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EDITORIAL

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The clinical trials are serious endeavors in terms of cost and the risks entailed in generating the best-practice evidence. The science of clinical trials needs to be considered in essence in order to design studies which answer clinically meaningful questions. There are serious hazards to the safety of the participants once they sign the informed consent to undertake the experiment. Generally the design of the trial is set before actual recruitment of the patients. Any change in the conduct of the trial is considered fraudulent behavior. The conventional parallel arm trial has well defined principles for design and analysis. Contrary to the popular belief the analysis of the clinical trial is simple contingent on the design of the trial. With correct design, the analysis is simple and straight forward.[1] However, there is an increasing awareness that some of the assumptions that were made before the start of the trial turn out to be wrong. The adaptive design challenges some of these assumptions and takes in to account the information as it accrues. This piece discusses issues related to the trial design.

It is surprising to note that the most important aspect of clinical trials is left to element of chance alone. Randomization ensures that elements, known or otherwise, are distributed equally in two groups. It is expected that the outcome in the two groups will be attributed to the intervention rather than baseline characteristics of the participants.[1] The science of sample size calculation is also based on certain assumptions which need to be there in order to know the working numbers.[2] This is also far from being an exact science contrary to the popular belief. However, without the numbers, the actual logistics and other practical planning will be impossible. Consider, for example, the mortality or the effect size in the control group was substantially higher (or lower) making the assumptions related to the response rate in the intervention group somewhat redundant. Alternatively, certain arms of the trial like a dosing schedule might show a substantial benefit over others.[3] Research team is left with the option of either to complete the trial and plan another project keeping in view the findings or change the design of the trial on some 'predefined criteria'? The latter is the case with adaptive trial designs which has been proposed by the Pharmaceutical Research and Manufacturers of American (PhRMA) in their introductory white paper.[4] The former option will delay introduction of novel compound in to clinical care, if proven to have value. The delay can be in terms of many years. Generally speaking, it takes about 12 - 13 years for the new compound to get the licensing approval.

Clinical trials are grouped in to various stages based on the stage of the drug or vaccine development. Phase I and II are considered to be early phase trial which focus on the safety, tolerability and pharmacokinetics of the drug during the development phase. Since the focus is on the safety in the early phase trials, therefore, the sample size is deliberately kept low, i.e. in the range of 50 - 80 healthy volunteers.[5] The phase three trials typically explore the therapeutic efficacy of the agent against a placebo or gold standard treatment in those affected with the disorder. The phase IV or post-marketing surveillance collects the information after its regulatory approval on long-terms side effects or other adverse events.

It is important to recognize that sometime the distinction between the phases is not clear cut. Phase I and II can be merged to look at the tolerability and bioequivalence and phase II and III are merged to test the efficacy in those who are recognized to be high risk for the illness. Adaptive trial design takes this in to account and could have the potential to merge the early phase trials with the therapeutic efficacy checked in the phase III trials.[6] For example, a trial could start with various dosages of the therapeutic agent A (for e.g. 5 mg, 10 mg and 15 mg) and only the best dose (results) are carried forward to the stage II of the trial, thereby reducing the time required to develop and license a potentially beneficial medicinal product.[6] There are various definitions of the adaptive trial design but the key components which make the trial adaptive is change in the conduct of the trial based on unblinded results. The change can be related to the sample size re-estimation, allocation ratio (1:2 vs. 1:1) in favor of favorable dose/intervention or dropping one arms of the trial altogether are based on interim analysis. The criteria are pre-defined in terms of changes to patients' accrual and the statistical power required demonstrating the efficacy of the results.[4] An independent Data Safety and Monitoring Board (DSMB) carries out the interim analysis and recommend the changes in a manner which does not affect the blinding of the participants and the investigators. Recently, it has

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been suggested that the sponsor (Pharmaceutical Industry or University) should also be made part and parcel of the DSMB since cost is also a matter of discussion once the trial design is changed.[7,8] Although there are no set characteristics of the adaptive trials, changes in the specific design features of the trials make them adaptive. The general parallel arm trial can be modified to fit the specific requirement in the cluster-randomized, non-inferiority and factorial trial design.

The cluster randomized trial (CRT) is ideally suited to deliver interventions targeted towards a groups rather than individual. The intervention might be targeted at group level and the outcome is measured at the patient level.[9] Generally, there is a close association between various group members and independence cannot be assumed, which has a bearing on the design.[10] Geographical demarcation, villages and towns make natural clusters for intervention. However, they might differ in terms of important variables like socio-economic status, housing, and other important baseline covariates. In such cases, clusters are generally stratified by variables associated with the outcome measure. Randomization is planned at the level of each stratum. In analyzing the CRT researcher has to take in to account the design effect and the between-cluster correlation. The design effect has to do with the correlation between the individuals within the cluster (intra-cluster correlation coefficient) and the number of individuals within the clusters.[11] The design effect is considered to be the sampling variation of the parameter, as estimated by the square root of the standard error.[12] Another important statistics, which researcher has to consider, is the inter-cluster correlation. The inter-cluster correlation ranges from -1 to +1, implying perfect correlation at +1 and otherwise at -1. Stratification on variables which are correlated with the outcome tends to increase the precision of the study. Therefore, sample size needs to take stratification in to account with randomization planned at the level of each strata.[12] Allocation without consideration of the baseline risk factors tends to distribute these variables unequally in the intervention groups, with subsequent loss of power to detect the difference in these groups. Stratification tends to increase the power to detect the effect estimate in each stratum.[13] Care has to be taken that clusters are geographically far enough in order to avoid the issue of contamination, i.e. participants talking to each other and sharing the knowledge related to intervention thereby unblinding the others.

The design to test the effectiveness of two active interventions against a control can also be done through a factorial trial design. The intervention will be assessed in the combination of 2 x 2 x 2 (8) groups with each unit randomized at least 3 times in to various combinations of treatment plans. The main disadvantage with the factorial designs is lack of power to detected 'interaction' among the combination of interventions.[14] One of the main reasons for conducting a factorial design is to test multiple interventions in a single trial thereby saving the resources with the assumption of lack of interaction between their combinations. However, if such an interaction occurs, the trial is underpowered to detect the effect in the subgroups. The other disadvantage of the factorial trial has to do with the practical management and the compliance of the participants. As the number of interventions increases the trial management becomes more cumbersome.[15] Patients also might not want to try different combinations and grow vary of the participation.

The non-inferiority and equivalence trials look to test the new intervention against a gold standard.[16,17] If there is an already established intervention which is efficacious and well established that rationale for new drug development is poor. However, if the new intervention has less side effects or better mode of delivery then non-inferiority trial can look to demonstrate that the new intervention is as good as the standard one or is no more clinically inferior than standard one. The minimal clinical detrimental effect is identified in advance and used to estimate the sample size and power of the study. In terms of statistics, lower tail or one sided confidence interval is examined in order to see the effect estimate. The measured intervention may turn out to be non-inferior or better than the standard intervention.

In conclusion, the clinical trial research has increased in recent years with added complexities of the intervention in itself. Specialized programmes and courses are being developed to aid the researchers. It is time that credentialing bodies like College of Physicians and Surgeons Pakistan make concerted efforts along with other stakeholders of clinical trials to develop the research-capacity among physicians in Pakistan.[19]

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