NEWSLETTER
Association for Rational Use of Medication in Pakistan

CLINICAL TRIALS

Clinical trials: value & Problems

A clinical trial is done to give definite answer(s) to questions about the management of health problems. A large number of trials tell us nothing of any value because they have been badly designed, poorly done or wrongly analyzed.

Most of the clinical trials done in Pakistan fall in this category. Almost all of them are sponsored by the pharmaceutical industry and most of them are non-randomized, non-controlled and are open. The only idea behind these so called clinical trials is to increase the sale of these drugs.

On the other hand good trials give us important information about one of several treatments used for a particular condition.

In the present issue of the newsletter Professor Andrew Herxheimer has eloquently discussed the ways the clinical trials should be done and what these trials tell us illustrating it with an example from recent literature.

Most of our readers are not familiar with the methodology of clinical trials as nowhere in their medical or pharmacy training are they exposed to it.

A checklist has also been provided which will help in scientific appraisal of clinical trial reports, so diligently passed on to doctors by the representatives of the industry.

The use of this checklist will reveal that most of these so called clinical trials are worthless and will help the prescribers to critically evaluate the evidence of effectiveness of the products provided by their promoters. This would also help the medical practitioners to make better and rational treatment choices for their patients.

Unquestioned acceptance of the results of clinical trials and then prescribing these drugs in other words mean exposing patients to in-efficacious, dangerous and expensive products.

THE NETWORK
Association for Rational Use of Medication in Pakistan

Dr Andrew Herxheimer
is a world renowned clinical pharmacologist. He is founding editor of "Drugs & Therapeutics Bulletin" from the UK and remained associated with this fortnightly for more than 30 years. These days he is spending an active retired life.
He is one of our valuable international advisers and we are extremely grateful for his contributions, especially for this feature on clinical trials.
-Editor

What do Clinical Trials tell us?

Clinical trials are done to give clear answers to questions about the management of disease. It is necessary to restate the basic ideas that underline clinical trials because if these are unclear it may be difficult to understand some of the other issues surrounding trials.

Whenever we are ill we have to decide whether to do anything about it - to treat ourselves or to consult someone else. Whatever we decide we then make further choices, often a whole series of them, based on what we estimate will be the likely consequences - the benefits, disadvantages and costs in terms of convenience, time and money. And, if we consult somebody, they will use their knowledge and experience of disease and its treatment to help us make such estimates. But making good choices requires reliable information about the outcomes of the relevant treatments for a particular condition. This information is best obtained from clinical trials.

Controlling clinical trials

A clinical trial is done to give a definite answer to a question about the management of a health problem. This is not as straightforward as it sounds. It is not enough simply to give a new treatment to some patients and see what happens. The answers that this would produce would often be wrong and always be unreliable, partly because the course of an illness is so variable and partly because of biases in favor of or against one or other treatment. Many illnesses get better even when no treatment is given and a treatment is of value only if the patients receiving it do better than those not receiving it. A comparison group, called the control group, is therefore needed to control conclusions.

Randomization

To make sure that any differences in outcome between the test group and the control group can be attributed to the treatment being tested, everything else about the two groups should be as similar as possible. The most reliable way of making sure of this is to determine by chance which group each participant will be in, that is, to allocate them to the groups at random. The larger the groups the more alike will they be in all their various characteristics. This is usually done by using random number tables, or an electronic random number generator. Randomized controlled trials enable us to make the most reliable comparisons between treatments or treatment packages, including management without any specific treatment, and to reduce bias.

Cross-over trials

In some trials it is possible to compare the test treatment with the control in the same patients, by giving them one treatment for a certain period then the other for a similar period, often with an interval in between - a cross-over trial. It is quite possible that patients do better on whatever treatment is given first, so in such a cross-over trial half the patients (selected at random) start on each treatment to cancel out any difference due to the order.

Blinding trials

Bias can arise from people's beliefs and preconceptions about treatments. If a doctor, nurse, patient or investigator knows what treatment the patient has had, their expectation can influence what they observe or experience. Ideally, everyone involved in a trial should be blind to which treatment the patient is getting, that is, the trial should be a double-blind trial.

What do clinical trials tell us?

A large number of trials tell us nothing of any value because they have been badly designed, poorly done or wrongly analyzed. But good trials can give us important information about one of several treatments used for a particular condition.

To establish the value of a trial we need to know: what condition was studied; what the diagnosis was and what it was based on; how it was confirmed and how certain it was; what sort of people were included and excluded; what the setting of the trial was; what interventions were compared. If a drug was tested, the dose used and the duration of treatment is very important, and also the pharmaceutical formulation and even the source of the drug. If it was a therapeutic apparatus or an operation being tested, sufficient detail must be given in the report to relate it to other things that have been published and to clinical practice. The report must also state what outcomes were looked for, how they were observed, how they were recorded, the particular measurements that were made, what techniques were used and when that was done in relation to the treatment, and how long people were followed up. Once the validity and usefulness of the trial has been established then the results can be considered - did the effectiveness of the treatments differ? In what way did they differ and by how much? There are many aspects to effectiveness, for example, greater survival, speed and degree of recovery, relapse rate, duration of recovery and relief of various symptoms. When evaluating a clinical trial one has to look at whether there are any important endpoints that have not been considered. Scientists and investigators design trials to ask questions that they think are scientifically important. Until now, consumers (patients) have had little influence on the design of trials. But there are things that matter to patients that trials need to address. One of these is obviously unwanted effects. Also it is important to know how representative trial patients were of all patients with the condition being treated.

Subgroups

Subgroups can only provide useful information if the trial was designed to examine them. The best that can be said about a subgroup pulled out at the end of a trial is that the result raises an interesting question that may deserve further investigation in a trial designed to answer that specific question.

Cost versus benefit

It is important to consider how treatments compare in convenience and cost. Most trials do not give direct answers to these questions. However, it is possible to tell from what happened to the patients: how convenient, pleasant or unpleasant a treatment was and what happened to the people in the two comparison groups. It is also possible to make some estimates of costs, in terms not only of money but of time spent by patients, people doing the trial and people caring for the patients.

Reliability of results

The question of the reliability of results can only be approached by statistical evaluation of data. Could the results in a trial have come about by chance? Something might be statistically significant but not clinically significant. It is very common for a clinical trial to give an uncertain result. The difference between the active treatment and the control may be in the predicted and hoped-for direction, but could easily have arisen by chance. This happens especially in trials that have included relatively few patients, or when the real difference between the treatments is small, or when there is great variability among patients. It is important to decide beforehand what strength of evidence is needed to be convinced that the treatment effect is real and then to combine the results from all the relevant trials in a systematic and reproducible way.

Meta-analysis

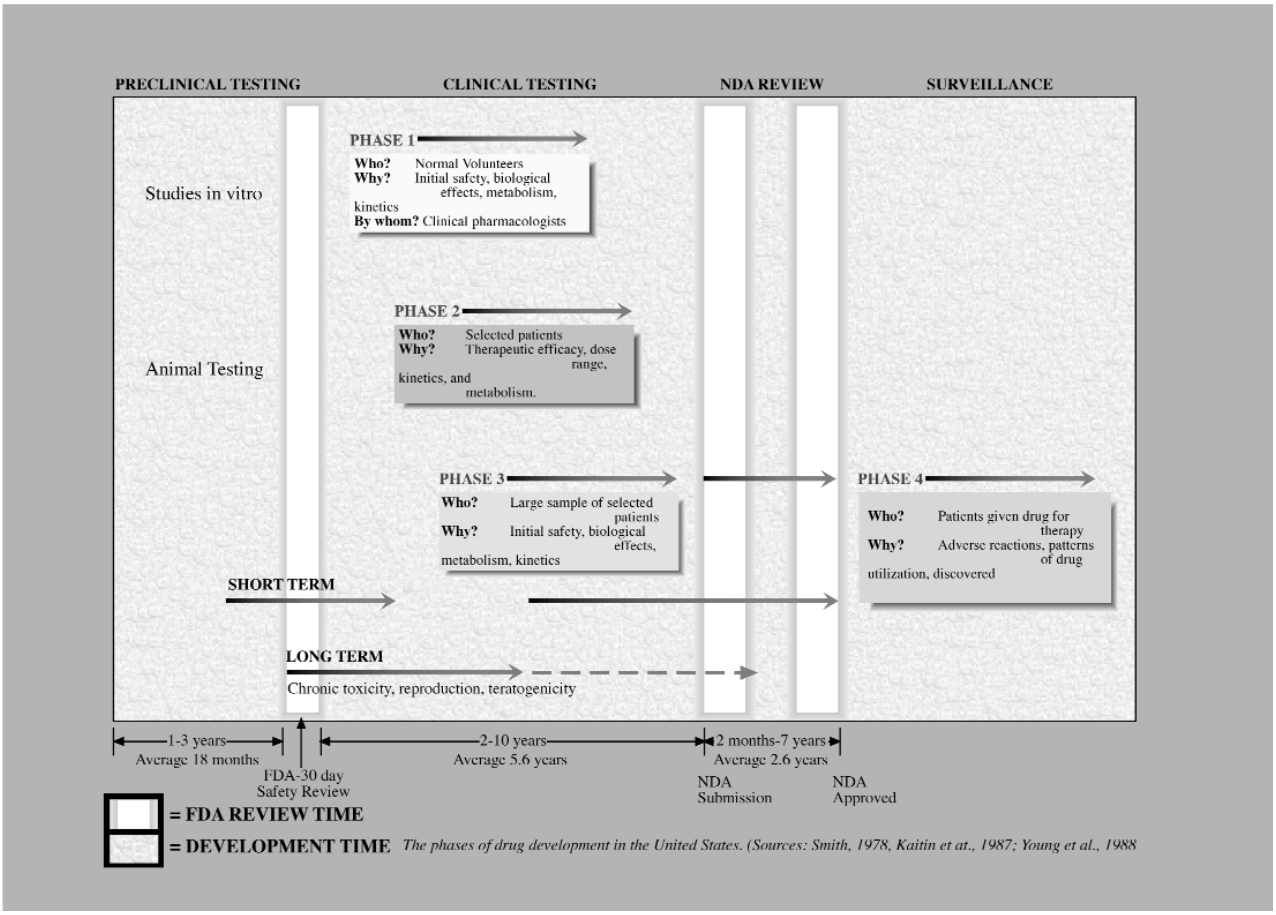
One method for combining data is meta-analysis. It is not appropriate to add the results of trials unless they are sufficiently similar. When meta-analysis is justified and possible, the combined results can give a clear answer that could not have been obtained from any of the individual trials. The methods of performing such systematic reviews of clinical trials have now been well worked out.

Reasons for a trial

Finally, it is important to elicit the reason(s) that, made the authors choose the questions asked in a particular trial and to decide whether the questions matter to patients and/or doctors. Many trials are done by pharmaceutical companies to provide evidence of effectiveness for their drugs so that they can give the trial results to the regulatory authorities to obtain a license and market the drugs. That does not mean that the questions those trials ask are medically important. In fact, the drug may be duplicating something for which a good treatment already exists.

Conclusion

Clinical trials should give us clear answers to questions about the management of disease. Randomized controlled trials are the best way of making reliable comparisons. The art of designing and performing trials is to ask questions that are important for patients and that can be answered. Trivial or unanswerable questions are not worth investigating. A single trial can provide definite answers to no more than one or two questions, so the results of related trials need to be combined whenever that can be done.



The phases of drug development in the United States. (Sources: Smith, 1978, Kaitin et at., 1987; Young et al., 1988

CLINICAL TRIALS

At different phases of drug development

Drugs develop in many pre-clinical and clinical phases. The objective of the pre-clinical phase is to find out the efficacy and safety (teratogenicity, carcinogenicity & mutagenicity) of the test compound in animals. If permitted, clinical trials are then conducted in human beings.

Phase I study
Carried out on about 100 healthy human volunteers. Pharmacokinetics, pharmacodynamics and metabolic effects of the drug are observed.

Phase II study
Involves administration of the drug in about 500 patients to find out the optimum dose and pharmacological effects in a particular disease.

Phase III study
Multi-centric clinical trial: The candidate drug is administered in 1000-3000 patients to check efficacy and adverse drug reactions (ADRs). Data obtained is submitted to authorities and if they are satisfied license is granted to manufacture and market the drug.

Phase IV study
Post marketing Surveillance: the objective is to find out the long-term safety as well as any new indications. This is done by monitoring ADRs of the new drug being used by millions of patients. If several reports of any unacceptably serious effect are obtained, the authorities may ban the drug.

No "new drug" development takes place in countries like Pakistan. The companies sponsor few clinical trials but their aim is more promotional than evaluative. Most disturbingly, Phase IV studies, which are also statutory requirements in Pakistan, do not take place. This coupled with absence of any effective ADR monitoring system, one never knows what harm drugs are causing to the people. Post marketing surveillance in developing countries mean only marketing surveys by companies to grab wider market share.

A randomized, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure

An example of a good clinical trial

Background

Anal fissure is most commonly treated surgically by internal anal sphincterotomy. However, there is some concern over the effects of this procedure on continence. Nitric oxide donors such as glyceryl trinitrate (GTN) have been shown to cause a reversible chemical sphincterotomy capable of healing fissures in a small series of cases. This study reports a prospective, randomized, double-blind, placebo-controlled trial to test the hypothesis that topical GTN is the best first-line treatment for chronic anal fissure.

Methods

80 consecutive patients were randomized to receive treatments with topical 0.2% GTN ointment or placebo. Maximum anal resting pressure (MARP) was measured with a constantly perfused side-hole catheter before and after the first application of trial ointment. Anodermal blood flow was measured during manometry by laser Doppler flowmetry. After initial treatments, patients were given a supply of ointment (either GTN or placebo) to be applied to the lower anal canal twice daily. Patients were reviewed 2-weekly. At the initial and follow up visits patients were asked to record pain experienced on defecation on a linear analogue pain score. Endpoints were healing of the fissure or condition after 8 weeks of treatment.

Findings

After 8 weeks, healing was observed in 26/38 (68%) patients treated with GTN and in 3/39 (8%) patients treated with placebo (pC0.0001x2 test). Linear analogue pain score fell significantly in both groups after 2 weeks of treatment. This fall was maintained in those treated with GTN but pain scores returned to pre-treatment values by 4 weeks on treatment with placebo. MARP fell significantly from a mean of 115.9 (SD 31.6) to 75.9 (30.1) cm H_2O ($p<0.001$, Student's paired t-test) in patients treated with GTN but no change was seen in MARP after placebo. Anodermal blood flow measured by laser Doppler flowmetry significantly increased after application of GTN ointment but was unaffected by placebo.

Interpretation

Topical GTN provides rapid, sustained relief of pain in patients with anal fissure. Over two-thirds of patients treated in this way avoided surgery which would otherwise have been required for healing. Long-term follow up is needed to assess the risk of recurrent fissure in patients with GTN.

Lancet 1997; 349: 1 1-14

The Cochrane Collaboration

In 1979 Archie Cochrane pointed out the need for "… a critical summary, by specialty or subspecialty, adapted periodically, of all randomized controlled trials". In response to this challenge, The Cochrane Collaboration has developed as an international network whose mission is to prepare, maintain and disseminate systemic reviews of the effects of health care.

For further information see The Network's Newsletter, Vol.5, No.2, page 16 or ask for more relevant references.

Check List for Appraising a Clinical Trial Report

Methodology of Clinical Trial

1. Whom is the study about?

- how were the subjects recruited?
- who was included and whowas excluded from the study?
- were the subjects studied in "real life" circumstances?

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2. Was the study design sensible?

- what intervention was being considered?
- what outcome(s) were measured and how?

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3. Was the study adequately controlled?

- If a "randomized" trial, was randomization truly random?
- Were the groups comparable in all important respects?
- Was assessment of outcome "blind"?

Questions about Material Provided by Medical Reps.

4. Was the study large enough and continued for long enough, and was follow up complete enough, to make the results credible?

1 Does this material cover a subject that interests me and is clinically important in my practice?

2 Has this material been published in independent peer reviewed journals? Has any significant evidence been omitted from this presentation or withheld from publication?

3 Does the material include high level evidence such as systematic reviews, meta-analysis, or double-blind randomized trials against the drug's closest competitor given at optimal dosage?

4 Have the trials or reviews examined a clearly focused, important and answerable clinical question that reflects a problem of relevance to patients? Do they provide evidence on safety, tolerability, efficacy, and price?

5 Has each trial or meta-analysis defined the condition to be treated, the patients to be included, the interventions to be compared, and the outcomes to be examined?

6 Does the material provide direct evidence that the drug will help my patients to live a longer, healthier, more productive, or symptom free life?

7 If a surrogate outcome measure has been used, what is the evidence that it is reliable, reproducible, sensitive, specific, a true predictor of disease, and rapidly reflects the response to therapy?

8 Do trial results indicate whether (and how) the effectiveness of the treatments differed and whether there was a difference in the type or incidence of adverse reactions? Are the results clinically as well as statistically significant?

9 If large amounts of material have been provided by the representative or company, which three papers provide the strongest evidence for the company's claims?

Adapted from: Trisha Greenhalgh. How to read a paper: the basics of evidence based medicine. London: BMJ Publishing Group, 1997.
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