International Journal of
Regional Anaesthesia

Research

Randomized Controlled Trials

Nidhi Bhatia[1] Anju Grewal[2]
[1] Department of Anaesthesiology & Intensive Care, PGIMER, Chandigarh, India.
[2] Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.

Abstract
A randomized controlled trial (RCT) is a prospective, comparative, quantitative experiment / study that is performed under controlled conditions with random allocation of interventions to comparison groups. Among all the clinical study designs, evidence generated from RCTs is considered to be at top of the evidence pyramid. There are many different RCT designs and they can be classified on the basis of interventions evaluated, participants' exposure and level of blinding. All RCTs should be planned prospectively, a research question should be formulated, sample population approached and informed consent obtained from participants of the trial. These consented subjects are randomly assigned to any of the study arms and the changes are then measured over time. The basic principles to designing an RCT include formulating a research question, developing a protocol, randomization, allocation concealment, blinding, sample size calculation and registering of RCTs. Appropriate guidelines for reporting RCTs should be followed and RCTs should only be conducted if they are ethically viable, economical and clinically worthwhile.

Keywords: Randomised Control trial (RCT)

Introduction

Clinical studies are conducted among human participants to generate new knowledge by evaluating the impact of interventions. The main aim of all clinical studies is to evaluate interventions with respect to an associated outcome [1]. There are many different clinical study designs and the quality of evidence generated by any study is determined by its experimental design [1, 2]. Of all the clinical study designs, evidence generated from randomized controlled trials (RCTs) is considered to be at top of the evidence pyramid.

What is Randomized Controlled Trial?

A randomized controlled trial is a prospective, comparative, quantitative experiment/study that is performed under controlled conditions with random allocation of interventions to comparison groups [2]. While performing an RCT, robust, high quality evidence can be generated that greatly helps in evaluating the safety and effectiveness of an intervention as well as determining the cause-effect relation between an intervention and an outcome. Furthermore, RCTs yield themselves well to systemic reviews and meta-analysis, thus providing strong base for synthesizing evidence generated by such studies [2].

Why is Evidence Based on RCT Considered of Highest Quality?

RCTs are considered to be at the top of the evidence pyramid because:
- Concealed random assignment eliminates/greatly reduces confounding from known and unknown factors
- Blinding eliminates bias

In a prospective study, there are often systematic differences between the groups. As a result of these differences, the outcome of the groups may be different. This is known as confounding. Bias, on the other hand, is defined as the systematic tendency of any factors associated with the study to make the estimate of the effect of intervention deviate

Address of Correspondence: Dr. Anju Grewal, Professor & Head, Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.
E-mail: dranjugrewal@gmail.com

DOI: 10.13107/ijra.2021.v02i02.037 | www.ijrajournal.com |

from its true value [2]. The only way to best eliminate these differences is by randomization and blinding. Blinding refers to concealment of group allocation from one or more individuals involved in clinical research study. Randomization is allocating each individual to one or the other intervention at random. Thus, the probability of any individual receiving one or the other intervention is decided solely by chance. As a result of random allocation, if the sample size is adequate, all factors influencing outcome are likely to be distributed equally between groups [1, 2]. This can minimize the differences in characteristics of the groups that may influence the outcome.

RCT Designs

The simplest RCT design has one treatment group (or 'arm') and another control group. There can be variations in design by having multiple treatment arms or a factorial design [3]. The two key features of an RCT is 'random sampling' and 'random assignment'. Random sampling refers to how samples are drawn from one or more populations, whereas, random assignment refers to how groups or individuals are assigned to either a treatment group or a control group [3].

RCT Classification on The Basis of Interventions Evaluated: [4]

1. Explanatory Trials: These trials are designed to evaluate whether an intervention works.
2. Pragmatic Trials: These trials not only determine if a trial works, but also describe all consequences of the intervention.
3. Efficacy Trials: Evaluate effectiveness or efficacy of an intervention.
4. Phase 1, 2, 3, 4 Trials: These are the phases of a trial conducted for introduction of a new intervention, traditionally a new drug.

RCT Classification on The Basis Of Participants' Exposure:

1. Parallel Design: In this each group of participants is exposed to only one of the study interventions.
2. Crossover Design: Each of the participants are subjected to all the study interventions over successive periods.
3. Factorial Design: Two or more experimental interventions are not only evaluated separately but also in combination and against a control.

RCT Classification on The Basis of Level of Blinding:

1. Open RCT: Everyone involved in the trial knows which intervention is given to each participant.
2. Single-blinded RCT: A group of individuals involved in the trial (usually patients) do not know which intervention is given to each participant.
3. Double-blinded RCT: Two group of individuals involved in the trial (usually patients and treating physician) do not know which intervention is given to each participant.

When and How Should RCTs be Planned?

All RCTs need to be planned prospectively and are suitable for pre-clinical and clinical research. The participation in the trial needs to be carefully controlled with the experiment in mind. RCTs cannot be conducted retrospectively [3]. Its other salient features include: [2]

- An RCT tests the effectiveness of one or more interventions.
- The intervention being tested is allocated to two or more study groups.
- The control group may receive no intervention, a standard treatment or a placebo.
- There should be sufficient uncertainty about the utility of the intervention, known as equipoise.
- The question to be answered by RCT design should be safe for the participants.
- The research question should be ethically appropriate.
- In an RCT it is impractical to study outcomes that are extremely rare or may take a very long time to develop.

Designing an RCT [1, 2, 3, 4]

The basic framework to conducting an RCT is fairly simple. The research question is formulated, the sample population is approached, and patients consented for participating in the trial. The consented subjects are randomly assigned to any of the study arms and the changes are then measured over time. The basic principles to designing an RCT include the following:

Formulating Research Question: A research question guides the research. A good study should have one research question and one hypothesis, which should be precise. The research question should be in the 'PICOT' format: P-Population of Interest; I-Intervention; C-Comparator Intervention; O-Outcome; T-Time duration for intervention/outcome. In addition, 'FINER' criteria are used in the development of a good research question, according to which the research question should be Feasible, Interesting, Novel, Ethical, Relevant. These criteria highlight relevant and useful points that increase the chances of developing a successful research project.

Developing a Protocol: The protocol should be developed in collaboration with other researchers in the team, statisticians, investigators, necessary regulatory authorities

and funding bodies [2, 5]. The protocol should have clearly defined aims and objectives, inclusion and exclusion criteria, consent process, interventions and outcome definitions. It should be reviewed and approved by an independent ethics committee and prospectively registered with a publicly available trial registry prior to recruiting any participants.

Randomization: Randomization ensures that each patient has an equal chance of receiving the intervention. The main purpose of randomization is to eliminate selection bias and balance known and unknown confounding factors. Methods of randomization include using a table of random numbers or a computer program that generates random number [6]. Generation of random sequence should be done by an independent person, usually a statistician. Block randomization is designed to randomize participants into groups that result in equal sample sizes. Cluster randomization can be used when randomization of individual participants is not feasible, in which case hospitals, clinics, geographical areas, etc can be used as units for intervention allocation [2].

Allocation Concealment: This is an essential component of RCT and is useful in situations where blinding is not possible. It means that neither the investigators nor the participants are aware of whether the next eligible participant will be receiving control or treatment intervention. It is important that the person who generates allocation sequence is not the person who determines eligibility and entry of participants [2, 5].

Blinding: Blinding helps in eliminating bias. It refers to keeping the trial participants, assessors and/or investigators unaware of the assigned intervention. Blinding maybe single-blinded, double-blinded, or triple-blinded (double-blind trial that also maintains a blind data analysis). Although blinding is important, however, it may be difficult or impossible in certain trials.

Sample Size: The study or the trial should have an adequate sample size and power. The conclusions generated from studies with adequate sample size can be applied to larger populations. The sample size required to test a hypothesis should be governed by effect size and derived from previous observations and trials. For calculating sample size, it is important to know baseline estimate of outcome rate in control group. Further, it is important to know what percentage of patients are expected to benefit from the intervention. The difference in primary outcome between the 'control' and 'intervention' groups is said to be 'significant' if the probability of this difference arising solely by chance is < 0.05 [2]. This is the probability or p-value. The chance that a difference will be found even if there is no real difference is known as Type-I error. This is usually fixed at 0.05, though other levels of significance (0.01 or 0.005) may also be chosen. Type-II error is the inability to demonstrate a significant difference even when one does exist. This is set at 0.2 to 0.05. Power of the study is the chance that the study will be able to demonstrate a significant difference if it is present. Conventionally, power of the study is fixed at 0.8-0.95 (80-95%). In RCTs where effect size is measured in proportion, sample size can be calculated using these values. However, if the effect size is measured as a continuous variable, then in addition to Type-I and Type-II values, one would need mean and standard deviation of the variable in each group to calculate the sample size [2].

Ethical Considerations: While conducting RCTs strict ethical principles should be followed. Evaluation of risks and benefits to the society and the participants, obtaining ethical approval and taking written, informed consent is important. Further, before an RCT is conducted, there must be equipoise (genuine doubt whether one course of action is better than the other) [2, 4]. While conducting medical research, it is the duty of the physician, conducting the research, to protect the health, life, privacy as well as the dignity of human subjects. This is guided by a statement of ethical principles in the 'Declaration of Helsinki', which was developed by the World Medical Association for medical research involving human subjects, including research on identifiable human material and data [6].

Registering RCTs: RCTs are considered the premium methodological design in science. However, there is considerable variance in the ways RCTs are reported in the peer-review literature. In order to ensure systematic standards in the reporting of evidence as well as to have greater public transparency in the way RCTs are conducted and reported, it is now mandatory that all RCTs are prospectively registered, prior to starting the trial/enrolling the first participant, in a database open to public access [7]. India launched its own free online public registry, the Clinical Trial Registry of India (CTRI) on July.20, 2007, for registration of clinical trials conducted in India.

Reporting of RCT

It is important to be aware of the quality of reporting RCTs and the limitations of the research methods. Appropriate guidelines for reporting RCTs should be followed. The CONSORT (Consolidated Standards of Reporting Trials)

Statement, first published in 1996 was designed to assist reporting of RCTs and is still followed [4, 5, 8].

Conclusion

RCT is one of the most robust research methods used to generate evidence in basic, translational, and clinical research. Although formulating, designing, and conducting them may require more effort, however they are still considered a 'gold standard'. Nonetheless, RCTs should only be conducted if they are ethically viable, economical, and clinically worthwhile.

Conflict of interest: Nil **Source of support:** None

References

1. Zabor EC, Kaizer AM, Hobbs BP. Randomized Controlled Trials. Chest 2020; 158: S79-S87.

2. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. Acta Obstet Gynecol Scand 2018;97:380-387.

3. White H, Sabarwal S, De Hoop T. Randomized Controlled Trials (RCTs): Methodological Briefs 2014; Impact Evaluation No. 7, Methodological Briefs no. 7.

4. Stolberg HO, Norman G, Trop I. Randomized controlled trials. AJR Am J Roentgenol 2004;183:1539-44.

5. Thiruvenkatachari B. Randomized controlled trials: The technique and challenges. J Indian Orthod Soc 2015;49:42-7.

6. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;31:2191–2194..

7. Elliott TR. Registering randomized clinical trials and the case for CONSORT. Exp Clin Psychopharmacol. 2007 Dec;15:511-8.

8. Akobeng AK. Understanding randomised controlled trials. Arch Dis Child 2005 ;90:840-4.

How to cite this article: Bhatia N, Grewal A | Randomized Controlled Trials | International Journal of Regional Anaesthesia | July-December 2021; 2(2): 107-110.