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Nuts and Bolts in Clinical Research

Designing randomised controlled trials in rheumatology – What, why, and how

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ABSTRACT

Randomised controlled trials (RCTs) have become the workhorse for evaluating efficacy of various healthcare interventions. The basic plan is to compare the outcome experience of two or more prognostically similar groups of patients with study intervention being the only difference between them. It involves key elements such as random allocation, concealment of allocation, and blinding to guard against design-related biases. This article explains these key features and the steps involved in designing an RCT in the context of rheumatological diseases.

1. Introduction

Randomised controlled trials (RCTs) have achieved a pre-eminence in the present era of evidence-informed healthcare. Some of the reasons for this ascendancy are – i) RCTs provide a reliable estimate of the treatment effect, when designed and conducted properly; ii) the RCT design is well suited to detect modest-sized treatment effects; and iii) unlike other research designs, RCTs could be used to infer a cause-effect relationship. Especially, in the past two or three decades there has been an explosion of RCTs evaluating various healthcare interventions, both therapeutic and diagnostic, on individual patients as well as populations. However, an improperly conducted RCT could be more damaging to participants as well as future patients. Hence, it is indeed necessary for a modern-day clinician to understand the lingo of clinical trials. It is required not only to comprehend the published literature but also to design and conduct RCTs on their own. In this context, the present narrative would focus on RCTs that are aimed at evaluating the efficacy of therapeutic interventions (Phase 3 trials) randomising individuals, using the two arm (1:1 allocation) parallel-group superiority design as the prototype, unless stated.

2. Why do we need controlled clinical trials

Typically, a clinician forms a personal impression about a treatment from the limited number of patients he/she had treated in the past. More often, such experience is limited to a

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handful of patients. Unless the intervention has dramatic effects, like saving the life of a patient with a uniformly fatal illness (e.g. rabies), it is impossible for anybody to be really sure that the clinical improvement was indeed due to the treatment offered. Because, many illnesses may improve spontaneously or at the least show temporal fluctuations in severity as is the case with many rheumatological conditions. Further, the clinical improvement could be a placebo response to the treatment offered. So, we need another group of patients with the same condition, but did not receive the treatment, for comparison to draw a conclusion. This design is called a controlled clinical trial.

3. Why do we need random allocation

The problem with a controlled clinical trial is deciding which patient would receive the investigational treatment or otherwise. If this is left to the discretion of the investigator, it is natural to expect that the two groups of patients would end up quite dissimilar to each other with respect to disease severity and prognostic characteristics, yielding a biased and confounded estimate of true treatment effect. The only reliable way of obtaining two or more comparable groups of patients is by random allocation to the study groups. When properly carried out, random allocation eliminates selection bias and confounding by measured, unmeasured, as well as unmeasurable factors in a large clinical trial. In addition, random allocation facilitates blinding and also provides a valid theoretical basis for the statistical analysis methods.

4. The three virtues of an RCT

The proverbial double-blind RCT has three important design-related attributes – randomisation scheme, allocation concealment, and blinding – that are essential for reducing the role of bias and confounding in the study design (Fig. 1).

4.1. *Sequence generation and randomisation scheme*

Random allocation does not mean erratic allocation. Its true meaning is that any given patient enrolled into the RCT has a defined probability of being allocated to a particular arm of the trial, and more importantly it is not possible to predict which arm the next eligible patient would be assigned to (unpredictability). Typically, this is done with the help of random numbers. They could be obtained from any of the several sources – random number tables found in standard texts on biostatistics; statistical softwares such as Stata and SPSS; free on-line random number generators (e.g. http://www.graphpad.com/quickcalcs/randMenu/; http://www.random.org/sequences/; http://www.rand.org/pubs/monograph_reports/MR1418.html); or else one can generate random numbers using the Microsoft Excel programme also (Fig. 2).

Randomisation scheme refers to a pre-defined strategy for generating the allocation sequence. One may use a simple randomisation scheme, also known as unrestricted randomisation – i.e., if one wishes to randomise say 100 patients in total to a two arm trial, the statistician generates a single list

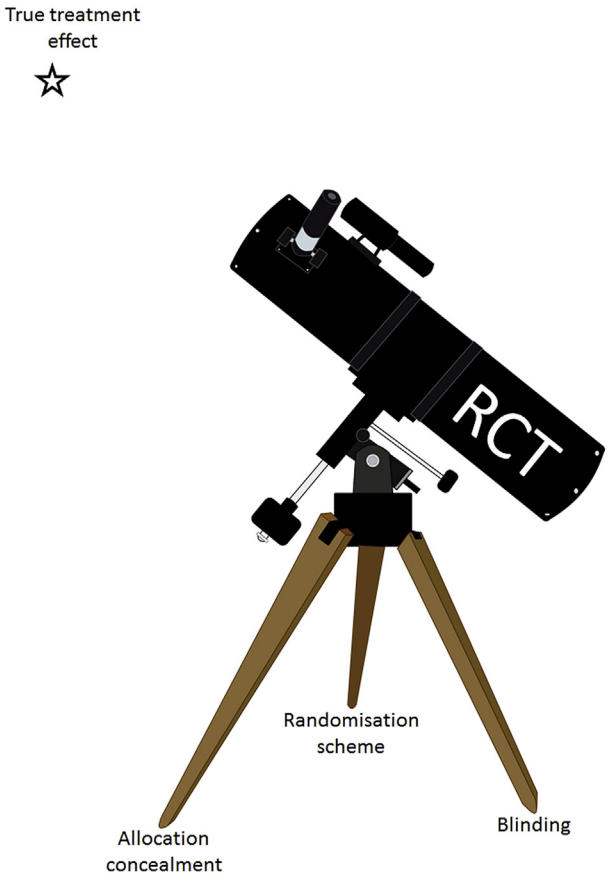

Fig. 1 – If the RCT is a tool (the telescope) to get a view of the true treatment effect (the star), then the three design-related features, namely randomisation scheme, allocation concealment, and blinding, would form the legs of the tripod on which the tool rests. *Courtesy*: *www.openclipart.org*.

of 100 random numbers by any of the above described methods. A potential problem with simple unrestricted randomisation, particularly in smaller trials, is that there could be unintended imbalance of important prognostic factors (accidental bias). To avoid this, it is advisable to choose a stratified randomisation scheme in which separate random sequences are generated for each stratum – one for patients with the prognostic factor and another for patients without the prognostic factor. For e.g. in systemic lupus erythematosus trials, patients could be stratified by pre-randomisation variables such as disease activity score, race, heavy proteinuria, etc. The number of such random sequences required would be equal to the product of the number of subgroups in each stratifying variable. For this reason, too many stratifying variables should be avoided (not more than 4 even in a large trial). Otherwise, randomisation would become difficult to manage. It should also be appreciated that if the potential number of patients in the smaller stratum is too few for any imbalance to confound the treatment effect, stratification by that variable may not be necessary. Stratified randomisation marginally improves the precision in smaller trials. However, if the size of each treatment group is bigger than 50, the benefit from stratification is