Design and interpretation of clinical trials

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(1)

- **Phases of trials**

1. Phase 1:
   - first stage in testing a new intervention in humans
   - Usually 10-30 people
   - Identify tolerable dose, provide information on drug metabolism excretion and toxicity
   - Often not controlled
2. Phase 2:
   - 30-100 people
   - Preliminary information on efficacy, additional information on safety and side effects
   - Sometimes controlled, sometimes not
3. Phase 3:
   - 100+ people
   - Assess efficacy and safety
   - Controlled, usually randomized

- **Types of trials**

One trial may fall into one or more than one of these types.

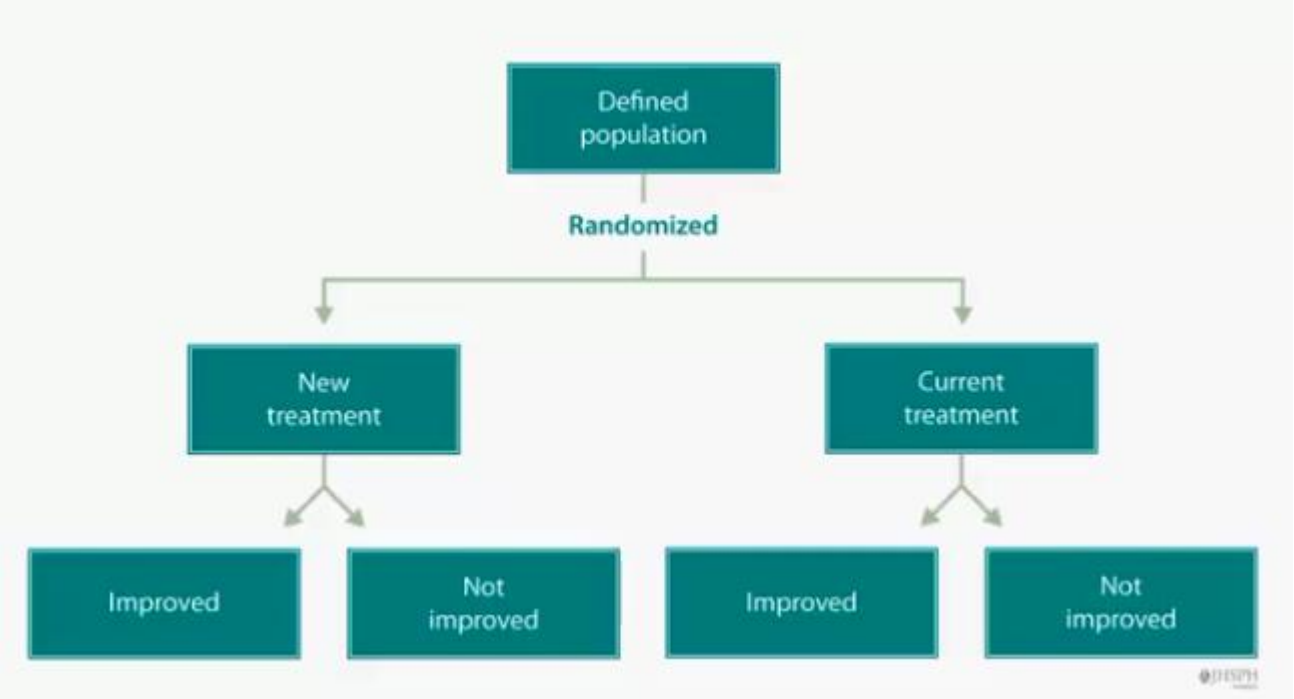
- **Comparison structure trial**

Compare experimental group to control group.

- Parallel

Each person is randomly assigned to only one treatment group.

Use randomization to remove treatment selection bias and promote comparability of treatment groups.



- Crossover

Randomization of order in which treatments are received.

Each patient takes two or more treatment in different order.

Each patient serves as his/her own control.

Advantages:

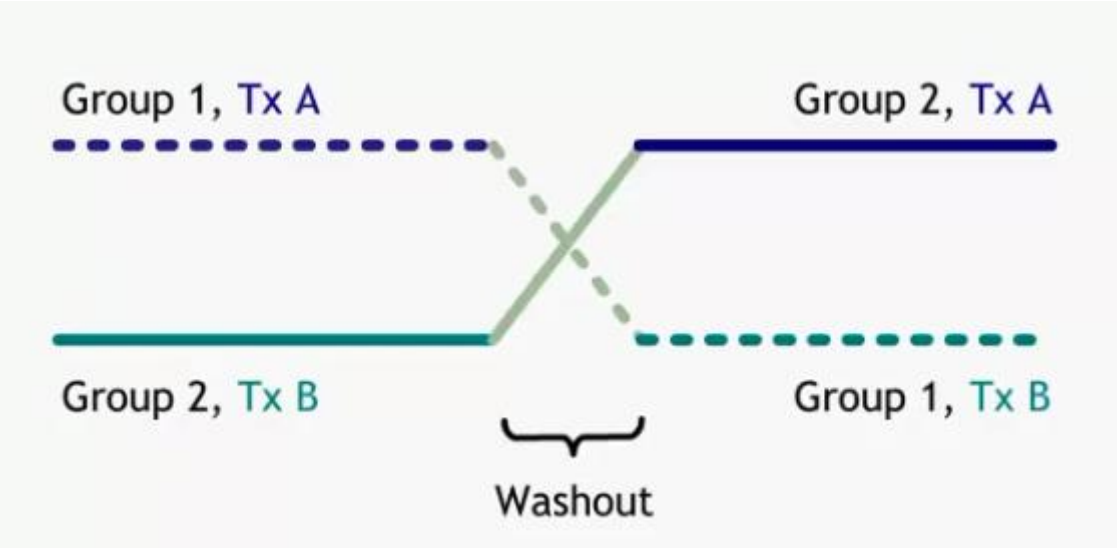
- Variability reduced because less variability within patient than between patients.
- Fewer patients needed.

Disadvantages:

- Treatment cannot have permanent effects or cures
- Potential carry-over effects of first period treatment to second treatment
- Test for period by treatment interactions not powerful
- Dropouts more significant: if lose a participant, lose information from all treatments for that participant.
- More difficult

Uses:

- Constant disease: asthma, hypertension, arthritis
- Short-term treatment effects
- Metabolic, bioavailability, or tolerability studies. Sometimes in early phases of studying a drug.

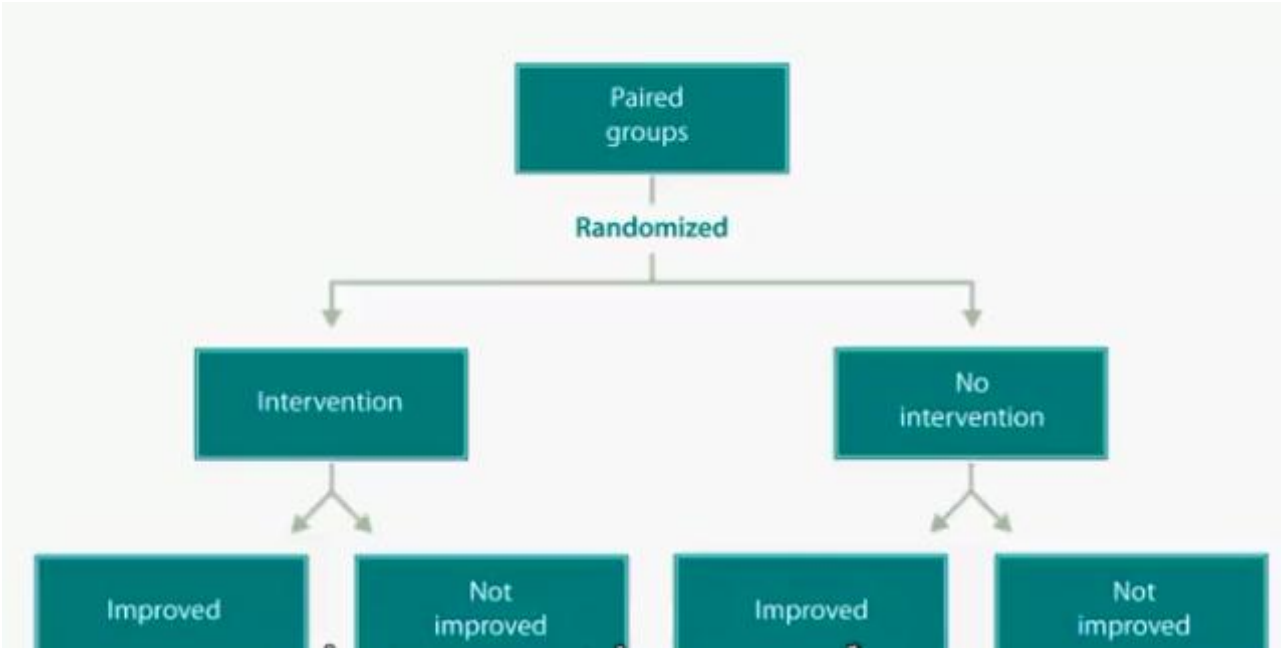


- Group allocation (cluster randomization)

  Randomization unit[1] is a group of individuals (community, school, clinic)

  If there is a correlation in the responses within a group, design loses some efficiency (more individuals required).

  It is used when individual randomization is not practically feasible or when it is taught to be unacceptable.



■ Extension of the parallel design

- Factorial

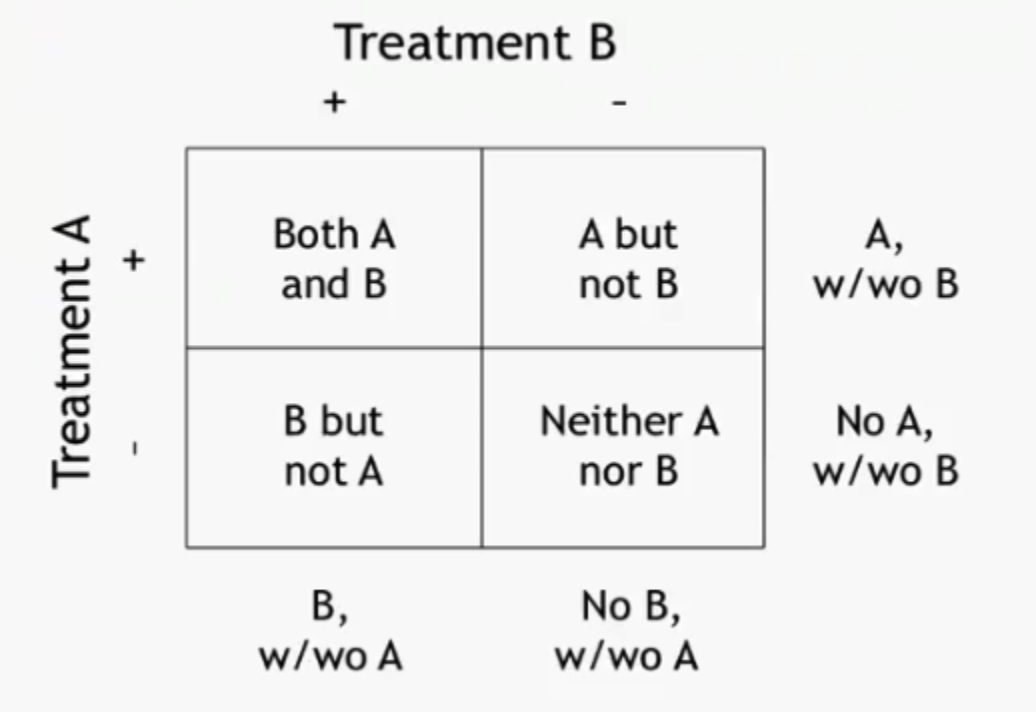
  Test two or more experimental interventions simultaneously.

  A vs. control of treatment A; B vs. control of treatment B; …

  - Economical : the most common reason
  - Can be used to test the interaction between treatment A and B

[1] Randomization unit: the level of which the randomization is applied.

In fact, we usually assume there is no interaction between the treatments and they have independent mode of action.



- If interested in interaction: B | A vs. not B | A (usually not powerful unless the sample size is large enough)
- If not, A vs. not A, regardless of assignment to B

- Large simple design
  - Very large sample size (usually tens of thousands)
  - To detect modest benefits or small clinical effect
  - There are unlikely to be many treatment interactions
  - Less precision (more error, increased variance)
  - Easily administered intervention
  - Easily ascertained outcome
  - Has very limited data collection at baseline

- We have to have confidence that simple data will be persuasive enough

- **Testing for hypothesis other than superiority**
  - We might think treatment A as good as or the same as treatment B for treating or preventing a specific condition. But we believe that the use of treatment A might have other kind of benefit such as less severe adverse events, or A might be cheaper than B.
  - Head-to-head comparisons of two or more established treatments for a specific condition.

- Equivalency

  Trying to demonstrate the equivalence of the two treatments, instead of which one is better.

  - How large can the difference be between two treatments
  - We want the difference between treatments within a certain small margin in order to call the two treatments equivalent.
  - Large sample size is needed.

  Hypothesis testing

  - Null hypothesis: there is a difference
  - Alternative hypothesis: there is no difference
  - Type Ⅰ error: showing no difference when there is one
  - Type Ⅱ error: showing a difference when there is not one
  - Two-sided

- Non-inferiority

  To determine whether A is at least as good as B.

Null hypothesis: A is worse than B.

It is one-sided.

It does not require as large a sample size as equivalency trial. But level of confidence is lower.

- **Adaptive design**

➢ Adaptive

Definition: a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypothesis based on analysis of data (usually interim data) from subjects in the study.

- Adaptations are planned and detailed before data are examined.

  + define adaptation trigger in protocol

  + define adaption

Possible adaptations:

- Randomization probabilities
- Sample size
- Visit schedule

  + shorten/lengthen follow-up time

  + change number or timing of visits

  + treatments (dose/duration, concomitant meds)

- Hypothesis tested

  + non-inferiority to superiority or vice versa

  + population (eligibility criteria)

+ outcomes (measure, timing, order of primary/secondary, components of composite)

+ analytic methods (covariates, model)

Advantages

- Flexibility
- May be more efficient (shorter duration, fewer people) (not necessarily so)
- May be more likely to show effect if one exists

Limitations

- Difficult to explain design and interpret results
- Rely on interim results to change trials
- Provide interim information on efficacy and safety to investigators and sponsor
- Hard to implement

  + need quick access to data

  + extensive documentation