DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL | Harvard Pilgrim Health Care Institute

CLINICAL EPIDEMIOLOGY AND POPULATION HEALTH

Key Points – Randomized Controlled Trials

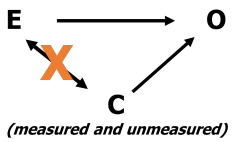
I. A randomized controlled trial (RCT) is an *experiment*. In its purest form…

- The researcher controls the exposure.
- In a 2-arm RCT, the researcher starts with two groups of comparable subjects (randomly assigned to a given study arm) and exposes one group to Intervention A and the other group to Intervention B (or placebo), under identical circumstances.
- This approach allows the researcher to isolate the effect of the intervention, measure it, and usually attribute the intervention as the cause.
  - ***Random assignment eliminates potential confounding because it ensures there is no correlation between the exposure and any confounders!***

II. In human clinical trials it is, of course, impossible to exert the type of control of subjects possible in a laboratory. In human trials, we do the best we can to:

A. Control the exposure.
B. Distribute the potential confounders, both known and unknown, equally in the study's groups through random assignment.

III. Key aspects of clinical trials include:



A. *Randomization* (random assignment of the exposure), if successful, eliminates potential confounding because it ensures there is no correlation between the exposure and any confounders (observed or unobserved).
B. *Blinding:* Prevents bias
   - Types of blinding
     - Only subject is blinded = "single blind."
     - Subject & researcher (including those measuring the outcomes) are both blinded = "double blind."
     - Subject, researcher, and data analyst = "triple blind."
   - Examples of bias in non-blinded trials:
     - Knowledge of intervention influences medical treatment.
     - Knowledge of intervention influences assessment of outcome.

IV. Subjects don't always get the full intervention. Sometimes they may even switch ("cross over") from one arm of the study to another. How should we analyze the data?

A. *Per protocol* analysis includes subjects who actually completed all aspects of the study as assigned (e.g., took the medication for the entire period, participated in all sessions of a behavior change intervention). This analytical approach may overestimate benefit (resulting in bias), since it does not account for the reasons that study subjects stopped taking active therapy or began taking it if in the placebo arm. If these reasons for switching arms also predict outcomes, they are now confounders because they are associated with both exposure and outcome.
B. *Intention to treat* (ITT) analysis includes all patients assigned to each arm at randomization (not just those who completed the trial, had good adherence, did not have side effects, etc.). This analytical approach is a better reflection of the likely benefit to a patient in the real world

(outside the study) - and is the preferred primary analysis. Because exposure was randomly assigned, there cannot be confounding in this case.

C. Ideally, we want the per protocol and ITT populations to be very similar – when we do our ITT analysis, most or all of the intervention participants actually got the intervention, and most or all of the control participants did not. To maximize our chances of such "good compliance," investigators have very stringent research protocols and may have very strict inclusion criteria for study subjects, restricting enrollment to participants who are very likely to maintain their assignment. This approach, however, might limit generalizability.

V. Design Features

A. Levels of randomization:
- Individual randomization – each person randomly assigned, independently of the prior person's assignment
- Cluster randomization – groups of people within a pre-determined category are assigned together (e.g., all patients receiving care at a given hospital, one physician's practice, children all attending the same school). This approach reduces the chance of contamination, but also reduces power, which means you need a larger sample size than randomization at the individual level.

B. Ways to ensure good numerical balance of participant characteristics in the treatment and control group. *These are all just specialized approaches to ensuring that confounding is minimized.*
- Stratified randomization – investigators randomize subjects within strata of a third variable or risk group (e.g., separate randomization schema for men vs. women, or for those under vs. over age 50).
- Matching – investigators match individual participants (or in the case of cluster randomization, similar hospitals or physician practices) based on certain observable characteristics (to create pairs of similar participants) and then randomize one of each pair to the treatment and one to the control group.
- Block randomization – similar to stratified, but typically grouped into blocks according to a variable not of interest to the researchers (most often, time – e.g. block the first 100 patients recruited then randomize within that group so that 50 are assigned to intervention and 50 to control… then do the same thing with the next 100, etc. This keeps you from having the bad luck that, for example, most of your intervention subjects are assigned early and most of your control subjects assigned later in the study, if things like season, or secular changes in care would matter for your outcome.

VI. Strengths of randomized trials

A. Strongest design for internal validity.
   i. Best for control of bias (if blinded) and confounding
   ii. Analysis and statistical testing are often straightforward.

VII. Potential Limitations of randomized trials:

A. *Generalizability*, a.k.a. *external validity*.
   i. Often research subjects are not representative of other patients and external validity is poor..
      - Can be limited by restrictive selection criteria.
      - Those who volunteer may be quite different from those who don't.
      - There is often a tradeoff between internal validity and generalizability.

   ii. Trials might assess the *efficacy* of an intervention - its effect under tightly controlled conditions.
   iii. In contrast, *effectiveness* describes how the treatment works in actual practice.

- For example, a weight-loss program may work well when patients are hospitalized on a nutrition research ward (high efficacy) but may work less well in actual practice with free-living individuals (low effectiveness).

B. Cost.
C. Feasibility.
D. Ethical issues. (For example, you can't randomize people to smoking vs. non-smoking)
    i. There is an expectation that researchers be in "equipoise" about the two arms of an intervention. That is, to conduct the trial they must not have knowledge that one arm is substantially better than the other.
E. Sometimes, despite randomization, subjects in one arm of a clinical trial may not be similar to subjects in the other arm at baseline – by bad luck your randomization failed! Maybe your sample size was too small, or maybe you should have done stratified or block randomization.
    - In this case, you might apply the techniques from observational epidemiology for analysis of these data from a clinical trial, even though it is a controlled experiment. Thus, you might stratify, match, or do multivariable modelling using the RCT data.

VIII. Number needed to treat (NNT)

A. The NNT is a calculation that estimates how many individuals need to be exposed to an intervention to see the outcome of interest.
    - If the intervention is a treatment, then the outcome will be a beneficial one, e.g. cure of infection
    - If the outcome of interest is adverse, e.g. a side effect of a medication, we might call it the number needed to harm (NNH). If the exposure is a screening test, we might call it the Number Needed to Screen (NNS). The math is the same.
B. You can calculate NNT either from a randomized trial or an observational study comparing two treatment alternatives
C. Calculated as the reciprocal of the risk difference (aka attributable risk) = 1/RD
D. E.g. consider a randomized trial of the efficacy of adding a new inhaler to the usual maintenance treatment of asthma, compared with usual treatment + placebo
    - 15% of patients on placebo had an exacerbation vs. 10% with the new inhaler during a 1-year follow-up
    - Treatment difference (= risk difference, attributable risk) = 15% - 10% = 5%; that is, five patients are prevented from exacerbation for every 100 patients who added the new inhaler over 1 year instead of adding placebo
    - The NNT is then simply 1 / (15%–10%) = 1/(0.15-0.10) = (1/0.5) =20. You would have to treat 20 individuals with the new inhaler to prevent 1 person from having an asthma exacerbation over 1 year of follow up.