Review

A Simple Guide to Randomized Controlled Trials

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Abstract

Randomized controlled trials represent the cornerstone for the regulatory approval of drugs and evidence-based medicine and policy. Compared with observational studies random assignment of participants to each study arm guarantees an equal distribution of potential confounders thus achieving impartiality in the evaluation of between group differences and allowing for causal inferences to be drawn. These complex and costly medical experiments are tightly regulated and require substantial planning with great attention to several methodological aspects ranging from allocation concealment and blinding to sample size estimation, statistical analysis, and handling of protocol deviations. This brief guide offers useful insights into the design, conduct, and interpretation of clinical trial findings for beginners.

Keywords

randomized controlled trials, interventional studies, clinical trials

Randomized controlled trials (RCTs) are an experimental (or interventional) study design used to test efficacy claims predominantly for pharmaceutical products, but covering also several other types of medical, dietary, or psychosocial interventions such as surgical procedures, devices, and behavioral counseling. Compared to observational studies RCTs are considered at the pinnacle of validity because they can eliminate confounding and thus establish causality. Along with systematic reviews and metaanalyses,[1] they represent the highest level of evidence in therapeutic decision making.

In a clinical trial, participants are recruited and followed prospectively while an active intervention is administered and assessed forward in time against an appropriate control (Figure 1). The random allocation of subjects to either the intervention or control arms ensures that all groups are comparable with respect to baseline characteristics and therefore intergroup differences at the end of the trial can be safely attributed to the intervention under evaluation. In other words, the randomization balances out all measured and unmeasured prognostic factors and protects against selection bias.

Formulation of the Research Question

Transforming a clinical scenario into a well-structured research question should be thoroughly planned in advance, because it sets the stage for the entire research endeavor.[2] The PICO format (ie, Population, Intervention, Comparator, Outcomes) serves as a good starting point to formulate the research question. The study population is a priori-defined based on unambiguous inclusion and exclusion criteria. The impact that these criteria will have on study design, ability to generalize, and participant recruitment must be taken into account. Broad eligibility criteria could lead to a heterogeneous sample of trial participants complicating the generalizability of study findings to certain subsets of patients. On the other hand, a narrow focus approach makes the trial less pragmatic, while meeting recruitment targets might be more arduous. Moreover, from an ethical perspective, the investigators might want to avoid the

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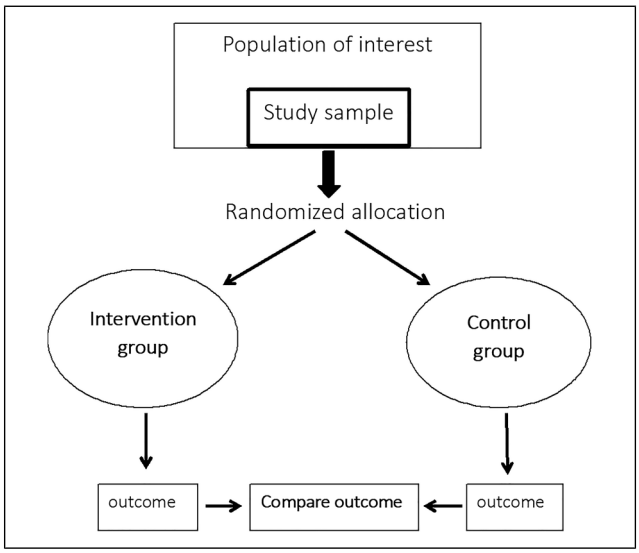

Figure 1. The basic structure of a randomized controlled trial.

enrollment of subjects that could be exposed to undue health risks such as pregnant women or people with certain comorbidities.

The clinical trial is typically designed with a focus on a single primary outcome, whereas one or more secondary endpoints might be considered as well. Trial design is centered on the primary questions in which investigators are more interested in and are capable of answering. Secondary outcomes are complementary to the main question and are used to generate future research hypotheses. Regarding the choice of an appropriate outcome, surrogate markers are less invasive and easier to measure and can reduce the size and duration of the trial, nevertheless, the translational potential to hard clinical endpoints might be limited. Examples of surrogate endpoints include changes in glucose or cholesterol levels and bone mineral density, whereas rates of cardiovascular events and fractures respectively can be referred to as substantive outcomes. There is growing agreement that for a specific field a standardized collection of outcomes should be measured and reported at a minimum, known as a core outcome set (https://www.comet-initiative.org/).[3] Of note, composite endpoints are often employed by combining multiple interrelated outcomes into a single measure. Composite endpoints can yield more precise treatment effects and reduce the required sample size, although clinical interpretation of the findings might become challenging.[4]

When developing clinical trial protocol researchers should have the FINER framework in mind, an acronym that stands for Feasible, Interesting, Novel, Ethical, and Relevant.[5] The proposed study should not only make a significant contribution to the current state of knowledge but also have a meaningful impact on clinical practice. The research plan should offer value for money and investigators should ensure timely and adequate patient recruitment while safeguarding the well-being of participants and implementing contingency measures to attain recruitment targets. Evaluation of grant proposals often relies on the FINER criteria. Moreover, the PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary 2) tool can help trialists through design decisions across 9 domains including eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis.[6] Based on the rating of each domain the trial might adopt different directions: either explore the effectiveness of an intervention under a real-life setting (pragmatic approach) or try to establish efficacy in ideal conditions giving the intervention under evaluation its best chance to demonstrate a beneficial effect (explanatory approach). Finally, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guideline outlines all necessary items to be included in a clinical trial protocol.[7]

Phases of Clinical Trials

Before a clinical trial is undertaken candidate drugs are extensively tested in preclinical studies including cell cultures and animal models to gather initial data about efficacy, toxicity, and pharmacokinetics. Phase I clinical trials, also known as first-in-human studies, recruit only a limited number of healthy volunteers with the aim of assessing the safety of the drug product. Phase II clinical trials are also known as proof-of-concept studies because they aim mainly at establishing the efficacy of the investigational drug in vivo, while obtaining more information about safety. Phase III clinical trials are large randomized experiments designed to explore the effectiveness of the investigational product in comparison with other approved therapeutic options. Trial results from this phase inform the regulatory approval. Of note, only a limited number of medicinal products make it from the bench to the bedside, because during this meticulous process, the vast majority of candidate molecules are rejected. Phase IV clinical trials are postmarketing surveillance studies that are sometimes imposed by drug regulators to monitor potential long-term adverse effects.[8]

Randomization

Various types of randomization are available[9]:

- *Simple randomization:* This method is equivalent to tossing a coin and is usually sufficient for large sample sizes (over 100 participants).
- *Blocked randomization:* For smaller sample sizes participants can be randomized within blocks to

ensure equal numbers in each intervention group thus minimizing potential numerical imbalance due to chance. To limit the predictability of blocked randomization, particularly in open-label trials investigators could use variable block sizes or start with an uneven block size or a simple randomization element. Importantly, the block size should never be disclosed to recruiting sites.

- *Stratified randomization:* This is a two-stage procedure in which patients who enter a clinical trial are first grouped into strata according to important baseline characteristics that could influence outcomes. Within each stratum, patients are then assigned to interventions according to separate randomization schedules. For instance, it is regarded as good practice to use stratified randomization per study site for multicenter trials to avoid variation in the delivery of care.
- *Minimization:* Using this method a small number of participants are first allocated at random and subsequently, as the groups build up, subjects are deliberately assigned with a weighted probability to each group depending on the characteristics of those already allocated. Minimization and other baseline adaptive randomization designs such as biased coined methods can virtually guarantee balance with respect to predetermined prognostic covariates.

Allocation Concealment and Blinding

Allocation concealment prevents foreknowledge of treatment assignment before a decision is made to participate in a clinical trial. In this regard, allocation concealment protects the random sequence working in tandem with randomization.[10] Without proper concealment the effect of randomization is obliterated and such studies are commonly referred to as "pseudo-randomized." Adequate methods to achieve allocation concealment include (Table 1):

- Sequentially numbered, opaque, sealed envelopes (SNOSE).
- Central computerized or interactive voice response system (IVRS).
- Sequentially a number of drug containers prepared by an independent pharmacist, which can be useful for randomization in the setting of a medical emergency.

On the contrary, blinding (or masking) protects treatment allocation after the randomization minimizing bias in the ascertainment of the outcomes. Patient-reported outcomes (eg, pain levels) are especially prone to lack of blinding. The utility of placebo and active-controlled trials is presented in Table 2. Although allocation concealment is always possible, blinding might be impractical due to the nature of the intervention (eg, invasive procedures).

Table 1. Relative merits and drawbacks of techniques used to conceal the random sequence.

Technique	Advantages	Disadvantages
Sequentially numbered, sealed, opaque envelopes (SNOSE)	• Can be used in situations where randomization is immediate (eg, A&E) to avoid delay in the delivery of care • Might be useful for resource-limited settings	• The number of stratification variables is limited because multiple randomization lists are required for every covariate • Potential for subversion
Central computerized or interactive voice response system (IVRS)	• Easy to adopt randomization • Ensures concealment of the allocation sequence	• Uninterrupted telephone or internet access required

Table 2. Pros and cons of placebo- relative to active-controlled trials.

Comparator arm	Advantages	Disadvantages
Placebo	• Participants and practitioners blinded • Increased statistical power (smaller sample sizes required) • Subjective outcomes can be used • High internal validity	• Unethical if standard-proven therapy exists • Possible placebo effect • Low external validity
Standard of care or active treatment	• All participants receive some treatment • More ethically acceptable • High external validity	• Variation in the delivery of standard care • Reduced statistical power (larger sample sizes required) • Low internal validity

Nevertheless, even if blinding at the participant and provider levels cannot be implemented, masking of outcome assessors might still be possible. De-identified reports of clinical events are submitted to an independent panel of experts known as the Endpoint Adjudication Committee to be assessed in a standardized manner. Notably, sham operations have been occasionally utilized with major practice-changing implications.[11,12] For drugs with different appearance (eg, tablet or injection) the double dummy technique that involves the administration of 2 alternating, matching placebos can be utilized.[13] Template for Intervention Description and Replication (TIDieR) can facilitate the completeness of reporting for interventions in RCTs including the adequate description of placebo and sham controls.[14]

Losses to Follow-Up and Other Protocol Deviations

Losses to follow-up are unavoidable in the context of a prospective study and can occur for many reasons including lack of efficacy and need for rescue therapy, discontinuation due to adverse events, death, or consent withdrawal.[15] Ideally, attrition rates should be minimal and equally distributed among trial groups. As a rule of thumb discontinuation rates < 5% are considered acceptable, whereas attrition rates > 20% may considerably undermine the validity of trial findings. Large RCTs with long follow-up periods extending over several years are inevitably associated with higher discontinuation rates. Moreover, the impact of discontinuation rates must be considered in the context of the control event rate, particularly for rare events where even small drop-outs could significantly influence the observed outcomes. Study procedures should be streamlined to avoid overburdening of participants and maximize their retention. Moreover, a run-in phase to exclude nonadherent subjects who might be unwilling to return for follow-up visits is sometimes warranted. Participant flow into the trial should be depicted with a flow diagram.

There are 2 primary options for handling of missing data:

- *Intention-to-treat (ITT) or as randomized analysis:* Participants are analyzed as members of the initial randomization group to respect the randomization regardless of whether or not they received or completed the treatment. Although poor adherence may result in lower effect estimates and decreased study power, this conservative approach is more pragmatic and clinically relevant for establishing the real-world effectiveness of an intervention. Imputation methods are usually used to adjust for missing outcome data. The multiple imputation technique involves predicting the missing values based on all observed values in the dataset and is probably considered the least biased approach to handling of missing data. Conversely, single imputation methods that utilize replacement values such as the last observation carried forward (LOCF) are generally discouraged.[16]
- *Per protocol or as treated or complete case analysis:* Excludes all patients who deviated from the protocol, such as those who did not adhere to treatment, switched groups, or missed measurements. This approach gives insight into the efficacy of the intervention under ideal conditions, however, patients are analyzed according to how they self-selected rather than how they were randomized.

A novel approach to handling deviations from the intended course of treatment is the estimands framework.[17] Investigators are asked to prespecify the possible intercurrent events and plan in advance how they will be dealt with in the respective section of the protocol. An intercurrent event is an event of interest occurring after treatment initiation, which can affect the interpretation of the treatment effects in a study, such as a participant taking rescue medication or a participant prematurely discontinuing the allocated intervention. The most commonly applied strategies are:

- *Treatment policy strategy:* Resembling the ITT principle this strategy ignores the occurrence of intercurrent events and the observed measurements are included in the analysis irrespective of lack of adherence or use of rescue medication.
- *Hypothetical strategy* (*also known as trial product estimand*)*:* Values acquired after the occurrence of an intercurrent event are not included in the analysis and appropriate statistical modeling is used to estimate the treatment effect that would have been observed had the intercurrent event not occurred.
- *Composite strategy:* An intercurrent event is integrated into the definition of the outcome measure resulting in a composite endpoint.
- *While on treatment strategy:* For endpoints measured in multiple timepoints this strategy evaluates the treatment effect prior to the occurrence of the intercurrent event and subsequent data collection is terminated.

Sample Size Calculation and Statistical Analysis

One of the pivotal aspects of planning a clinical study is sample size estimation. If the sample size is too small, the trial will be underpowered to detect a statistically significant difference between the study arms, if it truly exists, wasting resources and ethically compromising participant involvement in a trial that is not adequately powered to answer the research question. Conversely, an unnecessarily large sample size can hinder the feasibility and funding opportunities of the trial. The following assumptions should be taken into account for sample size calculation[18]:

- *Level of significance* (*type I error*)*:* It represents the acceptable rate of false positive findings. The *P* value is usually set at .05, although lower values may be used as well.
- *Study power* (*type II error*)*:* Denotes how often a study will fail to detect a true difference. Power > 80% would be sufficient for most studies.
- *Effect size:* The minimally clinically important difference that investigators aim to detect between study groups. The larger the effect size that investigators are willing to detect, the smaller the sample size required. Large sample sizes are able to detect even tiny effect sizes, but the clinical utility of such small effects might be limited.
- *Standard deviation* (*for continuous outcomes*)*:* This is a measure of dispersion or variation in the measurements that investigators anticipate in the population studied. A smaller sample would be required for a homogenous population (low standard deviation) because in that case, it is easier to discriminate between true underlying effects from "noise" due to the dispersion of the measurements.
- *Control event rate* (*for binary outcomes*)*:* Prevalence of the condition under study in the population that is usually estimated from previous literature.
- *Drop-out rate:* The sample size will have to be inflated to incorporate the expected losses to follow-up.

The Statistical Analysis Plan (SAP) is a separate document that elaborates on information presented in the trial protocol. It includes a detailed explanation of the statistical methods and any underlying assumptions, defines the analysis sets, and outlines how missing data will be dealt with. The SAP may even contain mock tables and diagrams and is usually produced at a later stage after the protocol has been finalized and sometimes even after the initiation of the trial, but clearly, before unblinding occurs.[19]

Datasets from clinical trials are usually analyzed with linear regression models for continuous outcomes to estimate the between group difference in the change from baseline, whereas for dichotomous outcomes odds ratios or risk ratios may be calculated using logistic regression. The Kaplan-Meir survival curves and the Cox-proportional hazards model are fitted for time-to-event outcomes. A summary baseline table showing the distribution of prognostic factors by treatment group is also provided, nevertheless, formal statistical comparison for baseline differences should be avoided. Notably, stratification or minimization variables are part of the study design and should be adjusted for in the model.[20] Finally, readers should be cautious when interpreting subgroup analyses which are more of exploratory in nature. Because multiple testing carries the risk of spurious findings, these analyses should be limited and prespecified in the protocol to avoid dredging after looking at the collected data. Formal statistical tests of interaction should be used to check for differential subgroup effects and specific methodological tools are available for their correct interpretation.[21,22]

Data Management

Investigators tend to worry about high-level statistical issues, yet the most common errors involve far simpler mistakes due to sloppy data handling. Proper data management is not only a regulatory mandate but also a researcher's ethical responsibility. A lot of planning and input from a statistician is required during the design phase and case report forms (CRFs) either in paper or electronic format (Table 3) should be pilot-tested before actual data flow commences. Once a project has moved to the production phase, changes to data collection instruments are very difficult to implement. Trialists should allow for the possibility of missing values and capture the reasons for missing data. Continuous variables should not be coded but rather stored intact in their original form. Moreover, study personnel should not be asked to calculate values (eg, body mass index), but rather record raw variables (eg, height and weight). Collection of unstructured data such as free text should be avoided because it is almost impossible to make sense of them during the analysis. It is

Table 3. The choice between paper or electronic data capture in clinical trials.

Data collection	Advantages	Disadvantages
Paper	• Readily accepted • Shorter start-up time	• Printing, distribution costs • Transcription errors • Storage and archiving • Potential for more missing data • Increased workload for query resolution
Electronic	• On-entry data validation checks • Fewer queries and faster resolution • Faster time to database lock from receipt of last data	• Equipment and software design/maintenance costs • Internet access required • More complex security issues and compliance with data protection laws • Back-up service • May not be feasible in a particular trial context

also essential to create a data dictionary with a detailed description of all variables in the dataset and keep audit trails of all data modifications.[23] Use of custom-designed software for electronic data capture is advised such as REDCap™ (Vanderbilt University, Nashville, TN), a secure web application fully compliant with data protection legislation specifically geared to support not for profit clinical research activities that are endorsed by a global consortium of academic institutions.[24]

Ethical Approval and Trial Oversight

Experiments involving human subjects are tightly regulated. The Declaration of Helsinki was set fourth back in 1964 by the World Medical Association and represents a pivotal document outlining the fundamental ethical principles guiding human experimentation. A clinical trial can be ethically justified only if clinical equipoise is met, meaning that there should be genuine uncertainty based on a deep understanding of the scientific background about the comparative therapeutic merits of each arm in the trial. In other words, if there is sound scientific rationale supporting that the intervention administered in each one arm of the trial is significantly outperforming the other arm(s), then it would be unethical to knowingly assign patients upfront to an intervention that is deemed inferior. An independent ethics committee (IEC) also known as an institutional review board (IRB) is officially designated to review and approve the study protocol as well as monitor trial progress ensuring a fair distribution of risk and benefits to participants. Regarding the composition of the IEC, apart from physicians, scientists from other disciplines and lay public representatives are commonly involved. The regulatory approval framework is quite complex and may vary between healthcare settings.[25] Finally, study personnel should receive formal training in a minimum set of unified quality standards defined as Good Clinical Practice (GCP).[26]

The informed consent form (ICF) is the main source of information for individuals considering taking part in clinical trials and is subject to review and approval by the IEC. This document must be signed off before any trial-related activities and should communicate potential risks and harms using simple wording that the lay audience can easily understand. Participation in the trial is on a voluntary basis and participants who revoke their consent do not need to further explain their decision and should continue to be cared for based on standard clinical practice.[27]

To ensure participants' well-being for ongoing studies a Data Monitoring and Safety Committee (DMSC) might be appointed by the IEC, comprising independent experts in the field that have access to unblinded, comparative interim results.[28] Based on a review of accumulating data and prespecified trial-stopping rules the DMSC has the authority to recommend either premature termination, if safety concerns arise, or other study modifications. Of note, to avoid overinterpretation of interim findings due to repeated significance tests the type I error rate should be adjusted for multiple testing. Occasionally, DMSCs are faced with difficult decisions about the continuation of a major trial, which could also affect the future evidence base for a particular clinical setting. Empiric evidence suggests that trials stopped early for benefit might overestimate the effect sizes.[29] The final decision for the proposed amendments rests with the Trial Steering Committee which oversees the trial's conduct. Certain low-risk trials might be deemed exempt from a DMSC.

Trial Registration and Reporting

Sponsors must submit key information about the clinical trial protocol in a publicly available registry such as ClinicalTrials.gov or EudraCT before enrollment of the first patient. This practice acts as a safeguard against publication bias and selective outcome reporting. Publication bias occurs when the research output influences the decision to publish the trial, a practice that distorts the available evidence base in favor of positive findings. Reporting of negative findings is equally important and should be encouraged because it can prevent unnecessary duplication of research efforts. Selective reporting involves cherry-picking from the originally recorded outcomes and analysis methods, only those that look more favorable for the final publication. Of note, prospective trial registration is deemed a prerequisite for publication by the International Committee of Medical Journal Editors (ICMJE).[30]

The final step in the lifecycle of a clinical trial is the dissemination of its findings. Apart from publications or presentations at scientific conferences, the trial sponsor has the obligation to submit a clinical study report (CSR) to the competent regulatory body and post key study results in the respective trial registry. Clarity and Openness in Reporting: E3-based (CORE) Reference is a manual to assist medical writers with preparing CSRs.[31] Moreover, the Consolidated Standards of Reporting Trials (CONSORT) statement and extensions thereof provide a comprehensive list of critical information that should be included in all published reports of RCTs to promote transparency.[32] Beyond that, some journals even encourage the publication of the study protocol, SAP, and ICF either in a web appendix, in a public repository, or as a standalone publication.

Conclusions

RCTs lie at the top of the evidence hierarchy for the unequivocal evaluation of medical interventions. This experimental study design is very resource-intensive and requires meticulous planning beforehand. To accomplish the trial's objective a multidisciplinary team of content area experts, methodologists, statisticians and experienced data managers is essential.

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