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Target audience this issue:

- ✓ *Classroom faculty*
- ✓ *Clinicians*
- ✓ *EIP instructors*

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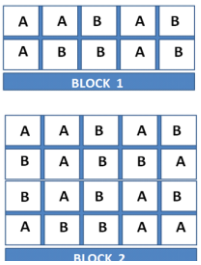
Randomized Controlled Clinical Trials

When searching for primary research papers, one consideration is whether a particular paper that you have found has the best research *design* to answer your question. It is important for the practitioner to understand that different study designs offer different *levels of evidence* to support or refute the benefits of a particular treatment. *Randomized controlled clinical trials* (RCTs) are generally the first choice when searching for studies on treatment, but RCTs are either scarce or not suitable for questions about health risks, prognosis, or the accuracy of clinical tests.

RCTs are carefully planned experiments that introduce a treatment or exposure and then measure its effect on patients over time. RCTs are designed to reduce the potential for bias (e.g., by randomization and blinding) and allow for an even-handed comparison between intervention groups and comparison groups. Well done RCTs can provide sound evidence of cause and effect or help validate the benefits of one treatment compared to another. Their weakness is that because they are generally small and so tightly controlled their results are not always generalizable to the larger public, and frequently the treatments underperform or fail when applied on a large scale.

Randomization has two main advantages: 1) It eliminates bias in the selection of which subjects get which treatment (or placebo)--but only if randomization is coupled with *concealed allocation*! 2) It attempts, based on the laws of probability, to evenly distribute potential baseline characteristics (which can act as *confounders*) that might give one group an advantage over the other, obscuring the true value of the intervention itself. Inappropriate randomization can lead to overestimation treatment effects up to 40%. (Schul 2003)

Simple Randomization. The coin flip is one of the most basic methods of simple randomization. More commonly, random number sequences can be generated by a computer or lifted from a random number table found in a statistics book. One problem is that these methods can lead to an uneven number of subjects in each group (20 heads and 30 tales) especially if the sample size is small. Likewise, key baseline characteristics may be unevenly distributed (e.g., more men in one group, or subjects with poorer prognosis). (Manchikani 2008)



Block randomization. This method is used to ensure even out group numbers as the trial progresses. After a block of 10 participants are randomized, 5 would be allocated to each arm of trial. Then a block of 20 participants could be assigned, with 10 allocated to each arm. The numerical balance is improved but the allocation toward the end of each block can become predictable. Even though the order of interventions varies randomly within each block, a person running a trial could deduce some of the next treatment allocations if they discovered the block size.

Help your students understand the importance of study design outcomes when reading clinical research evidence.

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Even with block randomization, groups may be generated that are not comparable in terms of key *covariates*. In this context, a covariate is a factor that, if present, might change the outcome and obscure the true relationship between a treatment and its observed results. For example, comorbid medical conditions can confound the data and generate misleading results. In small trials, sample size and covariates must be balanced or at least "adjusted" for in the final statistical analysis.

Stratified randomization. Subjects are grouped into "strata" based on subject characteristics. These characteristics could be age, sex, or known co-variants that would act as confounders. Then each strata (e.g., all patients with chronic symptoms vs acute) is randomized into even blocks making up the intervention and control arms of the trial. The stratification is done by an independent center. Although stratified randomization is relatively simple and effective (especially for smaller clinical trials), it may not be practical if there are too many covariates.

Other methods of randomization include rolling dice, drawing different colored balls, and drawing of ballots from an opaque bag. Examples of inadequate methods are alternating subjects, birth dates, social insurance/security numbers, dates they are invited to join the study, or hospital registration numbers. (Furlan 2009)

RCTs: What kind of comparison?

The comparison used in an RCT can vary depending on the goals of the study.

A treatment invention may be compared to

- A placebo or sham treatment that closely mimics the "active" intervention
- A "watchful waiting" or waiting list group to representing natural history
- An approach identified as "usual care" (sometimes the intervention *plus* usual care is compared to usual care alone)
- Another "active" intervention that is currently used in practice thought to be effective. In pragmatic studies two entire treatment approaches may be compared (e.g., usual medical care for low back pain vs "chiropractic" care).

Teaching Tip: Students may misinterpret what can and ***cannot*** be concluded from an RCT. When two active treatments are compared to each other, evidence may support one treatment over the other in a particular group of patients —but this is not evidence that the *treatment is more effective than natural history alone (i.e. doing nothing)*. Likewise, a study demonstrating that a particular exercise program is more effective than a waiting list provides evidence that the *totality* of the intervention was superior to doing nothing, but we cannot say whether the benefit was due to that specific intervention, increased physical activity in general (could be *any* activity), a placebo effect, or the extra *attention* from the providers. The conclusions one draws from reading a study are limited, in part, by the design and goals of the study itself. ***When reading an RCT (or discussing a study with a student), it is important to define clearly what the goal of the study was!***

Furlan AD,Pennick V, 2009 Updated Method Guidelines for Systematic Reviews in the Cochrane Back Review Group, Spine 2009;34:1929–1941

Manchikanti L, Hirsch JA, et al. Evidence-Based medicine, systematic reviews, and guidelines in interventional pain management: Part 2: Randomized Controlled Trials, Pain Physician 2008;11:6:717-773

Schul KF, Grimes DA. Allocation concealment in randomized trials: Defending against deciphering. Lancet. 2002;359:614–8. [PubMed] [Google Scholar] There are a number of ways to achieve randomization.