

Randomized Controlled Trials (Experimental Studies)

Second Edition Authors:

Lorraine K. Alexander, DrPH

Brettania Lopes, MPH

Kristen Ricchetti-Masterson, MSPH

Karin B. Yeatts, PhD, MS

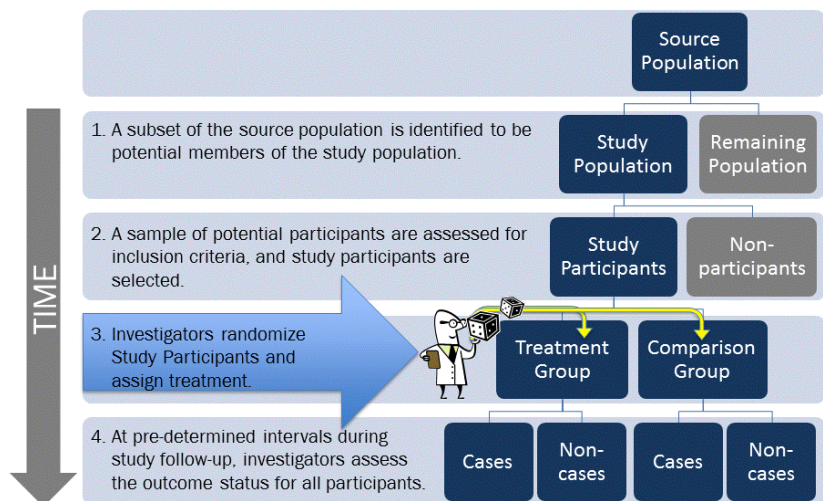
What are randomized trials?

Randomized trials are epidemiological studies in which a direct comparison is made between two or more treatment groups, one of which serves as a control for the other. Study subjects are randomly allocated into the differing treatment groups, and all groups are followed over time to observe the effect of the different treatments. The control group may either be untreated (*placebo-controlled*) or undergo a “gold standard” established regimen against which the new regimen will be assessed (*active-controlled*). Randomized trials provide the most direct evidence for causality. However, they are also fraught with a number of additional considerations not present for observational research.

For example, unless researchers are genuinely uncertain about the potential harms or benefits of a treatment, it is unethical to assign it to one group of people while withholding it from others (*equipoise*). This limits the types of questions that can be answered using experimental studies.

A *placebo-controlled* randomized trial might compare the effect of vitamin E supplement in one group of schizophrenia patients (the treatment group) against the effects of a placebo on a separate group of schizophrenia patients (the control group).

An *active-controlled* randomized trial might compare diabetic patients with implanted insulin pumps against diabetic patients who receive multiple insulin injections (the control group).



Randomized Trial Study Design

Randomization

Randomization avoids bias by eliminating baseline differences in risk between treatment and control groups. Randomization, if done properly, should make both groups similar in terms of the distribution of risk factors, regardless of whether these risk factors are known or unknown (thus eliminating confounding due to both measured and unmeasured variables). The larger the randomized groups, the greater the probability of equal baseline risks. However, participants in RCTs are often not representative of the target population, which introduces selection bias and limits generalizability.

Methods of randomization

There are different ways to randomize study participants into treatment groups. A simple way to randomize would be to roll a die or use a random number table to allocate individuals into the different groups. Another way investigators randomize study participants is through stratified random allocation. Under this method, the investigator first stratifies the participants by a baseline risk factor (i.e., smoking status) then randomizes the subjects in each stratum into either the treatment or control group. Stratified random allocation is appropriate when the investigator wants to be sure that a strong external risk factor is equalized at baseline between treatment and control groups.

Types of randomized trials

The two general types of randomized trials are *clinical trials* and *community trials*, with randomized clinical trials being by far the more common. A randomized clinical trial is an experiment with patients as subjects. The goal is to find an effective treatment for a disease or to evaluate an intervention to prevent the progression of a disease. Randomized clinical trials are often used to evaluate the efficacy of new drugs against standard treatments or against placebos, but they are also used to evaluate other therapeutic procedures such as a new form of surgery, a dietary regimen, or an exercise program for persons with pre-existing disease. Most often, patients who already

have some specific disease are the subjects of study in clinical trials. However, at times, subjects who are at high risk for a specific disease are entered into a randomized clinical trial to assess the efficacy of a drug to prevent the disease. For example, women with a family history of breast cancer may be entered into a clinical trial to study the effect of the drug tamoxifen on the prevention of breast cancer.

A community trial is also an experiment, but differs from clinical trials in that an entire community, rather than an individual patient, is the unit of observation. For example, water fluoridation was evaluated by experimentally assigning entire communities to have their public water supply fluoridated or not fluoridated. Units of observation for a community trial may be a town or city, a factory or office, a classroom or an entire school. All persons in the same unit of observation are experimentally exposed to the same intervention although it is not certain that all persons in the unit will be equally exposed, e.g. that they will drink the fluoridated water coming from their taps. Several community trials have been conducted to evaluate the effectiveness of mass media campaigns to prevent heart disease by encouraging more exercise, less use of tobacco products, and other lifestyle modifications.

Blinding or masking

Sometimes in clinical trials, participants, statisticians, and even investigators, are made unaware of whether the participants are part of the treatment or control group. When only study participants are unaware of their treatment status, but investigators and analysts are aware of treatment status, the trial is called *single-blinded*. When both the participants and the investigators are blinded as to the treatment status of the participants the trial is termed *double-blinded*. A *triple-blinded* trial is when subjects, investigators, and independent statisticians are kept unaware of subject treatment status.

Blinding the study participants by using placebos, or a sham treatment, is common practice in clinical trials. The

placebo effect occurs when participants report a favorable response when no treatment, but only placebo, is administered. Another bias that is prevented by blinding of subjects is *post-randomization confounding bias* where subjects' awareness of intervention may motivate them to be more cooperative or otherwise change their behavior. This motivation may correlate with other risk factors for the intended effect, thus destroying the design advantage of randomization.

Example

If individuals participating in a clinical trial to study the efficacy of a new weight loss drug are aware that they are receiving the weight loss drug, they may more closely comply with the prescribed study diet.

Another bias that is controlled for by blinding the subjects as to their treatment status is *selection bias*, or group differences in loss to follow-up. Symptoms of disease or side effects of the treatment may influence rates of loss to follow-up in subjects aware of their treatment status.

Bias due to differences in reporting of symptoms, a type of *information bias*, is also controlled by a double-blinded study. Study subjects who are aware of their treatment status may differentially report symptoms or side effects. Likewise, staff or statisticians may differentially evaluate subjects if they are aware of treatment status.

Example

In a study of the effects of a new drug on severity of migraines in which study members know their treatment status, the treated study members may believe that the drug will work and, therefore, report less severe migraines. If the investigator in this study knows the treatment status of the subjects, then that investigator may scrutinize the severity of the migraines in treated subjects more than that of the untreated subjects.

Additional threats to the validity of a randomized trial

Limiting the analysis to compliant subjects can create bias if compliance is correlated with other risk factors for the treatment effect. Analyzing the results without regard to subject compliance (called "intention-to-treat" analysis) can help to avoid this bias. That is, subjects should be included in the analysis whether or not they adhered to their treatment (or control) regimen.

Example

Suppose that in a clinical trial to look at the relationship between diet and risk of cancer, subjects were randomized to either a cancer-prevention diet or to a placebo diet. Suppose again that in the treatment group, those subjects with gastrointestinal symptoms that are precursors of cancer, were less compliant with their diet than subjects without symptoms. Exclusion from the analysis of the less compliant subjects would bias the results towards reporting a greater effect of the cancer-prevention diet. Only those subjects who were not at risk or who were at low risk of cancer would be included in the analysis. The appropriate analysis should include all persons originally assigned to their treatment group, whether or not they adhered to the treatments.

When noncompliant subjects are selectively excluded from an analysis, the benefit of randomization is lost, because unmeasured confounding factors may be associated with the lack of compliance.

Treatment crossover

Crossover, either planned or unplanned can create biases in experiments. In a *planned crossover*, group A (subjects treated with the new drug) and group B (subjects treated with a standard drug) would be switched to the other treatment at the midpoint of the trial. Two of the problems experienced with this experimental design are *carryover effects* and *diminished interest*. Carryover effects occur when the effects of the first drug last into the second half

of the study when the subjects are receiving the other treatment. Bias may also occur if there is diminished interest or lack of compliance in the second half of the study.

Unplanned crossovers occur when a clinician decides to switch a study member from the control to the treatment group, or vice versa, e.g. surgery vs. medical treatment for coronary artery disease. An unplanned crossover negates the benefit of randomization and introduces bias if switching is related to risk of the outcome.

Loss to follow-up

Neither randomization nor blinding can prevent *differential loss to follow-up*, or more subjects dropping out in one treatment group than in another. Bias is introduced if the rate of loss to follow-up is correlated with both exposure to the treatment and exposure to other risk factors for the outcome.

Threats to validity:

Loss to follow-up
Non-compliance
Crossovers

Analysis strategies to avoid bias

For purposes of analysis, study subjects should be kept in the original randomized group, even if they were lost to follow-up, switched to the other treatment group, or were non-compliant (the "intention-to-treat" principle). Analysis of any non-random subgroups threatens the validity of the study.

Practice Questions

Answers are located at end of this notebook.

1) Researchers conducted a multi-year ongoing randomized controlled trial of the association between daily meditation (such as relaxation techniques) and health behavior among patients following a skin cancer diagnosis. Researchers randomly allocated study participants into 2 groups. The first patient group received weekly classes on meditation practices as well as a self-taught manual on meditation. The second patient group

received only the self-taught manual on meditation. Data were collected at set intervals following the intervention to assess the patients' health behaviors. Studied health behaviors included data on the patient's diet, exercise, and mental health. Note: this is a hypothetical example.

a) In this example, why was it ethical for the researchers to allocate one group to receive weekly classes on meditation practices as well as a self-taught manual on meditation while the other group received only the self-taught manual on meditation?

b) Which of the following may bias the analysis? Choose all that apply.

- a) Changes over time in how the health behaviors were defined and assessed
- b) Inability to blind the researchers regarding which of the 2 meditation interventions each patient received
- c) Lack of use of a separate untreated control group (e.g. a group that received no meditation intervention at all)
- d) Patients that are not compliant with their assigned group (e.g. patients assigned to just the self-taught manual but who really want to be as healthy as possible so they show up at the weekly classes on meditation practices)

c) In this example study, would stratified random allocation have been useful?

References

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Answers to Practice Questions

- 1)** In this example, researchers must be genuinely uncertain about the potential benefits of mediation in order for it to be ethical to assign different meditation interventions to different groups. If the effect of meditation on health behavior has not been extensively studied in this study population, then that would make it ethical to conduct this study.
- b)** Answer choices a, b, and d are correct. If researchers make changes in how they assess health behaviors over time, that would bias the results of the study. If researchers are not able to be blinded in regard to which patients are in which intervention group, this may lead researchers to assess or question the study participants about their health behaviors in different ways depending on which group they are in. Randomization works to eliminate baseline differences in risk between the 2 groups being compared. If some patients are not compliant with the group they were randomized to, this can negate the benefits of randomization. Lack of use of a separate untreated control group does not introduce bias into the study. The comparison groups are chosen based on the researchers' study hypothesis and based on what is ethical. If the researchers wanted to study the effect of weekly meditation classes + a self-taught manual on mediation versus just the self-taught manual on meditation then this is a valid study hypothesis.
- c)** Stratified random allocation may have been useful. Stratified random allocation is when the researchers first stratify participants by a baseline risk factor and then randomize the subjects in each stratum into the 2 comparison groups. Stratified random allocation can be done when the researchers want to be certain that a strong external risk factor is equalized at baseline between the 2 comparison groups. In our hypothetical example, researchers may have hypothesized that those participants who had strong family support would be more likely to learn and adopt meditation practices and more likely to have positive health behaviors. So the researchers could have first stratified participants based on the level of family support they reported and then, after that, randomized subjects into the 2 comparison groups.

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