Methods & Protocols

Randomized clinical trial: gold standard of experimental designs - importance, advantages, disadvantages and prejudice

Ensaio clínico randomizado: padrão ouro de desenhos experimentais - importância, vantagens, desvantagens e preconceitos

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ABSTRACT | BACKGROUND: Randomized controlled trial (RCT) is the gold standard of experimental design or clinical trial design. Only by RCT in research, the cause-and-effect relationship between a set of independent and dependent variables could be demonstrated. RCT has added advantages over other experimental designs due to the presence of the control group. The importance of control in health research trials and its advantages to be elaborated. Though various threats to internal validity in health research trials could be minimized by RCT, various biases in RCT and disadvantages add to its discredit. **OBJECTIVE:** The aim of the present narrative review is to brief the characteristics, advantages, disadvantages, and various biases in RCT. **METHODS:** This review does not follow the PRISMA statement, as it was a narrative review. Two databases, namely, Medline through PubMed and Scopus, were searched from inception to July 2020 for the information pertaining to RCTs and included in this narrative review. Only English language articles were searched with the keywords, "Randomized controlled trial," "Randomized clinical trial," "experimental design," and "experimental study." These keywords are linked together by the Boolean words, "AND," "OR" and "NOT." Conference proceedings and only abstracts were not considered for the review. **RESULTS:** RCTs were explained under characteristics, advantages, disadvantages, importance, and advantages of controls in research, the principle of equipoise, RCTs in the pediatric population, RCTs in the geriatric population, threats to internal validity and steps to minimize them and various biases in RCTs. **CONCLUSION:** The narrative presentation of RCTs under various important topics have been explained in this review.

KEYWORDS: Bias. Control groups. Randomized clinical trial. Research designs.

RESUMO | JUSTIFICATIVA: Ensaios clínicos randomizados (ECR) são o padrão ouro para desenho experimental de estudo ou ensaio clínico. Apenas por meio de uma investigação do tipo ECR é possível avaliar e demonstrar a relação de causa-e-efeito entre um conjunto de variáveis independentes e dependentes. O ECR adicionou vantagens em relação aos outros modelos experimentais, principalmente devido à presença de um grupo controle. Existem várias críticas à validade interna das pesquisas em saúde, incluindo preconceitos e desvantagens que são apontadas para seu descrédito. **OBJETIVO:** O objetivo do presente estudo é informar características, vantagens, desvantagens e desvios deste método científico. **MATERIAL E MÉTODOS:** Análise crítica de método científico com base em revisão narrativa da literatura. Foi consultada a base de dados Medline por meio dos portais PubMed e Scopus, sem data de início e até julho de 2020, para extração das informações relativas aos ECR. Apenas artigos de língua inglesa foram incluídos, usando as palavras-chave "estudo randomizado controlado", "ensaio clínico randomizado", "projeto experimental" e "estudo experimental", intercaladas pelos operadores booleanos "AND ," "OR" e "NOT". Anais de conferências e resumos não foram considerados para a análise dos dados. **RESULTADOS:** Dos ECR selecionados, foram extraídas características, vantagens, desvantagens, importância e vantagens dos controles em pesquisa, o princípio de equilíbrio, ensaios clínicos randomizados na população pediátrica, ECR na população geriátrica, ameaças à validade interna e medidas para minimização de viéses e preconceitos em ECR. **CONCLUSÃO:** Tópicos relevantes dos ECR foram explicados nesta revisão que devem guiar pesquisadores clínicos.

PALAVRAS-CHAVE: Viés. Grupo controle. Ensaio clínico randomizado. Desenhos de estudo.

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Introduction

In research, the cause-and-effect relationship between a set of independent and dependent variables are demonstrated by experimental designs[1,2]. Experimental designs are divided into several types based on design characteristics. The main difference between them is the degree of experimental control. Study participants or patients are randomly assigned to two at least two comparison groups are considered as true experimental designs. The gold standard of true experimental design is a randomized controlled trial (RCT).

Randomized controlled trial

A clinical trial is basically defined as an experiment designed for assessment between two or more treatments' effectiveness. To evaluate the safety and effectiveness of therapeutic approaches to manage any conditions through prevention, screening, diagnosing, and treating evidence-based randomized controlled trials (RCT) are used. The evaluation of RCT occurs in 1948, a study on the effects of streptomycin on pulmonary tuberculosis[3]. Observational study and interventional study are two basic types of analytical studies. RCT is the relatively most powerful tool in medical research used to evaluate the efficacy of an intervention. It plays a crucial role in establishing evidence-based decision making treatment. RCT is the gold standard research design for true experiments[4]. RCT includes three components; randomization defines by the distribution of patients in the different group by any methods of randomization; controlled means that to establish the efficacy of any intervention the one variables should be controlled on which the findings of any intervention is dependent; trials suggests, that to establish any treatments, we need to investigate the effects of treatment through the different trials in between the subjects[5]. Any research design without randomization and control groups does not consider as randomized controlled trial. The essential component of the experimental study is the use of controls[6]. Controls may be defined as no treatment, treatment with different dosages, or treatment with a different schedule. Control group can be chosen by any method of randomization, or both the group should be identical for all variables except the treatments under study[7]. Randomized controlled trials are effective when the value of the new treatment is volatile or controversial. Randomization plays an important role in RCT experimental study. It assigned treatment to patients without any assumptions. There are several advantages of randomization, such as; it expected the bias from the assigned group of treatments. The second advantage is that its balance treatment groups are covariates, whether or not these variables are known. This balance can truly compare the findings of the group. The third advantage is that it guarantees the validity of the statistical test of significance that used to compare the treatments. A major advantage of randomization is that it leads to balanced or comparable groups[8]. Randomization is the only means of controlling for unknown and unmeasured differences between the comparison group as well as the known group. In an RCT distribution of groups with randomization assigned each patient's treatment as a chance[9]. RCT is the best study design that allows the researchers to collect information that needs to answer a research rationale. RCT can provide strong evidence for one particular research question to determine whether clinical intervention work. RCT's are prospective and experimental means dependent variable and independent variables are collected under controlled conditions[10]. All experimental studies are not RCT's; however, all RCT's experimental study. Usefulness of trials depends on the extent to which a causal relationship can be inferred. Phase 1 trial to document the safety of the intervention in humans while phase 2 trial evaluates the efficacy of intervention in small group of patients and to determine the short-term risks and side effects. Phase 3 trials randomized controlled trials to assess the effectiveness and compare with establish treatment or a placebo and phase 4 trials for post-marketing studies of the intervention. RCT's have a powerful way to examine cause and effect relationships[11].

Advantages of RCTs

Randomized controlled trials have several advantages; it allows the researcher to evaluate the findings of the study by analyzing the single variable.

Analysis of each variable can represent the cause and effects of the treatments by analyzing the pre-intervention and post-intervention outcome scores of variables. RCT's include only prospective study design, as it includes the data only after the decision of the study. It helps to evaluate the treatment effect in all the participants. Before the randomization by controlling all the factors in both group participants except treatment, we can easily analyze the effect of treatment. With the prospective data, the significance of the treatment can be evaluated between the control group and interventional group findings. RCT uses its own hypothetico-deductive model. According to this, every research question for the study is formulated by hypothesis[12]. Hypothesis always seeks to be falsified, when the outcome findings of the study are not yet known. It compares the explanatory value of the hypothesis by testing the intervention. RCT's prevents biasing of the result by different methods, such as blinding of the patient, blinding of assessor and intervener blinding. In RCT's mainly biasing can be controlled by randomizing the samples into two identical groups. The major advantage of RCTs is that in later stages, it allows for meta-analysis, by combining the results of similar studies, establishing the evidence-based treatment. It provides a straight-forward investigation of cause-effect relationships with minimal bias and confounding factors. Observational studies also can be done to test the hypothesis and evaluate the findings. Different trials are designed to analyze the treatment outcome, but they differ from randomized controlled trials in terms of non-randomization, allocation, blinding and usually they adopt usual care settings[13].

Disadvantages of RCTs[2]

Though RCTs have several advantages, it is no exception of not having disadvantages[2]. First, the generalizability of study results to the wider population may not be possible due to the inclusion of homogeneous population. Second, due to the controlled laboratory situation in which intervention was given, the replication of them in real-world situations may not be possible. Third, the cost involved in conducting an RCT is much higher when compared to other study designs because of its complexities and more documentations. Fourth, in most of the situations, conducting an RCT may not be practically feasible and possible due to rare diseases or more severity in diseases (e.g., COVID 19) which prevent patients in allocating into controlled group[2].

Advantages of control in trials in health research

The advantages of the control group in randomized controlled trials increase the reliability of the study. By selecting control by the randomization process, the blinding improved. Poorly designed control groups may lead to misinterpretation of results or misleading statements. It eliminates the difference in intervention between individuals. The decision of participants in control groups decided by the chance of randomization[14]. Control may receive no intervention, standard treatment, or a placebo. It helps to compare the safety and efficacy of the intervention between the treatment group and the control group. In the control group, selection biases are equally distributed between groups. The choice of control in a randomized controlled trial depends on the type of research, and the therapeutic effect of the intervention can be examined. Various control group options can be implemented in RCT. In no treatment comparison condition, patients randomly assigned to receive the new treatment are compared with those patients assigned to receive no treatment at all[15]. Patients randomized to receive a new treatment are compared to those randomized to be on a waitlist to receive the new treatment. Patients randomized to receive a new treatment are compared to those randomized to receive treatment as usual. A direct comparison between two or more treatments to assess the best practice or standard of care. Parametric or dose finding usually done early in the development of a new treatment in order to determine the optimal dose or format of the treatment. Different forms of the intervention varying on factors such as the number, length, or duration of treatment comprise the conditions to which patients are randomly assigned. Treatment dismantling, also called component analysis in this approach, patients randomized to receive the full efficacious intervention are compared to those randomized to receive a variant of that intervention minus one or more parts of it.

Importance of control in RCT

The choice of control group depends on the question and knowledge about the intervention used in the study. The relationship between the treatment applied to the control group and other those not participating in the study will clearly define the relevance of between-group differences. Types of patients, types of measurements, and methods of comparison should be correctly correlated between both groups. The randomized patients in the control group, before randomization, if receiving any treatments, can show discrepancies between pre-randomization and post-randomization values in control groups. In any situation where the treatment in the control group cannot be easily anchored to participants, the dose-response relationship might be determined whether the better of two treatment levels is actually the best. For the control group, demographic and treatment should be comparable to the patient who not enrolled in the study. The utility of the control group can be tested at three stages of the study; at the design phase, during the study, and after completion. At the design phase, the treatment providing in the control group should be identical to standard care. It is a feasible option for many interventions. During the study, mortality and other outcomes trends will be monitored by the data safety monitoring board as well as reported adverse events. Detection of major changes in the treatment after randomization may indicate that the control group is no longer receiving usual care, and that result from the study will not address the hypothesis originally posed. By not keeping patient in a control group as per the researcher's interest, we believe that positive results in study[6].

Characteristics of RCTs

The Randomized controlled trials (RCTs) are the gold standard true experimental design[16] or clinical trial design[2]. RCTs provide guidance in interpreting and estimating clinical research data. RCTs Provide constitutive evidence for medical interventions and also helpful in assessing the efficacy of clinical research[17]. RCTs provide high-quality data, elaborate casual relationships in detail, and form the basis of evidence-based treatment. RCTs are straight-forward research helps in investigating the cause-effect relationship with low risk of confounding factors and bias. RCTs provide logically relevant and appropriate research questions[17]. RCTs are less prone to bias as compared with observational studies[18]. RCTs have an advantage in reducing bias by allocating each individual into groups randomly. Hence, the probability of receiving treatment is solely decided by chance. Therefore, randomization is the best way of reducing confounding and bias in experimental studies[18].

Principle of Equipoise

RCTs are designed with the motive to determine the quality and efficacy of the new intervention, and to provide the standard of care[17]. Principle of Equipoise states that conduction of experimental studies should be free of any intervention preferences, before random assignments of the participants, so that there should be sufficient uncertainty for the best intervention regimen related to the specific disease of interest. Therefore, the principle of equipoise should be followed before and during the experimental study[17].

RCTs in Pediatric Population

Evidence of high-quality RCTs is less in the pediatric population as compared with the adult population[19]. RCTs are poorly conducted in children, which leads to risks of biasing of treatment effects. RCTs in the pediatric population were of poor quality because of the inappropriate methodology includes random sequence generation and allocation concealment[19]. Measures of triallists awareness, application of existing reporting guidance, and the registration of trials prospectively are needed to improve the findings of the outcomes in the pediatric population. Due to the lack of RCTs in the pediatric population, the standard of care is limited. So, high-quality RCTs should be performed in the pediatric population with specific approach[19].

RCTs in Geriatric Population

The geriatric population forms the majority of patients and should be represented in RCTs[20]. Physical, social, and psychological functioning are different in the elderly compared with the adult and pediatric age

groups, so more number of RCTs should be conducted and needed in the geriatric population with specific and accurate outcome measures[20]. RCTs, including the geriatric population, are very few in number. The total number of studies specifically designed for the elderly is a total of 7%. So, there should be proper treatment guidelines for enrolling and conducting RCTs in geriatric population[20].

Threats to internal validity and steps to minimize them

Differences observed related to the intervention given in both the control and experimental group are referred to as internal validity[17]. It means how accurate or reliable the study results are[17]. Internal validity compromises the relationship exists between dependent and independent variables. There are some threats to internal validity[21]. These are History, Maturation, Statistical regression, and selection of participants, experimental mortality, testing of intervention, Instrumentation, design contamination, Compensatory rivalry, and resentful demoralization[22-24]. History can be a threat to one group pretest-posttest design rather than two group pretest-posttest designs. During the experiment, if some unexpected events occur and if these events affect the dependent variable or not. Mostly occurs in one group design[23]. History is not a threat for two-group designs because, in two group designs, there is a comparison between the control and experimental group[23]. Maturation is another threat to internal validity and mostly occurs in one group designs. Maturation refers to the changes in the dependent variable due to the normal process as a function of time[23]. Statistical regression also threatens internal validity. It is inversely proportional to the reliability of the specific test[23]. The selection of participants can also be a threat to internal validity. It affects two-group designs because randomization is happening only in two group designs. If subjects were not selected by random sampling and assignments, no one had an equal chance of getting treatment in experimental or control groups, and both the groups are not equivalent. To prevent the threat, Random allocation and assignment should be there. Experimental mortality is other threat, can occur in one group design and two groups designs. In experimental trials, new intervention or exercise were designed, if participants find difficulty in performing those exercises or face any difficulty during intervention, and ask for stopping the intervention, and then this refers to experimental mortality[23]. Instrumentation is one of the main threats occurs during measuring the outcomes or dependent variables. It mostly threatens one group design not two group designs. It can be prevented by performing blinding of the outcome assessors and participants[23]. Design contamination is another main threat, mostly occurs in two group designs. In this, participants in control group came to know about the experimental group, and starts comparing about the treatment they are receiving[23]. When participants in one group receiving goods or services, and if becomes known by the participants of other group, it affects the outcomes of treatment, and motivation level of participants, refers to compensatory rivalry[23]. Another major threat, which commonly occurs in two group designs, is resentful demoralization[23]. In this, if participants came to know that they are receiving intervention of less quality and less beneficial as compared to the another group. This type of threat also mostly occurs in two group designs[25].

The most common recommendations addressing threats to internal validity are choice of sample size (Power calculation, large sample size), randomized allocation (different methods of randomization), blinding (measurement analysis), dose-response relationship (Testing above or below therapeutic dose), and selection of appropriate control groups. The internal validity should be reduced by implementing, and following CONSORT guidelines[26]. By performing randomization, allocation concealment, sequence generation, blinding or masking, Intention to treat analysis, per-protocol analysis, baseline comparison of the intervention of both the groups, risks of threats to internal validity can be reduced[27].

Data analysis bias in RCT

Bias in research can occur when the error is introduced into sampling or selection of participants by testing, or one outcome is encouraged more during any phase of the study, including particular study design, during data collection, and in the processing of data analysis[21]. Some of the possible reasons, which cause bias in clinical trials are insufficient knowledge of the research in appropriated designing and conduction of experimental studies, bias related to funding[28].

Lack of resources and lack of proper encouragement affects the quality of research and further leads to bias[24].

Methods of reducing data analysis bias in RCT

Data analysis biasing can occurs if the researcher gives preferences to the conclusions of the study results in favor of their research hypothesis if the results are going against the hypothesis[23]. Bias can be introduced in various different ways during data analysis, such as by manipulating or fabricating the data[23]. Performing subgroup analysis is not favoring the main hypothesis or plan to find the statistically significant difference in the study. For data interpretation, accurate and appropriated statistical tests should be used; otherwise, it can lead to bias in data interpretation[27]. Data analysis bias can also occur because of the poor methodology, improper handling of missing data, and low quality of the analysis. To avoid selective inclusion of the participants in the analysis, the analysis data set must be predefined, before conducting the research. The 'Intention-to-treat' analysis and 'Per-protocol' analysis should be followed by randomized participants[27].

There are four main types of bias in data analysis[28]. They are confirmation bias, interpretation bias, Prediction bias, and information bias[28]. Confirmation bias occur when the researcher tries to prove the hypothesis of their own research and supports the evidence which only favors their research[28]. To reduce confirmation bias, the researcher should reexamine and reconsider the participant's response, and point of view[28]. Interpretation bias occurs when participants in two groups reacted distinctly when the same research question was posed in a different way. To reduce it, the researcher should understand the research question and must consider the data in every logical way and then draws a conclusion from it[28]. Publication bias occurs when participants are wrongly differentiated between the groups in a research study because of technical errors in machines or devices used for differentiation of participants based on their caste, religion, ethnicity, race, color, and gender. To limit such bias, the researcher should take help of secondary investigator to collect and analyze the data to make subtle differentiations, which can't be done by machines[28]. Information bias is increased search of different keywords related to same condition or disease, which is not a correct measure to determine the things[28]. It also refers to the bias which is occurring because of measurement errors. It is also known as observational bias[29]. Data Analysist should not be biased while collecting and analyzing the data, which favors their study. They should accept and consider all of their point of views, before coming to a conclusion[29].

Intended data analysis strategies must be opted and specified in the protocol[28]. The choice of an appropriate statistical test should be justified. Missing data because of the dropouts lead to the bias in RCTs, due to the unobserved measurements. Proper ways of handling the missing data must be specified in the protocol of the study. Available guidelines regarding handling of the missing data must be followed[28]. Randomization also plays an important role in the analysis of trial data. Randomization helps research designs to be valid, as it includes the allocation of treatment, which is more feasible compared with the non- randomized study. There are some other ways that helps in reducing data analysis bias. Multiple people should be used for data coding for the true agreement of interpretations[30]. Triangulation[28] should be followed, which means verification of the data from reliable sources or literature. Peer reviewing must be considered before drawing a conclusion[28]. Peer reviewing helps in identifying the research gaps, and can provide the affirmation to the data[28].

Even though high-quality RCT stays at higher hierarchy in the level of evidence than the observational studies, which includes cross-sectional study, case-control study, cohort study, and case-reports, the disadvantages of executing RCT should be considered.

Conclusion

There are various advantages of RCT over other experimental study designs. If the above-mentioned biases are taken into control, the RCT could be considered as, "golden crown" of study designs.

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Author contributions

Sharma N and Srivastav A were responsible for data curation, writing of the first draft and methods design. Samuel AJ was responsible for the study concept, methods design, writing of the first draft, critical review and supervision of the project.

Competing interests

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