

RANDOMIZED CONTROLLED TRIALS AND THE CREDIBILITY OF MEDICAL RESEARCH

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Although the number of medical journals published in Pakistan is increasing every year and so far 53 journals are included in *Index Pakistan*¹ (i.e. recognized by PMDC) and few more are expected to be included in the list in the near future, the poor quality of published research work is still a major concern among medical professionals.²

Evidence-Based Medicine (EBM) is the integration of best research evidence with clinical expertise and patient values.³ EBM provides a grading scale of various types of clinical evidences, based on the strength of their study designs with minimization of various biases. Centre for Evidence-Based Medicine, Oxford, categorized different levels of evidence for therapy/prevention/etiology/harm and listed systematic reviews of randomized controlled trials (RCT) on top as level-1 evidence.⁴ Unfortunately, the level of published research in Pakistani medical journals is not encouraging and the top two Pakistani medical journals (JCPSP & JPMA) had published only 9% of articles having level-1 evidence and 55% having level-4 evidence.⁵ The major bulk of articles (69%) were not clinical scientific articles, comprising of simple descriptive studies or surveys, case reports, editorials, review articles, letters to the editors or animal studies. Therapeutic studies were around 50% but had poor study designs. The interventional studies comparing two groups are usually not randomized thus leading to the poor credibility of the research work. In our set up, lack of awareness may be a key factor in planning research with a faulty study design as simply incorporating randomization will enhance the quality of the manuscript sent for publication to any journal. Since the publication of first RCT in 1948,⁶ random assignment of treatments has become an essential feature of experimental design in clinical trials⁷. Now many journals are not accepting the articles for publication unless criteria for RCT are fulfilled. Since 1991, the *BMJ* has developed a policy of not publishing trials without proper randomization.⁸ Even if the manuscript is published somewhere, it goes unnoticed as for most of the systematic reviews specially by *Cochrane Collaboration*, the basic selection criterion is randomized controlled trials.

Randomization is an important issue in a study design, conduct and statistical analysis of a clinical trial. It helps in eliminating the selection and confounding biases in a trial. Randomization is not simply the haphazard or alternate selection of the patients. Similarly taking the odd or even hospital number of patient is also not randomization. Randomization is a systematic process of assigning clinical trial participants to treatment groups

where every participants has got a known (usually equal) chance of being assigned to either of the treatments groups, however the treatment group to be assigned cannot be predicted.⁹ Tossing a coin is the simplest way of random allocation between two treatment groups, allowing each patient an equal chance of getting either treatment. However it can lead to uneven size of each group beside some other related issues like concealment, validation and reproducibility. Other than flipping a coin, the use of a sequence of random numbers from a randomization table or a computer-generated sequence is called *Simple Randomization*.

In small trials, due to imbalance in size of the groups, simple randomization is not a good choice and an alternative method called as *Permuted-Block Randomization* (also called *restricted randomization*) is preferred. Depending upon the sample size, the size of blocks is chosen. The sample size should be divisible by the block size and the block size should be divisible by the number of treatment groups in the trial. Random allocation of blocks will keep the balance in the size of two groups. With small block size, the groups will be almost matching in size; however this will lead to somewhat predictability of the next allocation and thus affecting the blinding process. Variable block sizes with random allocation sequence of the blocks may solve this issue.

Stratified Randomization is another method where patients are divided in to different subgroups (strata) based on two or more variables like age, sex etc. Stratified Randomization needs to produce a separate *block randomization* list (rather than *simple randomization*) for each stratum. This helps to maintain the balance of important characteristics without compromising the advantages of randomization. In a multicentre study where a central coordinated randomizing service is not available, the participants within each centre should be separately randomized taking each centre as a stratifying variable.¹⁰

RCT are aimed to eliminate the bias, which can be further achieved with the help of "masking" or "blinding" (study participants, attending physicians and outcome assessors are kept unaware of intervention received) and allocation concealment (the treatment to be allocated is not known before the patient is entered into the study) methods.

However there are some ethical issues¹¹ and some other limitations of RCTs.¹² The *external validity* or *generalisability* (whether the results can be reasonably applied to a definable group of patients in a particular

clinical setting in routine practice) of the results of RCTs is often poor.¹³ RCT may be more expensive and also difficult to assess uncommon adverse events, requiring a very large sample size.¹⁴ Despite these shortcomings, RCTs and the systematic reviews are the most reliable ways of measuring the effects of treatment. What we need is to plan our studies in consultation with epidemiologist and statistician and adopt proper randomization procedure to minimize the selection bias. This will enhance the credibility of local research and indirectly improve the quality of Pakistani medical journals. We can seek the help of randomization softwares and web based randomization services, some of these are offering free downloading facilities. Martin Bland is maintaining a directory of randomization software and services for clinical trials, including both simple *do-it-yourself software* and *24 hour telephone randomization services*.^{15,16}

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