-centered trials
- Data Safety Monitoring Boards (DSMBs) – required of all NIH-funded clinical trials

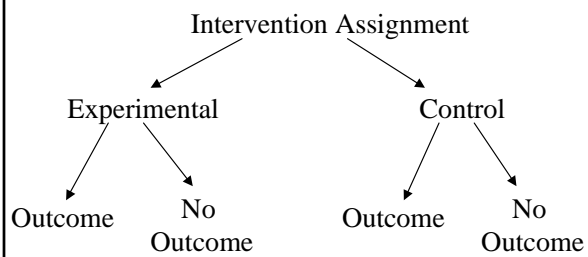
Efficacy vs. Effectiveness

- Efficacy
 - Does the treatment work under ideal circumstances?
- Effectiveness
 - Does the treatment work in ordinary settings?
 - Also takes into consideration relative good and harm of treatment

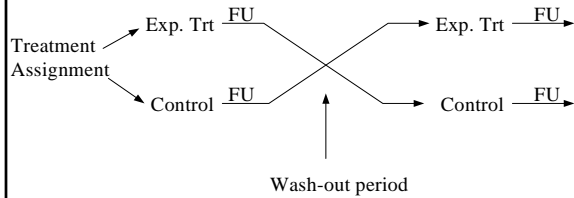
Summary

- Parallel group design RCT with effective randomization is the best method for eliminating selection bias
- However,
 - they are expensive
 - their findings are potentially poorly generalizable
 - the still may be subject to bias which may limit internal validity

Parallel Group Design



Crossover Design



FU=follow-up to determine outcome

Crossover Design (cont.)

- Key assumptions
 - No carry-over effect from first intervention
 - No difference in effects over time
- Benefits
 - Each participant serves as own control (reduces variance and therefore sample size)
 - All participants receive both interventions

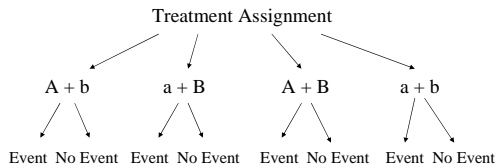
Crossover Design (cont.)

- Generally restricted to short-term outcomes
- Requires chronic disease or condition in order that symptoms/findings could be evaluated during both intervention periods
- Need data from other studies to test key assumptions
- If carry-over effect is detected, consider study as a parallel design and analyze data from first period only
- Modification: add more interventions, more periods, or both (e.g. ABB/BBA)

Factorial Design

- More than one intervention assigned in the same trial
 - A vs. a
 - B vs. b
 - High dose vs. low dose
 - Drug vs. placebo
 - Extended surgery vs. standard surgery
 - Can also use > 2 interventions with > 2 levels (e.g. 3 different vitamins all at 3 dose levels); if not all possible combinations are used, this is called **partial factorial**

Example of a full 2x2 factorial trial



Effect estimation

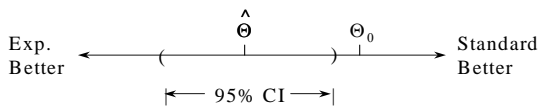
- As opposed to hypothesis testing
- Prescribe width of confidence interval to provide number of participants in the trial
- E.g. Design a trial with a lower bound of the CI for efficacy at 40% (as opposed to 0% in a standard trial)

Noninferiority Trials

- Designed to show that the experimental treatment is “no worse” than standard treatment (as opposed to “different than” in traditional trials).
- Rules out superiority of the standard treatment
- Uses one-sided p-value and a confidence interval approach similar to that described for effect estimation

Noninferiority Trials

Θ_0 = prespecified quantity at which the standard treatment is said to be “better”
 $\hat{\Theta}$ = observed effect estimate



Where Θ = RR, AR, etc.

Equivalence Trials

- Designed to show that two interventions are the same, with deviations in both directions being important
- Cannot demonstrate “equivalence” statistically even if effects are identical, but you can estimate the difference in the responses as precisely as desired by a large sample size
- Uses a CI approach, but always 2-sided.

Reference

- Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 3rd Edition.. Springer-Verlag New York, Inc., 1998.
