Fundamentals Of Randomized Controlled Trials
H Bhattacharyya, D K Brahma, S Pala, J B Wahlang, M D Marak

Citation

Abstract
The randomized controlled trial (RCT) is one of the simplest but most powerful tools of research. It is a form of study or scientific experiment in which people are allocated at random to receive one of several clinical interventions. These experiments are most commonly used in testing the safety and efficacy of any therapeutic or health care procedures. Preparing the protocol, specifying the methods of improving the transparency and validity of reporting the results of RCT’s and submitting for ethical review are basic prerequisites. Randomization reduces the risk of serious imbalance in important unknown as well as known factors that could influence the clinical course of the participants. Methods of Randomization include use of a table of random numbers, computer programs and tossing a coin etc. Apart from randomization, bias can be reduced by allocation concealment, blinding and minimizing the loss to follow. The basic study designs are concurrent parallel type, cross over type and factorial design. Other types include mega trials, sequential trials, fixed trials, explanatory and pragmatic trials. Valid inferences depend on how well the investigator designed, conducted and reported various procedures to minimize bias in the trial. The steps involved in conducting an RCT are selecting the reference population, selecting the experimental or study population, obtaining informed consent, randomization into treatment and control groups, application of intervention, follow up and final assessment of the outcome.

INTRODUCTION
Randomized Controlled Trial (RCT) is a type of scientific experiment or a form of clinical trial most commonly used in testing the safety and effectiveness of health care services or preventive or therapeutic procedures. [1]

In recent decades, modern medicine has been blessed with a pharmaceutical armamentarium that is much more powerful than it had before. A major factor for such rapid advance has been the development and refinement of the clinical research method known as the RCT. A clinical trial is defined as a prospective scientific experiment that involves human subjects in whom an intervention is initiated for the evaluation of a therapeutic procedure.[2] In an RCT, each patient is assigned to receive a specific treatment intervention by a chance mechanism.

These studies are the underlying basis for what is currently called “evidence-based medicine”. Nothing more clearly indicates the key role of an RCT in modern clinical research than the placement of this specific research method at the top of the list of levels of evidence in evidence-based medicine.[3]RCT, also known as true experiments or intervention studies, are considered to be the gold standard research design for demonstrating a cause-and-effect relationship between an intervention and an outcome. Results of an RCT are more definitive than any other type of clinical research information.

RCTs can be classified according to the different aspects of intervention evaluated. These include explanatory or pragmatic trials, efficacy or effectiveness trials and Phase 1, 2, 3 & 4 trials.[4] We present here an outline of the fundamental principles of RCTs.

IMPORTANT TERMS IN RCT
The people who take part in RCTs (the ‘study population’) are called ‘participants’. Participants can be patients, healthy volunteers, relatives of patients, members of the general public, communities, or institutions. The people who design and carry out the study and analyze the results are called the ‘investigators.’ For example, if an investigator, say ‘A’ and his colleagues are conducting a study in which patients with essential hypertension who are randomized to receive either a beta-blocker (or, say ‘drug X’) and a newly marketed drug, ‘Y’, say angiotensin receptor blocker (ARB), the ‘A’ and his colleagues would be the investigators; the participants are the patients with essential hypertension; and the interventions are drug X and drug Y.
RCTs usually try to measure and compare different events called ‘outcomes’ that are present or absent after the participants receive the interventions. RCTs are also considered as comparative studies as they are used to compare two or more intervention. One of the interventions is regarded as a standard of comparison or ‘control’, and the group of participants who receive it is called the ‘control group’ (receiving drug “X”, from the above example). The control can be conventional practice, a placebo, or no intervention at all. The other group is called the ‘experimental’ or the ‘treatment’ group.

REQUIREMENTS OF AN RCT

1. Protocol: One of the essential features of a RCT is that the study is conducted under a strict protocol. The protocol specifies the aims and objectives of the study, questions to be answered like testing the effectiveness of drug, criteria for selection of study and control groups, sample size, procedures for allocation of subjects into study and control groups, standardization of working procedures and procedures undertaken to minimize any bias in the trial.[5]

2. The consort statement: The protocol should clearly delineate the methods used to improve the transparency and validity of reporting the methods and results of RCT’s.[6] The Consolidated Standards of Reporting Trials (CONSORT) statement - a statement that resulted from an extensive collaborative process to improve the standards of reporting randomized controlled trials is an important source of information for investigators.[7] The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.[8]

3. Prospective registration: Prospective registration of the trial in a publicly assessible database to improve transparency.

4. Ethical review: As RCT’s are intervention studies, so ethical issues are vital. All trials should be peer reviewed by institutional ethical committees before approval.

BASIC STEPS OF AN RCT

1. The first step is to prepare the protocol and submit it for ethical review.

2. Choosing the reference population: A reference population may be as broad as mankind or may be limited to specific groups like age, sex, social or occupational groups depending on the type of the study.

3. Selecting the experimental or study population: The study population is derived from the reference population. It is the population which actually participates in the study. The basic characteristics of the experimental population are:
   a) They should have the same characteristics as the reference population and must always be randomly selected from the experimental population.
   b) They must give informed consent to participate in the study after having been duly informed about the objectives, interventions to be used and possible risks of the trial.

4. Randomization: It is a statistical procedure by which the participants are allocated into study and control groups randomly.

5. Intervention: The next step is to apply the intervention to the study group by administering the new drug or anything as laid down in the protocol. The procedures for performing the trial should be standardized and should be adhered.

6. Follow Up: This Implies examination or observation of both groups at defined intervals of time in a standard manner till final assessment of the outcome.

7. Analysis: The incidence of both positive or negative results/outcome are rigorously compared in both the groups and the differences are tested for statistical significance.[5]

BIAS IN RCT

Bias is a systematic distortion of the real, true effect that results from the way a study was conducted. Bias in a research can make a treatment look better or worse than its reality:

1. Internal validity: If proper methodology is used in conducting the trial and due precautions are taken to minimize bias, the study is said to have internal validity.

2. External validity: If the study findings can be generalized to the entire population then the study is said to have external validity. [1]

Four Types of Bias can occur in RCTs:

i. Selection bias: Biased allocation to study or comparison groups i.e the investigator may have bias in allocating the subjects into experimental or control group. For eg: Sometimes the investigator may allocate healthy subjects into the new drug therapy group to get a favourable result.

ii. Performance bias: Unequal provision of care or treatment to both the groups i.e. the investigator measuring the outcome of a drug may be influenced if he knows beforehand which drug or therapy or placebo the patient is actually receiving.

iii. Ascertainment bias: Biased assessment of outcome i.e the results of the trial may be systematically distorted when the patients/investigator knows beforehand which intervention
the participant is actually receiving.\[5\]

iv. Attrition bias: Handling of deviations from protocol and loss to follow up of patients due to death, migration or not willing to participate any more in the trial.\[5\]

v. Publication bias: There is a propensity for trials with statistically significant results to be published more often than trials reporting no significant results or no difference between two drugs. This tendency which appears to favour trials with positive results is called publication bias.\[9,10\]

MINIMIZING OF BIAS IN RCTS

There are various ways of minimizing bias in RCT’s out of which the basic ones have been highlighted.

1. Randomization (By Random Allocation):

The randomization procedure gives RCT’s its strength. It is the heart of RCT. Random allocation means that participants are assigned to one of the study groups by chance alone and the investigators, the clinicians, or the study participants cannot determine or influence the decision to which group they will be assigned. The basic purpose of random allocation is to keep the groups ‘balanced at baseline’. It is one of the most important parts of a study to be able to isolate and quantify the impact of the intervention that investigators are studying and also minimizing the effects from other factors that could influence the outcome (called confounding factors). Confounding factors may be either known or unknown ones having no direct relation to the intervention, but can influence the outcomes of a study. Though we are aware of what randomization is but many a times investigators are confused on how to practically apply randomization in their study design. The different ways of doing randomization are

i. By using of a table of random numbers: Random numbers table is available in all statistical books.

\[\begin{array}{|c|c|c|c|}
\hline
\text{Table of random numbers} & \text{00-04} & \text{05-09} & \text{10-14} & \text{15-19} \\
\hline
\text{00} & \text{56318} & \text{14518} & \text{36236} & \text{07253} \\
\text{01} & \text{09372} & \text{27651} & \text{30103} & \text{37004} \\
\text{02} & \text{44782} & \text{54023} & \text{61355} & \text{71692} \\
\hline
\end{array}\]

Using a table of random numbers: Let us say we are conducting a study in which there will be two groups- Group A and Group B. We will consider every odd number an allotment into Group A and every even number an allotment to Group B. We close our eyes and put our finger anywhere on the table. Let us assume we point at 7 at the intersection of column 06 and row 01. Now we can move horizontally to the right or any specified direction. The first patient is designated by an odd number “7” and will be allotted to Group A. The next patient is designated by an even number “6” and assigned to Group B and so on. In this case we have noted that the assignment of the next patient is not predictable which follows the rule of randomization.\[11\]

ii. By using Computer program: Computer program that can generate random numbers- Pseudorandom numbers. The program ensures that the numbers generated do not form any pattern, that the value of each number is not dependent or influenced by the numbers already generated, and that the sequence of numbers is not repeated during use. Randomization software may run on a local computer or may be hosted by an Internet server.\[12\]

iii. We can also toss a coin to decide the assignment of the patient into a study group.

iv. Stratified randomization: Sometimes some variables like age and sex may affect the results of our study eg: prognosis of a disease may be worse in older patients. Sometimes randomization may not ensure perfect comparibility between two groups with regard to some of these variables. One approach of dealing with this problem is stratified randomization. In this approach, we first stratify our study population by each variable that we consider important and then randomize participants to treatment groups within each stratum.

For e.g. if we are studying 2000 patients for a treatment outcome and are concerned that age and sex are important determinants of prognosis. If we randomize the groups may not be balanced with respect to age and sex, therefore we decide to stratified randomization.

We first stratify the 2000 patients by sex into 1200 males and 800 females. We then stratify the males and females by age. We now have four groups-young males, old males, young females, old females. We now randomize within each group, the result is a new treatment group and a current treatment group for each of the four groups. We finally end up with two randomized groups i.e. new treatment and current treatment but having initially stratified the groups we increase the likelihood that the two groups will be comparable in terms of age and sex.\[11,13\]

2. Allocation Concealment: Another aspect to be paid attention to in RCTs is concealment during allocation of random sequence. Allocation concealment means that the person who generates the random assignment remains
unaware to what drug the person will receive.[1] For example, drug ‘X’ or ‘Y’. If allocation is not concealed, research staff is prone to assign better and healthier patients to intervention rather than control group which can bias the treatment effect.

Concealment of the randomization sequence (how we allocate the patients) is crucial to avoid selection bias.

Methods of Concealment:
1. To ensure that allocating the participants by randomization are done by someone who is not conducting the study.
2. Use of coded containers with interventions administered to the patients which can be decoded only by the investigator.
3. Use of sequentially numbered, sealed, opaque envelopes with the allocation interventions inside.[1]
4. Blinding: In blinding, the researchers collecting data are prevented from knowing certain information about a participant (e.g., what treatment they are in) in order to prevent this information from affecting how they collect data. Blinding can be done in three ways:
   a. Single blind - The trial is so planned that the participant is not aware whether he belongs to the study or control group.
   b. Double blind - Both participant and investigator do not know the identity of intervention given to each patient.
   c. Triple blind - The participant, the investigator as well as the person analyzing the data are all blind to the interventions allocated to each patient.

3. Adequate blinding prevents performance & detection bias. In most RCT’s double blinding is commonly used.

4. Minimizing attrition bias: It is recommended that researchers should state clearly which participants are included in their analyses. One of the methods commonly used is called the intention to treat analysis.[1].

5. Minimizing publication bias: The only way to eliminate publication bias is through compulsory registration of trials from the start and publication of results of all trials. [14] The ability to make valid inferences from a trial depends on how well the investigator designed, conducted and reported various procedures to minimize bias in the study. Therefore, basic concept of bias and how to minimize this bias in any trial is the key to the conduct of a successful RCT in pharmacoepidemiology.

STUDY DESIGNS
There are various designs of RCT depending on the type of drug being tested, the profile of the participants, cost and time considerations, accuracy and validity of results to be obtained. Some of the basic designs are:

1. Concurrent parallel study design: This is the commonly used RCT design. In this design, comparisons are made between two randomly assigned groups, one group exposed to specific treatment, and the other group not exposed. Patients remain in the study or control group for the duration of the investigation.

2. Cross Over type of study designs: With this study design each patient serves as his own control. The patients are assigned into study (given drug) and control groups (not given drug or given a placebo) as before. The two groups are observed over a period of time. Then the patients in each group are taken off their medication or placebo to allow for elimination of drug from their body which depends on the pharmacologic properties of the drug being tested. After this interval the two groups are switched i.e those who received the treatment under study are changed to the control group therapy (placebo) and vice versa. In this way all patients can be assured that sometime during the course of investigation, they will receive the new therapy.

3. Factorial design: In this type of study design two drugs can be tested simultaneously considering that the anticipated outcomes of the two drugs are different and their modes of action are independent. Thus one can use the same study population for testing both the drugs.[11]

For example, a 2 x 2 factorial design generates 4 (four) sets of data to analyze: data on patients who received none of the interventions, patients who received treatment A, patients who received treatment B and patients who received A and B. [15]

There are also various RCT design based on the number of participants involved. They may be classified as:

1. Mega trials: RCTs with a simple design that involve thousands of patients and limited data collection are called megatrials.[12,13] Usually, megatrials require the participation of many investigators from multiple centres from different countries.[5]

2. Sequential trial: It is a study with parallel design in which the number of participants is specified by the investigators in advance before starting the study. Instead, the investigators continue recruiting participants until a clear difference or no difference (as per decision of the investigator) between the interventions are observed.[16]

3. Fixed trial: In fixed trial, the investigators establish
RCTS AND ETHICS

Since RCTs are intervention studies, so with it comes several ethical issues some of which are highlighted. Practices or substances already known to be harmful cannot be allocated by an investigator for further verification of its efficacy. On the contrary therapies that have clearly demonstrated to be beneficial cannot be withheld from an affected patient for the purpose of comparing with a new drug.[1] Ethical standards prohibit the exclusion of special populations without a scientifically sound reason. Conversely, special populations should not be studied out of convenience. The special population groups are women, children, prisoners, psychiatric patients etc.

The areas to be taken care of in conducting an RCT is informed consent process, ensuring confidentiality of reports, protocols to preserve safety and address adverse events, reporting results and addressing conflicts of interest.[12]

CONCLUSION

RCT is a qualitative, comparative, controlled experiment in which investigators study two or more interventions in a series of individuals who receive them in random order. It is also known as true experiments or intervention studies and is considered to be the gold standard research design for demonstrating a cause-and-effect relationship between an intervention and an outcome. Results of an RCT are more definitive than any other type of clinical research information. However a poor design may lead to biased outcomes and therefore investigators should strive for methodological rigour and report their work in enough details for others to assess its quality.

Intervention studies like RCT has a unique position in the rapidly growing field of pharmacology especially in a country like India. It is hoped that the present article will be helpful to the young Pharmacologists of our country to focus more on intervention studies and probe deeper in this arena so that they can practically apply it more frequently in their own research works for a greater goal of rational use of medications.

References

Author Information

Himashree Bhattacharyya, Dr.
Department of Community Medicine, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, India

Dhriti Kr. Brahma, Dr.
Department of Pharmacology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, India
dbdriti168@gmail.com

Star Pala, Dr.
Department of Community Medicine, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, India

Julie Birdie Wahlang, Dr.
Department of Pharmacology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, India

Maxilline D. Marak
Department of Pharmacology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS)
Shillong, India