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Editorial

Drug Trial

A search for newer and better drugs is as old as the practice of administration of drugs – of any origin and in any form. In ancient days medicine men must have tried new drugs based on anecdotes, hearsay, intuitions, stray observations, current fashions, sheer desparation etc. The eternal search for superior drugs goes on. Drugs in use do get thrown away by the wayside when better drugs are found or fashions change. In today's era of evidence based medicine, any aspiring new drug must prove its superiority over the one in use by scientifically convincing its virtues in the form of greater effectiveness or lesser side effects or better patient compliance because of taste, less frequent dosages, ease of administration etc. Cost does count, more so for diseases needing prolonged treatment and cost benefit ratio is always an important consideration, albeit secondary to the efficiency of the drug.

Planning / designing of the trial

Prior appropriate planning of the trial goes a long way in the smooth and meaningful conduct of the trial. The goal of the trial must be clearly defined at the outset. The trial may be meant to find the efficacy of the drug vis-à-vis an existing drug or to merely work out a better dosage, different frequency of administration, alternative route of administration like vaginal in place of oral etc.. Why is this trial being undertaken? Is it merely to comply with the mandatory production of a thesis for postgraduate examination or to add some publication to further academic career promotion or to help a pharmaceutical company or to primarily improve patient management? Whatever be the reason for undertaking the trial, it must be conducted methodically and scientifically. The full information about the drug must be obtained. All the existing literature must be studied at this early stage and not, as is often done, after analyzing study data. Proper designing of the trial is necessary to begin with. Methodology must be clearly defined. The end point must be precisely laid down, e.g., relief of pain, rise in hemoglobin level, lowering of blood pressure etc.. The number of cases needed to study for drawing a statistically valid conclusion must be carefully worked out in consultation with a competent biostatistician who would also decide upon the suitable statistical tools to be employed for analyzing and evaluating the data. In general, the smaller the difference the outcomes of the two treatments under comparison larger should be the number of patients to be studied. The number of patients that can be studied at one center depends on the frequency of the disease. A less common disorder like eclampsia needed a multicentric collaborative study to enroll adequate number of patients over a reasonable period of time[1]. The criteria for a patient's inclusion in or exclusion from the trial ought to be precisely and unambiguously laid down and must be strictly adhered to . It must be remembered that drugs giving wonderful incomparable relief - like penicillin introduced six decades ago or hopefully a drug giving total cure for AIDS in near future – are not easy to come by. Almost always a drug tried out has only a marginal or at best a moderate advantage over an existing drug. This rather small advantage can be convincingly demonstrated only by a properly randomized, controlled, double blind study which is needed to remove all possible biases. The control group must be reliably similar and comparable with the study group in all respects. The better the control group the more realistic and reliable the estimate of greater or lesser benefit. The study group receiving the new drug could be compared with the control group receiving the currently used drug or no drug i.e., placebo. The first randomized trial was published in 1948[2]. Now randomized controlled trials have become a gold standard for drug trials. Randomization is the only way to eliminate the influence of any unknown factors on the outcome. Randomization can be done away with only in very rare instances where the treatment being tried out is expected to have a substantially large benefit to the patient. The secrecy of randomization must be meticulously maintained till the point of the actual administration of treatment to the particular patient. Both the clinician treating the patient and the clinician independently evaluating the effect of the treatment must be blind to the actual treatment received by the particular patient until the compilation of final results is done. The biostatistician should now analyze the data. It must be remembered that inadequate concealment of randomization can substantially distort the outcome of the trial[3].

Women's empowerment regarding participation in the trial

The Nuremberg Code was established as a response to the disgusting medical experiments conducted by the Nazis on Jew prisoners. Now, it is criminal to conduct clinical trials on patients without prior informed written consent.

In India and in many developing countries, patient participation in clinical trials is taken for granted. Her consent for the same is either not taken or just considered a formality. But her informed written consent for participation in the trial is absolutely mandatory. She must be given complete information, necessarily in a language that she understands, about the drug being tried out, especially, its side effects and margin of expected benefits. Inconvenience to be caused to her in the form of additional visits to the treatment center, repeated investigations for assessment of treatment effect, additional cost (travel, drug, investigations, loss of wages etc.) must be spelled out. Additional visits are also demanding on a relative who invariably accompanies her. It must be emphasized that participation in the trial is purely voluntary and that she would receive proper treatment even if she refuses to participate in the trial. She clearly has the option of not participating in the trial. Refusal to participate in the trial is her absolute right and it is morally, ethically and legally binding on the clinician to protect it. With the advent of the Consumer Protection Act, all those conducting various clinical trials should take notice of this. Participants in clinical trials must be adequately informed and protected[4].

It is necessary to design proper documents to give to the patient eligible to be accepted in the drug trial. These must include all information about the proposed trial including the significance and implications of randomization. It is also necessary to draft a proper patient consent form in the light of the above mentioned facts. It is often said that uneducated patients are incapable and incompetent to give an informed valid consent. It must be emphasized, therefore, that lack of education cannot be equated with lack of intelligence. Uneducated women running their shops and businesses very competently and intelligently, abound both in rural and urban areas. Every clinician conducting a drug trial should be conversant with the Helsinki Declaration[5] and the relevant guidelines of the Medical Research Council[6].

Ethics Committee

Once the clinician intending to undertake a drug trial has properly planned and designed the trial, worked out patient information documents and consent forms, and arranged for financial support, he should present the proposal to the ethics committee of the hospital where the trial is scheduled to be conducted. The ethics committee looks into ethical, moral and legal issues involved in the trial including the role of funding agencies. Funding agencies often require a prior clearance of the trial by the ethics committee. The committee also looks into safeguards provided to the participating patients by way of patient information documents and consent forms. The actual trial can start only after obtaining clearance from the ethics committee.

The trial and the results

It is the clinicians responsibility to conduct the trial properly and faithfully sticking to the design and methodology of the trial and taking due care of the participating patients at every stage of the trial. He should be prepared for unexpected developments. All outcomes and developments, expected or unexpected, must be duly recorded. Unexpected serious developments, like grave adverse effects may mandate termination of the trial but not preclude its publication.

All data must be properly analyzed either at the end of the trial or at intervals predetermined in the design of the trial. The collected and properly analyzed data must be subjected to statistical evaluation by a competent biostatistician using appropriate statistical tools to determine the clinical significance of the outcome. The exact value of the probability ('p') must be presented. A mere statement that 'p' was less than 0.05 and hence the benefit of the treatment was significant is no longer acceptable. When the results are presented, the audience / readers would want to know whether 'p' was 0.049 or 0.011 or 0.004 to enable them to decide whether they should use the drug in their day to day practice.

During the study, incidental information / data might get collected regarding issues which do not form part of the study. These data should be looked into and presented as incidental findings but valid conclusions cannot be arrived at based on them since the trial was not designed to study these issues.

Dissemination of the results

The ultimate goal of any scientific investigation or study is to spread knowledge. The aim of any drug trial must be the publication of the outcome of the trial. The results of the study could be presented at conferences – local, regional, national, international – and published in authentic peer received journals. The results of the study should be evaluated and discussed taking into consideration the available literature irrespective of whether it concurs with the study or differs from it. While presenting or publishing the results, the benefits of the drug must not be exaggerated nor the outcome of the study distorted. Every statement made in the presentation or publication must be convincingly supported by the data obtained during the study. Ever

Negative results must be published and publicized with the same vigor and force as positive results. It is a widely known fact that most of the negative results of drug trials are never published. This is damaging to science and unfair to clinical practice. Every clinician would want to know the fact that a particular drug carries no benefit to his patient. Drug trial is of little use unless the results, positive or negative, are translated into patient care. The reluctance of pharmaceutical companies to see the unfavorable outcome of the trial published is understandable but not justified. Hence, every clinician conducting a drug trial at the behest of a pharmaceutical company must make it a condition that the results will be published even if they are unfavorable to the drug being tried out. The publication must honestly mention vested interests of all those involved in the trial e.g. pharmaceutical company, funding agencies, the hospital involved, clinicians conducting the trial etc..

Conclusion

Drug trials should be properly designed, meticulously conducted, faithfully analyzed and competently scrutinized statistically to evaluate the efficacy of the drug being tried out. They should be honestly presented to the audience at professional conferences and to the readers of medical journals. Results unfavarable to the drug being tried out must be published and publicized adequately.

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- Mahendra N. Parikh