ETHICAL CHALLENGES IN THE DESIGN OF CLINICAL TRIALS

Conducting clinical research in an ethically responsible and appropriate manner is the responsibility of every investigator and study sponsor. Much attention has been given to the protection of human subjects by investigators around the world, and protecting the rights and welfare of subjects is vitally important.[1] Such protections are, however, not sufficient to ensure the ethicality of a trial. Informed consent, full disclosure and independent oversight, all key factors in human subjects' protection, will not guarantee that a trial is ethical if the design or conduct of the trial is faulty.

The three ethical principles generally identified as governing clinical research[2] are respect for persons, beneficence and distributive justice, as articulated in the Belmont Report.[3] Although ethicists and others have debated the philosophical basis for these ethical principles,[4] they have nonetheless become the foundation upon which many ethical clinical trials are based.

Clinical trials that are poorly designed, poorly implemented or poorly conducted may violate any or all of these principles. This paper examines several common problems with clinical trials and briefly discusses the ethical implications of each.

The Principle of Equipoise: Is the Trial Justified?

See presentation:
Systematic Review of relevant evidence

The drug development process has become increasingly standardized with established guidelines regarding the types of studies and amount of data required before a trial can be undertaken.[5] However, the actual decisions regarding the appropriateness of a trial depend on more than just having done the required preclinical studies and even go beyond determining that the compound, device or procedure is likely to be safe. Levine has proposed that, *"It is now generally accepted that the ethical justification to begin a randomized clinical trial requires, at a minimum, that the investigators are able to state that there is an honest null hypothesis to be investigated."*[6] This is referred to as clinical equipoise. The concept of equipoise permits an investigator to ethically participate in a trial when there is a genuine professional disagreement among experts as to the preferred treatment.[7]

It may also be ethical to conduct randomized clinical trials (RCT) even when there is a strong reason to think that the new therapy may be superior.[8] For example, although the preliminary data may suggest a superior therapeutic effect that finding may not have been confirmed, or the nature and severity of adverse events may not be adequately understood, in which case further evaluation to determine the risk/benefit of the new therapy may be justified. However, once an adequate, well designed trial has disproved the null hypothesis then it is very difficult to justify an additional trial conducted merely to confirm the initial finding. When independent confirmation of the rejection of the null hypothesis is necessary, as is usually the case for drugs regulated by the FDA, all Phase III trials should generally be conducted concurrently.

Design of the Clinical Trial

For more information see presentation:
Evaluation of Public Health Intervention

An ethical clinical trial must be designed so that the data derived from the trial will adequately answer the hypothesis being studied. Regardless of how well informed subjects may be regarding the risks associated with participation in a given trial, they cannot ethically be exposed to those risks if the design of the trial is faulty. Put simply, a poorly designed clinical trial can never be an ethical trial. The principle of respect for persons demands that investigators respect the participation of patients/subjects and avoid

exposing them to risk, discomfort or inconvenience unnecessarily.

The RCT is the "gold standard" for the evaluation of new therapies with good reason. Of course there are other approaches to evaluating a new medical therapy, including open trials or the use of historical controls in place of active controls. But except in rare instances it is the RCT that will provide the best data to support a claim of safety and efficacy for a new drug or device.

As described by Levine,[9] the RCT has four main elements that help to ensure an ethical trial. First, it is a controlled trial. Simultaneous controls guard against committing the post hoc ergo propter hoc fallacy. Second, the significance of the results is tested using statistical methods. Third, where possible the trial is conducted in a blind fashion, either double-blind or if that is not possible single-blind. Blinding reduces bias on the part of both the investigator and the subject. Fourth, the trial is randomized. Randomization has two purposes in a clinical trial. The first, and most widely recognized, is to minimize bias. The less obvious ethical advantage of randomization is that it helps assure compliance with the principle of distributive justice, in that all subjects have an equal chance of receiving the new therapy and likewise an equal chance of being exposed to the risks of that therapy.

Choice of Controls

The choice of the control to be used has generated controversy among both researchers and ethicists, who grapple particularly with the issue of placebo controls. The use of a placebo control has advantages in increasing the "assay sensitivity" of the trial[10] and thus may be preferred by regulators. Lavori suggests that "The intent to use placebos follows from the wide recognition that a statistical tie between standard therapy and the investigational therapy is uninformative by itself."[11] From a practical perspective placebo controls generally permit the determination of drug effects in a smaller trial than would be possible in a trial that tested the novel therapy against an active control.

The ethical issue arises in those not infrequent situations where it is reasonable to believe that some patients would respond more favourably to standard treatment than to placebo. The principle of beneficence, which includes the precepts "to do no harm" and "to maximize benefits while minimizing harm," would seem to reinforce the view that placebos are ethically inferior, if not completely unacceptable, in such cases.[12] Allowing a disease to go untreated or undetected when there exists a therapy of known effectiveness could do harm to the subject and does not appear to necessarily maximize the benefit.[13] Temple[14] and others who advocate the use of placebos suggest that it may still be ethical to ask patients to risk being randomized to a placebo control, provided that the investigator could assure that subjects would experience no "unacceptable" risk as a consequence of receiving the placebo. Close monitoring of the subject's condition during the course of the trial, prompt removal from the trial of patients who demonstrate a lack of improvement or whose conditions worsen, followed by administration of appropriate proven therapy, offer ways to prevent unacceptable harm.

An example of a trial that meets this standard might be one for the treatment of mild to moderate hypertension, a condition for which the available medical evidence suggests that a modest delay in the initiation of treatment or a short interruption in treatment would not pose an unacceptable risk. Temple[15] gives the example of "mild headache" to illustrate what he considers to be "acceptable" risk or harm, and Lavori[16] extends this to the field of psychiatry using as an example the study of treatments for depression, suggesting that "this might correspond to one criterion symptom, but only to a mild degree of severity."

An example of when the use of a placebo control is in conditions where there are no known effective therapy is the CRASH-2 Trial (www.crash2.lshtm.ac.uk).

The burden of demonstrating that the use of a placebo control in a specific trial will not result in an "unacceptable" risk lies with the

investigator, who ought to make such a determination based on data and be able to quantify the degree of harm that is possible as well as the likelihood that a subject will suffer such harm.[17] The International Conference on Harmonisation (ICH) has issued a guidance document, E10: Choice of Control Group and Related Issues in Clinical Trials, that provides a practical discussion of these issues for pharmaceutical trials.[18]

Statistical Considerations

One of the core strengths of the RCT is that it permits the hypotheses to be tested statistically. The degree to which the outcome of the statistical analysis can be relied upon is a function of several factors. The first, and perhaps most important, is the choice of the statistical techniques to be employed. Increasingly sophisticated approaches to statistical inference testing, such as the use of Baysean rather than frequentist methods[19] certainly have the potential to improve the evaluation of new therapies. However, unless the techniques used are selected with a clear understanding of the endpoints to be evaluated, the nature of study population and the limitations of the data that will be available from the trial one cannot feel confident that an appropriate statistical analysis has been performed. Of particular importance, the statistical techniques to be used must be identified before the trial begins.

The trial must be designed so that the analysis will have sufficient power both to detect real differences and to reject spurious differences. Underpowered trials are a particularly troublesome problem because the study has produced data but the data have no predictive value because of the failure to gather sufficient data. Put another way, an under-powered study is both unethical and a waste of resources. This sad state of affairs usually occurs in one of two ways. The worst situation is that the study was not sufficiently powered (i.e., did not have a sufficiently large sample size) from its inception. This simply should never happen, since everyone involved in the design, review and approval of the trial should be cognizant of the need to have a clear power calculation and sample size estimate as part of the statistical plan for every trial. The ICH has issued a guidance, E9: Statistical Principles for Clinical Trials, that provides a basis for evaluation that can be applied by sponsors, investigators and institutional review boards when the protocol is reviewed.[20]

A trial that was originally planned with an adequate sample size may be flawed by a large number of subjects lost to follow-up or by excessive missing data. In both cases the value of the trial is jeopardized. These problems are best managed by prevention rather than cure. A scientifically sound and ethical protocol is of no value if the study is not properly conducted. The problem of subjects lost to follow-up is one that is frequently encountered, but realistic explanations of what will be involved in the trial during the consent process, frequent communications with subjects and efforts to make the clinical trial experience as easy for subjects as possible will go far in reducing the number of subjects lost. Also, prior experience should be used to establish probable dropout rates so that the initial sample size can be adjusted accordingly.

See presentation:
Sample size calculation for more information

The problem of missing or incomplete data is best addressed through training and monitoring of clinical investigators, coupled with an effective data management and query system. The statistical analysis plan should also anticipate the possibility of missing data and determine the approach that will be used to manage missing data in the analysis. Finally, the trial must be conducted in such a way that the data to be analyzed are accurate, complete and reliable. Without assurance that the data which underlie the analysis are valid it is not possible to assert the validity of the conclusion(s) drawn from the analysis.

Randomization

Randomization is another powerful way to minimize or avoid bias, but it is effective only if it is genuinely random. Pseudo-random assignment methods, such alternating assignment to treatments or using a factor such

as odd/even year of birth, do not produce true randomization. Randomization is ethical only to the degree that subjects are fully informed that their treatment will be assigned by chance[21] and only when that assignment is a genuinely random one. The ready availability of random number generation programs and the use of independent registrars make it simple to achieve genuine randomization in today's trials.

Conclusion

Clinical trails are essential to the evaluation of new medical therapies and the RCT is the gold standard for such trials. While issues related to the protection of human subjects are extremely important in assuring that clinical research is conducted in an ethical manner, the design and conduct of the clinical trial itself are also relevant. The principle to keep in mind is that no poorly designed or poorly conducted clinical trial can be ethical. Everyone involved in the clinical research enterprise owes it to the subjects to be sure that no subject is exposed to any risk in a clinical trial unless that trial addresses a scientifically meaningful question, is methodologically sound and is properly conducted.

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