Basics of Study Design

Basics of Study Design

- Bias and variability
- Randomization: why and how?
- Blinding: why and how?
- General study designs

Bias and Variability

- The clinical trial is considered to be the “gold standard” in clinical research
- Clinical trials provide the ability to reduce *bias* and *variability* that can obscure the true effects of treatment
- Bias $\Rightarrow$ affects accuracy
- Variability $\Rightarrow$ affects precision

- Bias: any influence which acts to make the observed results non-representative of the true effect of therapy

- Examples:
  - healthier patients given treatment A, sicker patients given treatment B
  - treatment A is “new and exciting” so both the physician and the patient expect better results on A
- *Many* potential sources of bias

- Variability: high variability makes it more difficult to discern treatment differences

- Some sources of variability
  - Measurement
    - instrument
    - observer
  - Biologic
    - within individuals
    - between individuals
- Can not always control for all sources (and may not want to)

Fundamental principle in comparing treatment groups:

- Groups must be alike in all important aspects and only differ in the treatment each group receives

- In practical terms, “comparable treatment groups” means “alike on the average”

Why is this important?

- If there is a group imbalance for an important factor then an observed treatment difference may be due to the imbalance rather than the effect of treatment

  Example:
  - Drug X versus placebo for osteoporosis
  - Age is a risk factor for osteoporosis
  - Older subjects are enrolled in Drug X group
  - Treatment group comparison will be biased due to imbalance on age

How can we ensure comparability of treatment groups?

- We can not ensure comparability but *randomization* helps to balance all factors between treatment groups

- If randomization “works” then groups will be similar in all aspects except for the treatment received

Randomization

- Allocation of treatments to participants is carried out using a chance mechanism so that neither the patient nor the physician know in advance which therapy will be assigned

- *Simplest Case*: each patient has the same chance of receiving any of the treatments under study

Simple Randomization

- Think of tossing a coin each time a subject is eligible to be randomized

  HEADS: Treatment A

  TAILS: Treatment B

- Approximately ½ will be assigned to treatments A and B
- Randomization usually done using a randomization schedule or a computerized random number generator

Problem with Simple Randomization:

- May result in substantial imbalance in either
  - an important baseline factor and/or
  - the number of subjects assigned to each group
- Solution: Use blocking and/or stratified randomization

Blocking Example:

- If we have two treatment groups (A and B) equal allocation, and a block size of 4, random assignments would be chosen from the blocks

  1) AABB
  2) ABAB
  3) ABBA
  4) BABA
  5) BAAB
  6) BABA

- Blocking ensures balance after every 4th assignment

Stratification Example

- To ensure balance on an important baseline factor, create strata and set up separate randomization schedules within each stratum
- Example: if we want prevent an imbalance on age in an osteoporosis study, first create the strata "< 75 years" and "$\geq$ 75 years"

  then randomize within each stratum separately
- Blocking should be also be used within each stratum

Alternatives to Randomization

- Randomization is not always possible due to ethical or practical considerations
- Some alternatives:
  - Historical controls
  - Non-randomized concurrent controls
  - Different treatment per physician
  - Systematic alternation of treatments
- Sources of bias for these alternatives need to be considered

Blinding

- Masking the identity of the assigned interventions
- Main goal: avoid potential bias caused by conscious or subconscious factors
- *Single blind*: patient is blinded
- *Double blind*: patient and assessing investigator are blinded
- *Triple blind*: committee monitoring response variables (e.g. statistician) is also blinded

How to Blind

- To “blind” patients, can use a placebo

  Examples
  - pill of same size, color, shape as treatment
  - sham operation (anesthesia and incision) for angina relief
  - sham device such as sham acupuncture

Why Should Patients be Blinded?

- Patients who know they are receiving a new or experimental intervention may report more (or less) side effects
- Patients not on new or experimental treatment may be more (or less) likely to drop out of the study
- Patient may have preconceived notions about the benefits of therapy
- Patients try to get well/please physicians

- Placebo effect – response to medical intervention which results from the intervention itself, not from the specific mechanism of action of the intervention

  Example: Fisher R.W. JAMA 1968; 203: 418-419

  - 46 patients with chronic severe itching randomly given one of four treatments
  - High itching score = more itching

Treatment	Itching Score
cyproheptadine HCl	27.6
trimeprazine tartrate	34.6
placebo	30.4
nothing	49.6

Why Should Investigators be Blinded?

- Treating physicians and outcome assessing investigators are often the same people

  $\Rightarrow$ Possibility of unconscious bias in assessing outcome is difficult to rule out

- Decisions about concomitant/compensatory treatment are often made by someone who knows the treatment assignment

  $\Rightarrow$ “Compensatory” treatment may be given more often to patients on the protocol arm perceived to be less effective

Can Blinding Always be Done?

- In some studies it may be impossible (or unethical) to blind
  - a treatment may have characteristic side effects
  - it may be difficult to blind the physician in a surgery or device study
- Sources of bias in an un-blinded study must be considered

General Study Designs

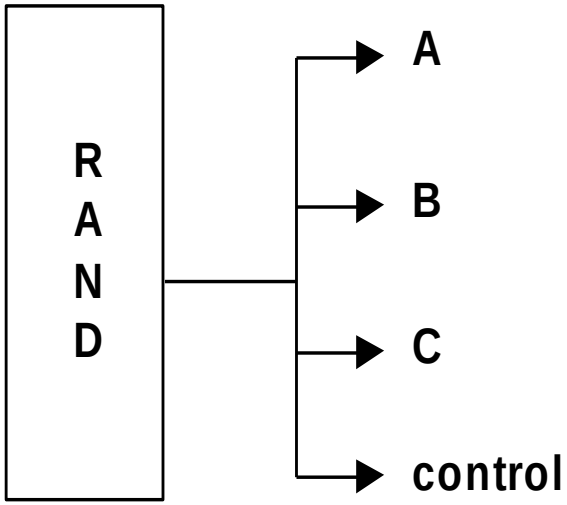
- Many clinical trial study designs fall into the categories of *parallel group*, *dose-ranging*, *cross-over* and *factorial* designs

- There are many other possible designs and variations on these designs

- We will consider the general cases

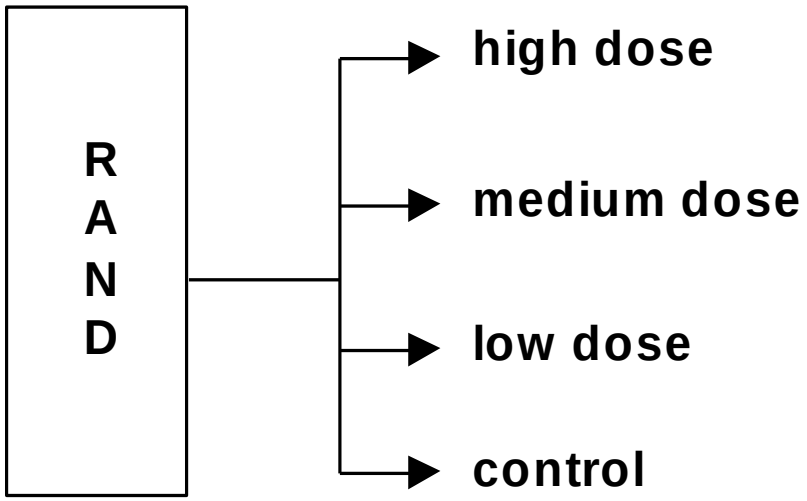
General Study Designs

- Parallel group designs



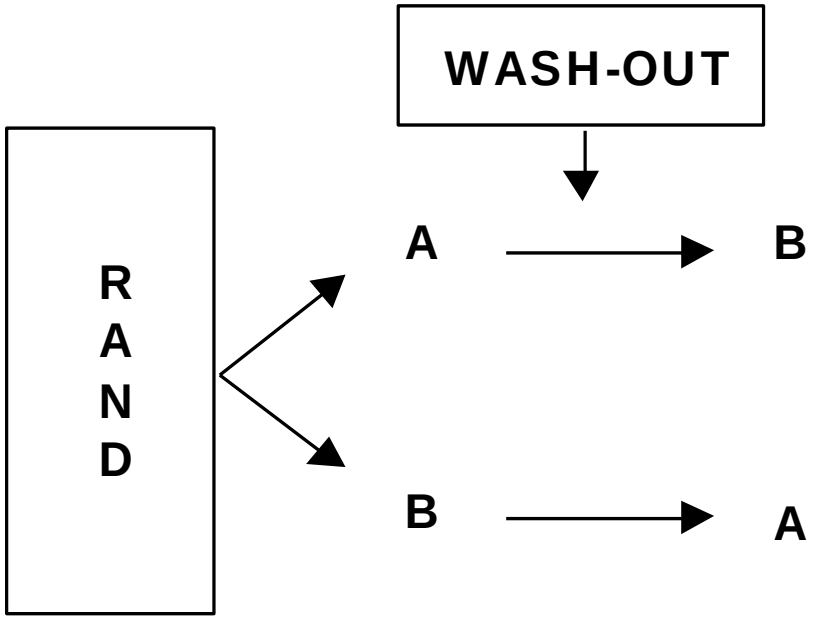
General Study Designs

- Dose-Ranging Studies



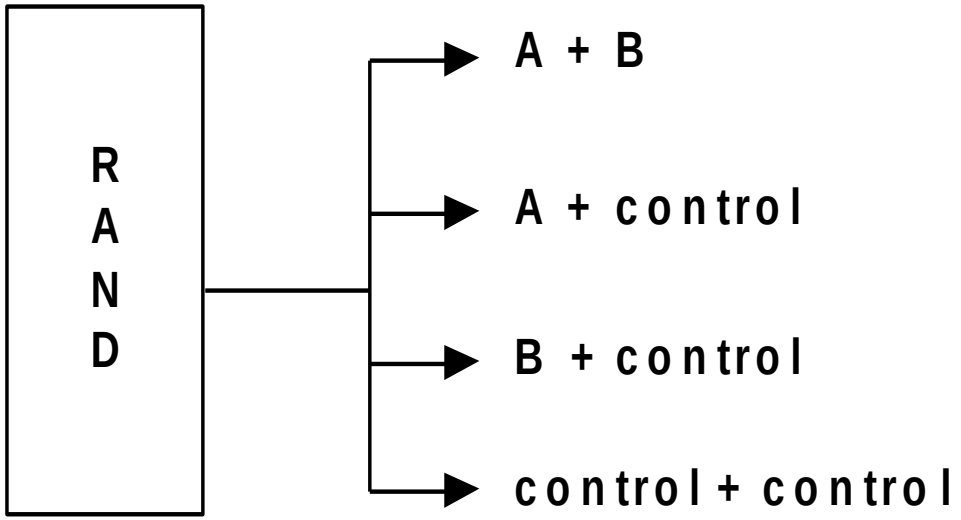
General Study Designs

- Cross-Over Designs



General Study Designs

- Factorial Designs



Cross-Over Designs

- Subjects are randomized to sequences of treatments (A then B or B then A)
- Uses the patient as his/her own control
- Often a “wash-out” period (time between treatment periods) is used to avoid a “carry over” effect (the effect of treatment in the first period affecting outcomes in the second period)
- Can have a cross-over design with more than 2 periods

Cross-Over Designs

- Advantage: treatment comparison is only subject to within-subject variability not between-subject variability

  $\Rightarrow$ reduced sample sizes
- Disadvantages:
  - strict assumption about carry-over effects
  - inappropriate for certain acute diseases (where a condition may be cured during the first period)
  - drop outs before second period

Cross-Over Designs

- Appropriate for conditions that are expected to return to baseline levels at the beginning of the second period

  Examples:

  – Treatment of chronic pain
  – Comparison of hearing aids for hearing loss
  – Mouth wash treatment for gingivitis

Factorial Designs

- Attempts to evaluate two interventions compared to a control in a single experiment (simplest case)
- An important concept for these designs is *interaction* (sometimes called *effect modification*)

  Interaction: The effect of treatment A differs depending upon the presence or absence of intervention B and vice-versa.

Factorial Designs

- Advantages:
  - If no interaction, can perform two experiments with less patients than performing two separate experiments
  - Can examine interactions if this is of interest
- Disadvantages:
  - Added complexity
  - potential for adverse effects due to “poly-pharmacy”

Factorial Designs

- *Example:* Physician's Health Study
- Physicians randomized to:
  - aspirin (to prevent cardiovascular disease)
  - beta-carotene (to prevent cancer)
  - aspirin and beta-carotene
  - neither (placebo)

Stampfer, Buring, Willett, Rosner, Eberlein and Hennekens (1985) The 2x2 factorial design: it's application to a randomized trial of aspirin and carotene in U.S. physicians. *Stat. in Med*. 9:111-116.