

# Clinical trials

Alexander Telia

Tbilisi State Medical University, Georgia

## INTRODUCTION

A clinical trial can be defined as "any form of experiment involving patients". The objective of a clinical trial is usually to determine whether a treatment is safe and effective for treating a particular disease. An important of such an experiment is that it is conducted on a sample of patients with a disease to generate results on which future treatment of all such tents with the same disease can be based. Planned experiments on healthy volunteers, such as **bioavailability studies** and **dose-finding studies** during the early **phase I** testing of new drugs are sometimes considered to be clinical trials but more often they area not. The term "**volunteer studies**" is sometimes used for studies but because all clinical trials require informed consent and hence "volunteering" by participants, this term best avoided [1].

## CONTROLS IN CLINICAL TRIALS

To infer whether a given treatment has worked, comparisons are required. The comparison may be of the states of patients (i) the states of patients before and after administration of the treatment (ii) the response of patients given the treatment and those of past patients (**historical controls**) who were given no or other treatments, or (iii) the response of patients given the test treatment and those of other patients given a control treatment, in the same study. Without a control group, interpretation of results is usually difficult. For example, consider a trial of a new remedy for the common cold. If treatment effects are measured two weeks after administration of the treatment, then a success rate close to 100% is to be expected simply because of the natural history of the infection. It is obvious that, except in exceptional circumstances, a clinical trial using concurrent control patients is likely to give the more robust results than one based on historical controls. The need for controls in the assessment of drugs was recognized in the early part of the 20<sup>th</sup> century. For example, in a study published in 1931, Burns Amberson, McMahon and Pinner recruited 24 tuberculosis patients and divided them into twelve pairs, with the cases individually matched with each other on the basis of clinical assessments. Group A was then assigned to receive the drug and Group B served as a control with the assignment based on "a single flip of a coin" [2].

## BLINDING IN CLINICAL TRIALS

Most investigators have firm views about which of a range of alternative treatments is more effective and often, which is more appropriate for particular groups of patients. As a result, there is a strong temptation by investigators to channel particular groups of patients to particular treatments (**channeling effect**). Moreover, there is also a risk of the investigators subconsciously losing their objectivity in their assessments of treatment effects simply because of their clear preference for particular treatments. Therefore in the design of clinical trial, efforts are made to overcome these potential sources of bias. Blinding (or **concealment of treatment allocation**) is an effective way of doing this. As both patients and

investigators are potential sources of such biases, blinding of both patient and investigators (**double-blinding**) is preferred over single-blinding. The issue of blinding is however still a controversial issue. For example, there is increasing recognition of **context effects** (non-specific treatment effects other than a placebo effect). Blinding nullifies such effects and may underestimate the efficacy of a particular drug in day to day clinical practice.

Moreover, blinding may of course be ethically unjustifiable in some circumstances as patients' preferences are ignored.

## RANDOMIZATION

Perhaps the most important development in the design of clinical trials was the introduction of randomization of treatment allocation. In other words, each patient is assigned to receive one of the treatments being considered in a clinical trial by a random assignment process (throw of a dice or computer generated random numbers). The idea of randomization, first introduced in the design of agricultural experiments by R.A. fisher, ensured that true treatment effect could be separated from other effects arising from differences in experimental conditions or differences in the subjects studied. The success of randomization in increasing the reliability of experimental results, and hence of inferences that are drawn from them, is due to the fact that it controls for influential factors that the investigators are unaware of. In other words, one can never be sere that patient groups, assigned to receive different treatments are truly comparable. Randomization should ensure ever distribution across the treatment groups. It is worth noting that the study by Burns Amberson et al, discussed earlier did not use effective randomization. The investigators assumed that they could identify all prognostic factors. Group but not individual randomization was resorted to. Effective randomization, balances any unknown, but potentially influential, factors out across the treatment groups. A further benefit of randomization is that it should control the channeling effect mentioned above. Such channeling is often subconscious randomization did not feature clinical trials until Bradford Hill introduced it formally in a trial of streptomycin for tuberculosis in 1948. Today randomization is regarded as an essential feature of a well conducted clinical trial [3].

## WHEN RANDOMIZATION FAILS

Randomization may fail when the randomization process is itself biased. For example, bias may be introduced when patients are assigned to treatment groups on the basis of when they attend the clinic. More often, randomization may fail because of small sample sizes. For example consider the extreme case of a trial involving four patients two of whom have, in addition to the disease being considered, a concurrent disease which affects the response to treatment. If the patients are subdivided into two groups of two and each patient is randomly assigned to receive one of two groups, then there is a 33% chance that both patients with the concurrent disease will be in the same treatment group. Be increasing the sample size, such

imbalance is made less likely. Increasing sample size of course also protects against clinically meaningful differences in responses being missed.

### **PROBLEMS WITH RANDOMIZED CONTROLLED TRIAL (RCT)**

Although the randomized controlled trial is widely regarded as the gold standard for evaluating the efficacy and safety of drugs, in practice they have several shortcomings which may limit their usefulness and reduce the validity of inferences made from their results: (i) Even well designed trials are generally powered to detect a change in the primary efficacy outcome measure and therefore usually do not have the necessary size to detect clinically important differences in adverse reaction profiles or new but rare adverse reactions. (ii) Clinical trials are generally short in duration because of both cost and practical reasons. Retaining patients in long-term trials is a very difficult task. Therefore robust can only be made about the short-term efficacy of the treatments being investigated from the results of most trials. This can be a major problem with the assessment of new treatments for chronic diseases such as rheumatoid arthritis or recurrent diseases such as asthma and psoriasis. Assessment of drugs intended to prevent disease is also a major problem. For example, lipid-lowering drugs may be administered for decades while even the best trials are conducted for a few years only. In estimating the efficacy of such drugs, extrapolation of results is the norm. (iii) The primary outcome measure chosen by investigators may not be the optimum and in some cases may not even be relevant for clinical decision-making. Surrogate outcome measures are for example often used in efficacy trials. (iv) Clinical trialists and indeed ethics committees do not generally like the inclusion of "complicated patients" such as the very young, the elderly, those with concurrent disease and those on concurrent medication in clinical trials. Yet such patients make up a large proportion of patients in clinical practice and not treating them is generally not an option for the clinician. (v) Clinical trials usually give little guidance on the value of dose adjustments because few doses are usually evaluated. Yet in clinical practice there is a great need for such guidance. With adjustment of doses, the separation of adverse effects from beneficial effects may be impossible because of non-parallel dose-response curves for efficacy and adverse effects.

### **OBSERVATIONAL STUDIES**

Given the limitations of randomized controlled trials it is not surprising that there has been much discussion and debate about how practitioners should use the results of such trials for guiding their practice. Indeed there are

some clinicians who argue strongly that observational studies provide better guidance a historical discussion of the controversies surrounding the introduction of the randomized controlled trial is provided by Mark [3]. No illustrate the current debates about the relative value of randomized controlled trials and observational studies, a recent question posted to the Cochrane skin group on its electronic discussion group asked: "Which is preferable a poor trial or a good observational study?" Although there can clearly be no simple answer to it, the question generated substantial debate. To even begin to provide an answer, there is clearly a need to have more information about the clinical question being posed and what was meant by "poor" and "good". This is often more difficult than is initially apparent. For example, even for the assessment of published randomized controlled trials there are more than 25 quality instruments available and there is no consensus as to which is to be preferred [4]. Moreover, in practice the aim is to integrate results from both, randomized controlled trials and observational studies.

### **REPORTING CLINICAL TRIALS**

To comprehend the results of a randomized controlled trial (RCT), readers must understand its design, conduct, analysis and interpretation. That goal can only be achieved through complete transparency from authors. Despite several decades of educational efforts, the reporting of RCTs needs improvement. Investigators and editors developed the original CONSORT (Consolidated Standards of Reporting Trials) statement to help authors improve reporting by using a checklist and flow diagram. The revised CONSORT statement presented in this paper incorporates new evidence and addresses some criticisms of the original statement. The checklist pertains to the content of the Title, Abstract, Introduction, Methods, Results and Discussion. The revised checklist includes 22-items selected because empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect or the information is essential to judge the reliability or relevance of the findings. We intended the flow diagram to depict the passage of participants through an RCT. The revised flow diagram depicts information from four stages of a trial (enrolment, intervention allocation, follow-up, and analysis). The diagram explicitly includes the number of participants, for each intervention group, included in primary data analysis. Inclusion of these numbers allows the reader to judge whether the authors have performed an intention-to-treat analysis. In sum, the CONSORT statement is intended to improve the reporting of an RCT, enabling readers to understand a trial's conduct and to assess the validity of results [5].

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