REVIEW ARTICLE

Critical Appraisal of Randomized Controlled Trials: An Overview

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Abstract

Randomized Control Trials (RCTs) are the major source of information on the efficacy and safety of new and repurposed therapeutic agents and treatments. Therefore, it becomes essential that RCTs are of good quality and free of any biases. In the ever-evolving field of healthcare, making the correct clinical decision is important. Critical appraisal of new medical findings is therefore of utmost importance since clinical judgments are made based on the evidence provided by the publications and trial reports. In this review, we analyze the process of critically appraising RCTs using various researcher-developed guidelines and The Critical Appraisal Skills Programme (CASP) checklist for RCTs.

Keywords: Critical Appraisal, Narrative Review, Randomized Control Trials.

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Introduction

The efficacy and safety of any new drug, intervention, treatment, or diagnostic test are assessed by conducting and reporting the results of clinical trials (CTs), especially randomized controlled trials (RCTs). In the ever-evolving healthcare field, making the correct clinical decision is of utmost importance. With the advance of technology, a clinician is flooded with new information every minute. Approximately on a weekly basis 300 newly published reports of RCTs are added to the online database.[1] Therefore, critical appraisal of RCTs and published clinical reports are essential to judge if they are of good quality and free of biases.

Critical appraisal is defined as a study's validity, completeness of reporting, methodologies, procedures, findings, adherence to ethical norms, etc. that are evaluated using the principles of evidence.[5,6] A methodological approach to critical appraisal using a simple checklist can be a very user-friendly tool to screen research publications, especially RCTs. Interestingly, in a critical appraisal carried out by Kavina Kudhail et al., they reported that out of the 40 RCTs included in their study, 19 (47%) had a significant risk of bias, with 11/14 (79%) of them originating from low to middle-income nations. Among 14 (35%) RCTs, bias was detected because the authors either used selective reporting of results or there were major protocol deviations.[2] In another similar analysis, Vinkers et al. reported the risk of bias found in published RCT reports.[3] They concluded that the risk of bias was mainly due to the process of allocation concealment (63–51%), randomization (57–36%), and blinding of outcome assessment (58–52%).

A critical evaluation of RCTs and other medical literature is thus critical for making sound clinical decisions.[4] It is important for clinicians to combine relevant information from RCTs with patient-specific research findings and individual patient needs and preferences. This will help to build a robust, evidence-based, and personalized medical care plan.[5]

In this review, we examine critical appraisals of RCTs using Young and Solomon guidelines[5] and the Critical Appraisal Skills Programme (CASP) RCTs checklist.[7]

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Critical Appraisal of RCTs

Many articles have discussed the method of assessing the validity of a trial,[1,6,7] the purpose of this article is to highlight factors related to the interpretation of clinical studies and trials.

Randomized controlled trials (RCTs) are prospective CTs where study participants are randomized to one of the study groups or cohorts. These trials are done to evaluate the safety and efficacy of new drugs, interventions, or diagnostic tests.[8]

Randomized controlled trials (RCTs) are classified into three kinds based on different assumptions of treatment effects:[8]

Superiority trials: These trials hypothesize that the new treatment (drug and/or intervention) is better or superior to the control or standard of care. As a general rule, in such trials, the null hypothesis is specified in the opposite direction of the expected outcome.

Noninferiority trials: These trials hypothesize that treatment A is not worse than treatment B. However, these trials are not conducted to determine greater treatment effectiveness. The remedy can be assessed for other parameters like cost-effectiveness, side effects, invasive nature, etc.

Equivalence trials: "Equivalence" does not mean "equal" or "same." We can find some commonalities between experiments by closely examining these possibilities. Superiority, for example, is a subset of noninferiority. Noninferiority is considerably easier to establish than supremacy. Equivalence is the result of two noninferiority studies being combined.[8]

CASP Checklist for the Analysis of RCTs

The Importance of a Focused Research Question

For the scientific community and industry to find research helpful and applicable, it must be responsive to their needs. An article must not only be fascinating, pertinent, and current to the needs of the practitioners for it to be relevant; it also needs to be written in an approachable and straightforward manner. Defining a good study question is the first step in designing a good RCT. The study question/hypothesis should address issues of clinical, social, and/or economic significance. In addition, the hypothesis should also be easily and accurately measurable.[9] Identifying and understanding the research question is the primary task of a critical appraisal. Depending on the quality of the research question, the downstream study design will be affected. Research questions can be directed toward the effectiveness of the treatment and/or intervention, or they can also address the prevalence or incidence of an event. Questions about the frequency of events are generally used for observational studies, epidemiological studies/surveys, and retrospective studies.[10,11]

Population, intervention, comparator, outcome, time-frame,[12] feasible, interesting, novel, ethical, and relevant[13] are acronyms researchers use to convey the notion of how to construct a good research question.[14] In order to assess if a trial has a focused research question, one has to consider if the study was designed to accurately assess the outcome.

A well-defined research question will address the key components:
- A well-defined study population.
- The intervention used.
- Comparators chosen.
- The outcome.

A focused research question should be formulated taking the following aspects into consideration:

- The population studied: In such studies, poor sampling techniques will reduce the validity of the study, as this is a potent source of sampling bias.[15] The sampling approach employed will decide whether or not the sample analyzed is representative of the target population.[9]
- The intervention used: The research question should be aimed at the clinical problem that needs to be addressed rather than focusing on the method of data collection. Clearly mentioning the intervention in the research question helps to narrow down the purpose of conducting the trial.[9,14]
- Comparator chosen: The comparator groups/cohorts chosen for RCTs are crucial. Multiple comparators should be avoided unless statistical power is sufficient to address the desired study outcome and statistical analyses have been adjusted for multiple testing.[14]
- Outcomes: Establishing a well-defined expected study outcome is important because based on it; the sample size calculations (effect size and power) will be made. It is advisable to avoid composite outcomes, as they complicate drawing conclusions from study findings.[16,17]
- Composite outcomes: Outcomes that have results combined from various endpoints. For example, studies combine several adverse events and death.[14]

Novelty Aspect

The novelty of the research question drives research and leads to innovations. Therefore, novelty is a crucial aspect of any study. Novelty aspects of a study/trial include new discoveries, rare reporting(s), new theories, unusual or groundbreaking methodologies, and/or results.[1,14]

Kinds of Novel Study Designs[18]
- Pragmatic trials.
- Cluster crossover trials.
- Stepped wedged trials.
- Adaptive trial (platform, basket, and umbrella).

Novelty Aspects
- Large patient cohort with minimum loss to follow-up.
- Real-world setting(s).
- Patient-centered outcome(s).
- Practical results, applicable to your own practice.

However, it is also important to remember that research that adds to existing knowledge is also important. Retrospective data analysis, observational studies, and case report findings are instrumental in the Indian context since we lack a robust, integrated disease database and data-sharing platforms.[19,20] India is both large geographically and complex in terms of its population. Therefore, population-based studies help substantiate the original research findings and also increase confidence.[21]

Study Design

Randomized controlled trials (RCTs) have a very well-developed method of study design, substantiated by various metanalysis of well-conducted RCTs.[2,3] However, in all circumstances, a RCT is not the best study design to choose. In nonpharmaceutical trials for example surgical trials RCT is not always feasible or ethically relevant.[22]

Randomization of Participants to Study Intervention

A simple assessment of whether randomization was carried out in a trial is not enough. One has to do a deeper analysis by considering the following aspects:

- Process of randomization.
- Validity of method of randomization.
- Elimination of systemic bias.
- Concealment allocation sequence concealed from investigators, data assessors, and participants.

Removing bias from a study design is crucial for the success of any study in terms of reliable outcomes and study validity.[23,24] If the process of allocation concealment is not done properly it can lead to a major source of bias.[25] Therefore readers must consider how bias may influence an RCTs outcome.[22] Bias can be a random error, attributed to chance or a systematic bias attributed to the study design.[1] Random errors decrease the accuracy of a study. Whereas systematic biases result in over or underestimation of the true expected result(s).

Inclusion of all Participants Who were Recruited for the Study for Entire Study Analysis and Conclusion

The success of a trial is measured by its rate of protocol adherence and the inclusion of all participants of a trial in its conclusion and analysis.

Loss to Follow-up and Exclusions after Randomization

- Loss to follow-up is a term used in clinical research trials to describe study participants who were formerly actively participating in a trial but became lost (either due to a mistake in a computer tracking system or by being unreachable).

Study participant attrition is a major problem in interventional RCTs. Participant attrition affects the reliability and validity of the RCT outcome.[27,28] Higher attrition rates lead to a smaller sample size at the time of final analysis, which affects the statistical power of the study.

Sacket et al., in their analysis state, that <5% loss to follow-up is acceptable but greater than 20% loss to follow-up affects trial validity.[27,29] Therefore loss to follow-up calculation is crucial and needs to be done by determining the correct denominator (total number of participants who were randomized in a trial).[27,29]

Intention-to-treat (ITT) Analysis

Intention-to-treat (ITT) principle requires that all randomized study participants are analyzed in the treatment arm to which they were randomized. This analysis is done regardless of whether the study participants followed protocol adherence or there was a loss to follow-up.[24,30]

Early Termination of Study

Clinical studies must sometimes be terminated early due to ethical concerns about exposing human participants to further possible danger by continuing the experiment. The three ethics scenarios are based on concerns about safety, benefit, and futility.[31] Another nonethical reason to stop a trial earlier could be to transmit research findings into the clinical arena more quickly and thus help patients.[31,32] In addition, the longer the trial runs, the greater the risk of participant attrition and/or loss to follow-up.

Early stopping of trials has certain disadvantages, too. Early discontinuation of a trial decreases the precision of the results. The Data Monitoring Committee (DMC) may recommend the discontinuation of a trial if they find a significant difference favoring one arm over the other based on a primary endpoint. A trial can be discontinued or terminated before analyzing secondary endpoints. However, although a trial may end early with the discontinuation of the intervention, the ongoing collection of secondary endpoints can still be done. For example, in the Systolic Blood Pressure Intervention Trial, the National Heart, Lung, and Blood Institute approved the DMC decision to discontinue the experiment early in August 2015 because of the lower rate of cardiovascular outcomes and overall mortality in the intensive arm of the trial.[33]

Methodology

The aspect of study methodology needs to be evaluated by analyzing the following aspects:

Blinding of the Study Participants

If participants are not blinded, their behavior may affect the study outcome. For example, a participant who is aware that they are not receiving active therapy may be less likely to follow the study protocol, seek additional treatment outside of the study, and be more likely to drop out of the study.[34,35]

Blinding of the Study Investigators

Although randomization reduces treatment group inequalities early in a study, it does not prevent inequitable treatment of groups later in the experiment or differential assessment of outcomes, both of which can contribute to biased estimates of treatment effects. Blinding in RCTs of surgical treatments is typically more difficult than in pharmacological trials.[5,35] Similarly, blindfolded doctors/investigators are considerably less likely than unblinded physicians to express their opinions to study participants or to treat the active and placebo groups differently.[34]

Blinding of the Study/Outcome Assessors

Blinding the individuals involved in data collection and outcome assessment and analysis (who are sometimes the same people) is critical to ensuring fair trial outcomes.[34] In an RCT involving patients suffering from multiple sclerosis, neither active treatment regimen was superior to placebo when blinded neurologists evaluated it, but treatment with an active treatment regimen had an apparent benefit when unblinded neurologists evaluated it.[36]

The Similarity of the Study Group at the Start of RCTs

Knowing the baseline characteristics of study participants enables readers to determine how closely they resemble patients observed in their own clinical practice, and hence determine how universal the trial's outcomes will be (also termed "external validity").[37] In trials where major baseline characteristics appear to be well balanced, any variations in outcome between the study groups are most likely the result of the studied intervention/treatment (one component of internal validity).[38] The baseline characteristics/demographics in a trial are designed to summarize important aspects of the participants enrolled at the start of the study. It should accommodate both categorical and continuous data.[39]

Internal validity of CTs: Investigates whether the study design, methodology, and analysis provide unbiased answers to the research questions.[41]
External validity of CTs: Investigates whether its findings or conclusions may be transferred to other situations or has a universal application.[41]

The following information should be included as a best practice:

- Gender (male, female, and third gender).
- Region of enrolment of study participants/ethnicity.
- Other relevant demographic characteristics (e.g. height, weight, and body mass index).
- Clinical aspects are relevant to the study, such as concurrent medication, existing comorbidities, the recent history of illness, etc.

Level of Clinical Care for the Study Groups

Patient care and safety are the hallmarks of a competently executed RCT. The horrors of Nazi-era CTs prompted the creation of the Nuremberg Code to assure ethics in clinical research as well as patient safety and care.[42] The World Health Organization (WHO) issued the Declaration of Helsinki in 1964, outlining rules for conducting ethical clinical research.[43] Following the lead of the WHO, governments throughout the world accepted and developed country-specific principles for ethical medical research. In the year 2000, the Indian Council of Medical Research issued the "Ethical Guidelines for Biomedical Research on Human Subjects," which were amended in 2006.[40] It outlines 12 broad principles of ethical clinical research and patient care.[44]

Therefore it is the duty of the principal investigator and his research team to ensure patient safety and care at each step of the

trial. Aspects like a well-defined care plan, details of intervention to be used, and follow-up schedules should also be documented in the study protocol to ensure compliance by all stakeholders.[45,46]

Reporting Trial Outcomes and Results

Comprehensive Reporting of the Effects of the Intervention

Reporting results of large RCTs can be a changeling process, as various aspects need to be collected, collated, and correlated to draw reliable and robust conclusions. From a clinical perspective, the results of RCTs are important, as they determine patient care plans. The CASP checklist,[47] is a reliable guide to understanding the large amount of clinical and statistical data that is generated from RCTs. The following aspects need to be carefully assessed to understand the outcomes of large RCTs:

- Identification of potential sources of bias.
- Outcomes were measured and were specified clearly in the study protocol.
- Presentation of trial results statistics used the justification of reporting the *p*-values.
- Follow-up data for each study group.
- Missing data, data about the loss to follow-up patients.
- Correlation of loss to follow-up and study outcome.

Protocol adherence, baseline statistics, randomization utilized, loss of follow-up data, and confounding variables are all critical milestones. While critically appraising an RCT and evaluating the defined outcomes, the following factors should be considered—(1) data monitoring report and (2) statistical analysis completed. During trial outcome analysis, it is important to show that potential confounders are evenly distributed between the two groups; it is a common practice when reporting an RCT to demonstrate the integrity of the randomization process by demonstrating that there is no significant difference between the baseline variables.[48,49]

Reporting Treatment Effect

Reporting Confidence Intervals (CI)

A good RCT must determine the extent of the therapy's impact. Unbiased estimations of the extent of a treatment's effects are provided by good clinical studies. In RCTs, the effect of treatment must be measured with the following criteria in mind—(1) consistency of the treatment, (2) local impact, and (3) it is guaranteed to have equal or better asymptotic precision.[50] CTs should provide an estimate of the average effects of a treatment since treatments are very patient-specific.[50,51]

There is always an element of uncertainty, even in the best-designed trials. The difference in treatment effect observed between various study groups is only an estimate and it is dependent on the sample size of the trial. As a result, the stated size of the treatment effect in the research is only an approximate measure. The degree of uncertainty associated with the size of a treatment effect can be described with a CI.[52,53] Most often, the 95% CI is used.[53]

Covariate Adjustment

Covariate adjustment improves precision and helps to reduce sample size for RCTs. Covariates are data from measurements done (e.g., demographics, baseline characteristics, etc.) on a participant before randomization.[51] These data are used for estimating and testing treatment effects. Benkeser et al. proved significant improvement by using covariate adjustment in CTs. They also reported that after covariate adjustment the sample size required to achieve statistical power can also be reduced.[51]

Clinically Worthwhile Treatment Effect

If therapy is clinically useful, its benefits must outweigh its costs, resulting in greater affordability. Clinical studies frequently report the magnitude of therapeutic effects, but they seldom provide information about treatment costs.[54] There are various kinds of economic-evaluation studies, which all differ in how they estimate health benefits.[55] The simplest technique to decide if a therapy has a clinically worthwhile impact is to first identify the lowest clinically worthwhile treatment effect. When considering whether or not to provide a certain therapy. In a clinical setting, most clinicians frequently assess the lowest clinically worthwhile benefit.[52]

Local Impact of RCTs

Given the Indian context, where access to healthcare is not uniform across the country and the medical cost burden is entirely borne by citizens, it is critical to properly analyze the local impact of trials.[56] In order to implement a new treatment based on the reports of an RCT the following aspects need to be considered and evaluated very carefully by a clinician:

- Are the study participants similar to the people you care for?
- Would differences between your population and study participants influence the results reported in the study?
- Are the results important to your population?
- Are there any additional results or information you would have liked the information about?
- Are there any limitations of the study that would influence your decision?
- What resources will be needed to implement this intervention considering time, finances and skill development or training needs?

Declaring Conflict of Interest

During the publication of trial findings, authors are required to state any conflicts of interest as well as the involvement of the research sponsor. This is done to assure the objectivity of a clinical trial or research. Conflicts of interest affect trial external and internal validity, as well as the risk of nonreporting bias.[54] Intriguingly, Østengaard et al. discovered a wide range of awareness among trial researchers on what constitutes a conflict of interest and when it should be revealed.[58] As a result, trial planners should put in place suitable training facilities for all trial stakeholders.[45,55] Circulation of precise and correct information among team members will result in improved understanding and compliance.

Conclusion

Critical appraisal of CTs is a well-documented process that attempts to evaluate the trial's clinical validity. CTs free of biases and conducted using proper methodologies are invaluable tools for assessing the efficacy and safety of a new drug, intervention, or diagnostic test. In the ever-evolving field of healthcare, making the correct clinical decision is important. Critical appraisals of new medical findings are therefore of utmost importance since clinical judgments are made based on the evidence provided by publications and trial reports.

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