Randomized controlled trials: Gold standard of evidence

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ABSTRACT

The randomized controlled trial (RCT) is considered as one of the most powerful tools for performing experimental research. It is a form of experiment in which subjects are allocated at random to receive one of the several interventions. These experiments are commonly used in testing the safety and efficacy of any therapeutic or health-care procedures. This study aims to give a brief introduction to the major concepts and approaches involved in designing and conducting an RCT.

KEY WORDS: Allocation, Clinical research, Evidence, Intervention, Randomization

INTRODUCTION

Research in a more simplified view refers to a search of knowledge. It is also regarded as an art of scientific investigation. The purpose of any research is to discover answers and questions through the application of scientifically sound procedures. Research can be functionally divided into basic research and applied research.

Basic research is usually considered to involve a search for knowledge without a defined goal of utility or specific purpose. Applied research is problem oriented and is directed toward the solution of an existing problem. Thus, the central aim of applied research is to discover a solution for some practical problems, whereas basic research is directed toward finding information that has a broad base of applications and thus adds to the already existing body of scientific knowledge.

The most commonly encountered applied research in health science and the research strategy by which evidence of effectiveness is measured is the randomized controlled trial, commonly known as an RCT. It is one of the most powerful tools in clinical research. It is considered to be the gold standard research design for demonstrating a cause-and-effect relationship between an intervention and an outcome.[¹] Randomized controlled trials are the most reliable methods available for testing new treatments.

IDEAL REQUIREMENTS OF RCTs

i. One of the essential features of RCT is it is conducted under a strict protocol. The protocol specifies the aims and objectives of the study, criteria for selection of study subjects, procedures for allocation of subjects, standardization of working procedures, and procedures undertaken to minimize bias.

ii. The Consolidated Standards of Reporting Trials statement is a set of recommendations for reporting RCTs.[²]

iii. Registration of the trial in a publicly accessible database to improve transparency.

iv. As RCTs are intervention studies, ethical issues are vital. All trials should be peer-reviewed by institutional ethical committees before the approval.

BASIC STEPS OF RCTs

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

ii. Choosing the reference population: A reference population may be as broad as humankind or may be limited to specific groups (age, sex, social, or occupational groups) depending on the type of the study.

iii. Selecting the experimental or study population: The study population which actually participates in the

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study is derived from the reference population. The basic characteristics of the experimental population are:

a) They should have the same characteristics as the reference 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.

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

v. Intervention: The next step is to apply the intervention to the study group as laid down in the protocol.

vi. Follow-up: This implies examination or observation of both the groups at defined intervals of time in a standard manner till the final assessment of the outcome.

vii. Data analysis: The incidences of both positive and negative outcomes are compared in both the groups and the differences are tested for statistical significance.\[3\]

**KEY COMPONENTS OF RCTs**

**Randomization**
The randomization procedure gives RCTs its strength. It is done to reduce bias and confounding. Random allocation means assigning participants to treatment and control groups assuming that each participant has the same chance of being assigned to each of the groups. The different methods of doing randomization are as follows:

i. Simple randomization: Using a table of random numbers or using computer program or by flipping a coin to decide the assignment of the patient into a study group.\[4\]

ii. Stratified randomization: Variables such as age and sex may affect the results of our study. One approach to deal 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.\[5\]

iii. Block randomization: The investigator divides subjects into subgroups called blocks, such that the variability within blocks is less than the variability between blocks. Then, subjects within each block are randomly assigned to treatment conditions.\[6\]

iv. Cluster randomization: This can be used when the randomization of individual participants is not feasible. In such a case, units can be considered for the allocation of intervention or control groups.\[7\]

**Allocation Concealment**
This means that investigators, participants, and assistants/health-care providers are unaware of whether the participant will be receiving treatment or control intervention. It is a technique used to prevent selection bias.

**Methods of Concealment**
i. Use of coded containers with interventions administered to the patients which can be decoded only by the investigator.

ii. Use of sequentially numbered, opaque, and sealed envelopes with the allocation interventions inside.\[8\]

**Blinding**
The core idea behind conducting an RCT is the elimination of bias. Blinding helps to eliminate the unconscious information bias.\[9\] Whenever possible, blinding should be used in an RCT. Blinding can be done in three ways:

i. Single blind – The procedure of blinding the participant.

ii. Double Blind – The procedure of blinding both the participant and investigator.

iii. Triple Blind – The participant, the investigator as well as the person analyzing the data are all blind to the interventions allocated to each patient.

**STUDY DESIGNS OF RCTs**

**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 another group not exposed. Patients remain in the assigned group for the duration of the investigation.

**Crossover designs**
With this study design, each patient serves as his/her own control. The patients are assigned into either study (given drug) or control groups (not given a drug or given a placebo). 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 the elimination of drug from their body (washout period), 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 and vice versa.

**Factorial design**
In this 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.

**Split-mouth design**
Here, each of the two treatments is randomly assigned to either the right or left halves of the dentition.
This design removes all differences between the subjects. Unfortunately, the treatments may have effects on experimental units other than those which they were assigned to carry-across effects. Hence, counterbalancing is necessary to control the carry-across effect.

ADVANTAGES AND DISADVANTAGES OF RCTs

RCTs are the strongest empirical evidence in the hierarchy of evidence and considered the gold standard of all study designs. Randomization minimizes bias and confounding factors. It demonstrates the cause-and-effect relationship. However, this study design is expensive in terms of time and money. Randomization requires clinical equipoise, as one cannot ethically randomize patients unless both the treatments have equal support in the clinical community. Some research cannot be ethically performed as an RCT.

CONCLUSION

RCTs are true experiments and considered as the gold standard research design for ascertaining the causal relationship between intervention and outcome. Results of an RCT are more definitive than any other type of research information. However, RCTs cannot yield adequate data unless they are methodologically sound, well planned, conducted, and analyzed.

REFERENCES


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