The Clinical Trial Research: How Random is Random?

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There is a rapid growth in the clinical trial market worldwide with an estimated annual budget of US$ 45 billion. The new trend of outsourcing the late stage drug development is expected to double the growth rate by 2015.¹ The developing countries have responded with equal enthusiasm, facilitating the cash flow (through market-interaction) and skills acquisition. In Pakistan, Drug Control Organization was established for facilitating local pharmaceutical units and drug importers in the registration and licensing. Federal Ministry of Health, Pakistan, has devised Drug Regulatory Authority Act, 2006, in order to provide framework for various activities in this regard.² Its aim was to establish the Drug Regulation System in Pakistan by ensuring production, availability and accessibility of quality, safe, efficacious drugs and medicines to those in need, besides promoting relevant research and development, pharmacovigilance and drug information.

It is encouraging to see that the number of Randomized Controlled Trials (RCTs) reports from Pakistan has increased over the course of last decade. An earlier survey carried out to look at the research productivity of psychiatrist identified 108 publications over the course of ten years (1993-2004). The mean Impact Factor (IF) of these studies was 2.75 (ranging from 2.21 to 3.29). There was only one RCT identified in that literature review. This situation has changed in various disciplines.³ A review of literature using the key word like ‘Randomized Controlled Trials’ (RCTs), ‘Randomization’, ‘Controlled trial’, ‘Blinded Experiment’, revealed more than a dozen well conducted trials reports published in high impact journals. The research-training perspective is also increasingly emphasizing the design and conduct of RCTs. This opinion piece will focus on the science of randomized controlled trial as an emerging discipline.

Randomized control trials are considered to be gold standard in terms of clinical decision-making. The three features of RCT which confers advantage over other uncontrolled experiments are randomization, blinding and a placebo-control group.⁴ These are fraught with potential pitfalls for clinical investigators as well. Through randomization, investigators ensures that characteristics, which are known (like socio-demographic characteristics) and those that are unknown (genetic predisposition, immune status, etc.), are balanced between the two groups. However, randomization only ensures balance when the sample size is large enough.

Sample size calculation is not only a matter of good science but also has to do with practicalities of time and resources.⁵ Though it is unethical to do an under-powered study, subjugating the participants to unwarranted risks, it is equally undesirable to waste resources once the research-question has been answered. In a clinical trial small sample does not ensure an automatic balance. There are techniques to ensure balanced allocation to both the groups. These can be grouped according to the various stage of the trial.

One way randomization can ensure a balanced base line characteristics is by stratifying the groups according to variables which are known to have prognostic significance (like age, gender, comorbidity status, etc.).⁶ However, the number of strata needs to be reasonable. In the planning phase, a (permuted) block randomization ensures that equal numbers of individuals are randomized to the intervention(s) and control group. Once the study is on the roll, investigators could allocate treatment through minimization in order to ensure a balance.⁷ This can be challenging since complete information should be available as the patients accrue over course of some time.

The second feature which makes the RCT robust is the elimination of bias. In scientific terms, bias is defined as an opinion or point of view without (objective) evidence to back it up.⁸ Bias can distort the trial at the planning, analysis or conduct of the trial. It can introduce systematic errors, which can make the results questionable.

There is a long tradition in RCT- research to tease out bias in order to make the investigation impartial and robust. Though a long-list of biases exist, discussion of which is beyond the scope of this write-up. It is important to bear in mind that bias at the design stage could mar the whole trial. A certain degree of distanced neutrality should be there when highlighting the clinical equipoise of the research question.

Clinical investigators are liable to ‘believe’ in their intervention, introducing a bias at the design stage. This might be less of a problem in a non-inferiority trial, where an established intervention already exists and investigators only serve to measure the equivalence of new
intervention with the gold-standard. However, investigator who happens to be a clinician is (also) invested in the outcome of newly designed intervention. The outcome of treatment is the sole focus for both the clinicians and clinical trial Investigators (Trialists). However, there is different form of investment from each individual. The former is keenly focused on the individual patient outcome while the latter is interested in generalizability of the findings to similar patient population. The trial outcome is something that should be free of bias in order to results to be credible.

Since science progresses through falsification of false evidence, eventually moving towards the truth, a pre-conceived notion of truth only serves to eclipse the reasoning-skill. Masking or blinding is one way of achieving the neutrality of observation. There are some circumstances in which it is extremely difficult, if not impossible, to construct an inert placebo. Ethical considerations also impede the use of Sham procedures or dummy patches.

Some discourse on the trial end point and outcome measure is also relevant when planning a trial. The outcome measure has to be quantifiable. It should also carry a clinically meaningful effect. The calculation of effect size is dependent on the response rate (or mortality) in the placebo group. The amount deemed to be significant in terms of clinical trial is a decision which investigators have to take at the very beginning. This estimation is always a trade-off between what is desirable and what is practical. Since time and resources are limited some deliberation should happen on the outcome.9

In recent years, there is an increasing trend to look at the surrogate outcome(s) as a trial endpoint. This can come handy in terms of quantifying the final outcome measures. However, there has to be a meaningful correlation between the surrogate and final outcome measures. A surrogate measure may yield a trial endpoint but its correlation with the final outcome needs to be looked in to keeping in view the natural history of the disease.10 The development of an antibody may indicate immune response but may not alter the mortality rates in the long-run. The investigators should finalize the trial endpoint at the very beginning in consultation with all stake holders including a statistician. He/she might be able to guide the principle investigator on the binary versus continuous nature of the outcome, thereby planning the appropriate analysis.

Blinding or masking serves to reduce the selection bias and differential treatment of the trial participants. All attempts should be made to mask the patients, investigators and the assessors in the clinical trial. Administration of a placebo or inert substance in order to mask the administration of active comparator is standard practice in drug trials. In recent years papers have been published describing the methodology of double dummy technique in order to mask two different forms of drug delivery methods, i.e. oral versus injectable. In circumstances when blinding is not possible, like comparison of medical and surgical intervention, efforts should be made to have blinded assessments.11

An important pre-requisite to conduct of a trial is systematic review of evidence on the question of interest. This not only saves the cost but also sets the research question in the light of available evidence.12 When combining the results of multiple trials in order to have a pooled estimate, biased trials will lead to an overestimation of treatment effect. This is more so in trials with small sample size, inadequate concealment of allocation sequence after randomization and disproportionate loss of follow-up and per protocol analysis as opposed to the intent-to-treat analysis. When a scatter diagram is plotted, it will display an inverted funnel. Classically, this visual display is seen as a measure of a publication bias. Absence of display dots (indicating individual studies) on the right hand side of the funnel indicates unpublished studies. They are expected to have insignificant results, deemed unpublishable by the authors and editors. Studies with significant treatment effects and small sample size, plotted on the middle to left side of the funnel, nevertheless might also be biased. Element of chance and random variation can also play a role in variable treatment effect; factors like variable adherence, investigators expertise and enthusiasm can also have a bearing on the treatment estimate. True to the adage garbage-in, garbage-out-biased trial will lead to significant heterogeneity and inadequate pooling of result in meta-analysis.

Another factor which could lead to biased estimate of treatment effect is the variable risk of the illness. Individuals with high initial risk are likely to respond better, with greater treatment effect then those with less risk to begin with. Intuitively this also makes sense. Individuals with great symptoms at baseline and higher morbidity risk will show greater reduction in the absolute risk compared to asymptomatic individuals. Additionally, subgroup data also need to be stratified when pooling in the combined effect from multiple trials in order to avoid heterogeneity and have valid results. Clinical trial stakeholders include the investigators, sponsor, ethics committees and the patients themselves. Safety of the patients is extremely important and cannot be overlooked. For this very reason, an informed consent is signed at the very start by the patient and the principal investigator. The study details are briefed by the investigator to the patient and consent is sorted. Investigator is liable to report any drug related adverse events to the ethics committee, sponsor and the relevant safety committees. The sponsor closely follows
the adverse drug events and investigator take appropriate pre-determined action as streamlined in protocol for the safety of the patient. It is important to note that it might not be ethically justifiable to withhold treatment from a group of patients, just for the sake of experiment, if an effective and reasonable intervention exists. However, the definition of effective intervention is a matter of debate among the community of experts. A trial is only undertaken if there is equipoise in terms of efficacy of treatment ‘A’ over ‘B’. A group of experts, scientists, ethicists and representatives of patients sit on an ethics review committee and debate over the scientific and ethical aspects of the trial. A trial is only undertaken if an independent ethics committee approves the conduct of the trial. This is supposed to ensure the safety of the patients enrolled in the trial as well as facilitation of the advancement of the science for general good of the society including the future patients.\(^{13}\)

The governance of clinical trials is an important issue, with guidelines streamlining the processes. Clinical trials should be carried out in compliance with the Good Clinical Practice (GCP) Guidelines, which are international, ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects.\(^{13}\) Compliance with GCP assures that the rights, safety, and well-being of the trial subjects are protected and that the clinical trial data are credible. GCP and other regulations on human research in drug development have now been formalized in many international and national guidelines and regulations. Adherence to the GCP Guidelines, constitution of Data Safety and Monitoring Board (DSMB) and Trial Steering Committee (TSC) are central to any sponsor led trial and investigating the medicinal product.\(^{14}\)

All over the World, clinical trial research has taken a new importance given the advancement of science, development of new drugs, prevention programmes meant to combat the ever increasing burden of diseases. Established Universities in Pakistan are also establishing Clinical Trial Units in order to streamline the research investigating the efficacy of various interventions in disease prevention and management. It is also important to make a concerted effort to build capacity in the area of clinical trial research and teaching. Short and long-term courses developed indigenously will serve to empower the researchers to test interventions in the local context of care. The College of Physicians and Surgeons Pakistan as the major certifying body needs to streamline the research and training initiatives. International collaboration with established Universities in the industrialized countries will also serve to strengthen the clinical trial research capacity.

**REFERENCES**