

Editorial

Drug Trial

for newer and better drugs is as old as the administration of drugs – of any origin and n. In ancient days medicine men must have drugs based on anecdotes, hearsay, intuitions, rations, current fashions, sheer desperation. Eternal search for superior drugs goes on. Drugs get thrown away by the wayside when better found or fashions change. In today's era of based medicine, any aspiring new drug must superiority over the one in use by scientifically its virtues in the form of greater effectiveness de effects or better patient compliance because ss frequent dosages, ease of administration does count, more so for diseases needing treatment and cost benefit ratio is always an t consideration, albeit secondary to the of the drug.

designing of the trial

ropriate planning of the trial goes a long way oth and meaningful conduct of the trial. The trial must be clearly defined at the outset. ay be meant to find the efficacy of the drug n existing drug or to merely work out a better ferent frequency of administration, alternative ministration like vaginal in place of oral etc.. trial being undertaken? Is it merely to comply mandatory production of a thesis for ate examination or to add some publication academic career promotion or to help a utical company or to primarily improve anagement? Whatever be the reason for g the trial, it must be conducted methodically ifically. The full information about the drug btained. All the existing literature must be his early stage and not, as is often done, after study data. Proper designing of the trial is to begin with. Methodology must be clearly he end point must be precisely laid down, of pain, rise in hemoglobin level, lowering of sure etc.. The number of cases needed to study g a statistically valid conclusion must be rked out in consultation with a competent ian who would also decide upon the suitable tools to be employed for analyzing and the data. In general, the smaller the difference mes of the two treatments under comparison hould 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 time¹. 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 1948². 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 trial³.

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.

dia and in many developing countries, patient participation in clinical trials is taken for granted. Herent for the same is either not taken or just considered formality. But her informed written consent for participation in the trial is absolutely mandatory. She be given complete information, necessarily in a language that she understands, about the drug being put out, especially, its side effects and margin of expected benefits. Inconvenience to be caused to her in form of additional visits to the treatment center, extended investigations for assessment of treatment, additional cost (travel, drug, investigations, loss of wages etc.) must be spelled out. Additional visits are 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 a 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 the fact that participants in clinical trials must be adequately informed and protected⁴.

It is necessary to design proper documents to give to the patient who is eligible to be accepted in the drug trial. These documents include all information about the proposed trial, including the significance and implications of the trial, and the risks of participation. It is also necessary to draft a proper informed consent form in the light of the above mentioned points. It is often said that uneducated patients are ignorant 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 competently and intelligently, abound both in rural and urban areas. Every clinician conducting a drug trial should be conversant with the Helsinki Declaration⁵ and the relevant guidelines of the Medical Research Council⁶.

Committee

When the clinician intending to undertake a drug trial has properly planned and designed the trial, worked out the patient information documents and consent forms, arranged for financial support, he should present a 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 approval 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 clinician's 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 reviewed 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 unfavorable to the drug being tried out must be published and publicized adequately.

References

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