

Randomized Control Trials (Experimental Studies)

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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.

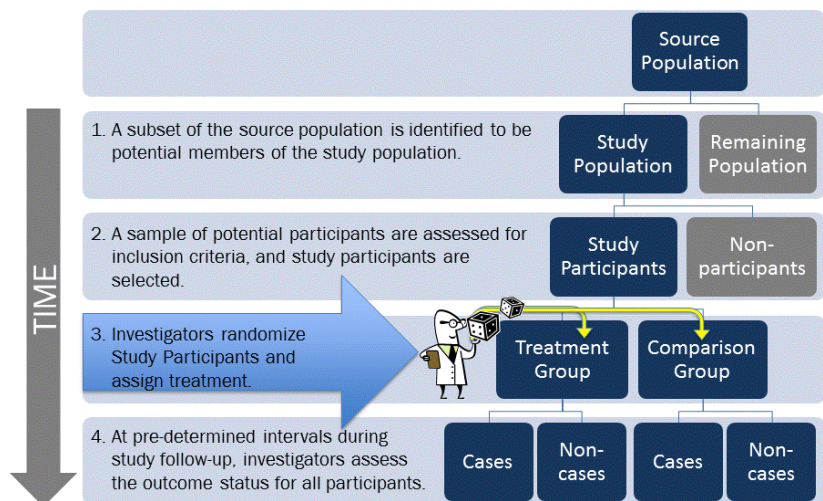
For example, unless researchers are genuinely uncertain about the potential harms or benefits of a treatment, it is unethical to assign it to one group of people while withholding it from others (*equipoise*). This limits the types of questions that can be answered using experimental studies.

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).



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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.

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