Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/12123
DOI URL: http://dx.doi.org/10.21474/IJAR01/12123

ISSN NO. 2320-5407

RESEARCH ARTICLE

AN OVERVIEW OF RANDOMIZATION IN CLINICAL TRIALS

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Manuscript Info

Manuscript History
Received: 05 October 2020
Final Accepted: 10 November 2020
Published: December 2020

Abstract

Randomization is a process of assigning the treatments to various experimental units in a purely chance manner to the control and treatment groups in clinical trials. The process of reducing the experimental error by dividing the relatively heterogeneous experimental units in to homogeneous blocks is known as local control. This paper describes some of the main steps in those performing reviewers of randomized controlled trials (RCT).

Introduction:-

In the 1920s RA Fisher introduced randomization as an essential technique of his approach to the design of experiments, validating significance tests. In its absence the experimenter had to rely on his judgment that the effects of biases could be discounted. Twenty years later, A Bradford Hill promulgated the random assignment of treatments in clinical trials as the only means of avoiding systematic bias between the characteristics of patients assigned to different treatments. The two approaches were complementary, Fisher appealing to statistical theory, Hill to practical needs. The two men remained on good terms throughout most of their careers.

To rule out subjective bias in subjects under study , blinding trials should be conducted. In single blind trial one group of patients is given one drug and another is given other drug of the same colour and size or a placebo. So no patient knows what he is given. In double blind trial not only the patient but also the observers do not know which patients are given drug and which patients are on placebo. In a triple blind trial neither the patients nor the observers nor the person analyzing the data know which patients are given drug and which patients are on placebo.

Random allocation of patients for treatment and controlled groups may be done by random numbers. All patients may be collected and distributed two envelopes red and white at random

Discussion:-

Designing of an experiment means deciding how the observations or measurements should be taken to answer a particular question in a valied and efficient way. As per to RA Fisher the basic principles of Design of Experiments are Randomization, Replication and local control. One of the main purposes of randomization is to improve comparability between treatment groups by balancing observed and unobserved covariates in expectation. Randomization furthermore helps to mitigate the risk of selection bias and, depending on the randomization procedure, can protect against imbalanced group sizes throughout the allocation process. Despite the many benefits of randomization, there are also some limitations; for a comprehensive discussion. One issue that cannot be addressed by randomization is that patients usually enter a clinical trial sequentially and are often treated

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immediately. Consequently, new patients will be enrolled and assigned to therapies, while others have already received treatment . This delay in time entails several potential sources of bias: On the one hand, the treatment success itself may be affected by unobserved time trends (chronological bias). These may result from, for example, improved treatment performance due to experience gain, or changes in inclusion or exclusion criteria. On the other hand, the sequential enrollment creates the risk for selection bias whenever blinding cannot be fully attained.

Before calculation of sample size , the investigator must see whether the type of outcome variable is quantitative(ie., continuous such as blood pressure, pulse rate, weight of a patient) or qualitative (ie., severity of disease, mild, moderate, intense, sign and symptoms: present/absent). A study is general should have single or primary outcome measure. Other measures should be secondary. If, however, more than one measure are of equal importance. Separate sample size calculations should be done and large sample size arrived at should e used. A rough idea about the outcome variable in the two groups is the most important input for calculating sample size.

In case of outcome variable being quantitative, mean and standard deviation would be the summary required while in qualitative outcome variable proportions would be needed. To be more specific for calculation of sample for any study requires that the investigator should specify the following fours parameters, so that the fifth parameter ie., the sample size could be calculated: 1. Investigator has to specify the amount of error is prepared to tolerate in concluding that difference exists when in fact no difference. This is known as Type-I error. 2. Probability of concluding that the amount of error prepared to tolerate in concluding that the difference between the two groups is real when in fact the difference is due to chance factor alone. This is known as type II error. 3. The third parameter is inversely related to the size of the study is the difference which is regarded as clinical importance.

The fixed randomization is used in two forms: 1. Simple randomization 2. Block Randomization. Simple randomization is the most elementary form of randomization. It is usually carried out using a random number table or random numbers generator from a computer. Hill Introduced Blocked randomization in 1951 to avoid serious imbalances in the two groups. Blocked randomization guarantees that at all time during randomization the number of patients in the two groups will be equal.

Summary:

The benefits of randomization are numerous. It ensures against the accidental bias in the experiment and produces comparable groups in all the respect except the intervention each group received. The purpose of this paper is to introduce the randomization, including concept and significance and to review several randomization techniques to guide the researchers and practitioners to better design their randomized clinical trials. Use of online randomization was effectively demonstrated in this article for benefit of researchers. Simple randomization works well for the large clinical trails (n>100) and for small to moderate clinical trials (n<100) without covariates, use of block randomization helps to achieve the balance. For small to moderate size clinical trials with several prognostic factors or covariates, the adaptive randomization method could be more useful in providing a means to achieve treatment balance.

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