CLINICAL TRIALS IN SURGERY

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In the past and still too often today medical therapies have emerged in a haphazard and trial and error fashion. Physicians did realise the significance of comparing the results of therapy for similar ailments, but because of imprecise diagnosis unfounded by investigations, lack of communication, personal likes and dislikes and above all mythical beliefs did not pave way for wide spread clinical trials.

Certain therapies particularly those propounded by the "giants" in the field attained glittering prominence, remained in vogue for a variable period, only to sink back into disrepute when evaluated by the uncompromising eye of time. On the other hand medical history is replete with many brilliant innovations which were accepted with great reluctance by ill-arguing colleagues. A classical example is Pare's application of a simple paste ofeggyolk, oil of roses and turpentine on the war wounds when the supply of all oil ran out in an apprehension. Surprisingly this treatment gave comfort to the patients instead of fever, swelling and pain experienced by those who were treated by the previously in vogue method of application of boiling oil and scalding iron. This revolutionised the management of war wounds but it was accepted with great reluctance by the seniors in the fields[1].

During the past few decades controlled, comparative, prospective, randomised clinical trials have emerged as complex and intricate research tools. These are scientific experiments in which laboratory has been transferred to the bedside or operation table. The conclusions drawn on a rational basis of selection of optimum treatment. This article highlights various disciplines and problems faced during conduct of scientific trials with special emphasis on surgical aspects.

The first ever comparative trial is recorded in the "Book of Kings", where a dispute between the followers of Elijah andAhab over the identity of True God is related in Circa 800 B.C. The conflicting hypotheses were tested by laying two bullocks on piles of wood which was won by Elijah as his sacrifice was accepted by the Holy Lord[2].

Until relatively recently, medical research had been generally regarded as the prerogative of doctors not engaged in the routine care of patients. Over the last 40 years there is general realisation of the value of careful assessment of surgical results. Joseph Lister and John Hunter can be credited as the fathers of modern scientific research. They appreciated the need for clinical investigations and indeed conducted careful and worth-while studies into many different disciplines of medicine[3].

The first large and fully organised clinical trial in United States was conducted for chemotherapy of tuberculosis immediately following World War-Il. This still acts as a prototype of the clinical trials of the modern days.

In 1964 World Medical Association drew up a code of ethics on human experimentation. This was later revised in 1975 and is known as "Declaration of Helsinki"[4].

"In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study it may entail. He or she should be informed that he orshe is at libertyto abstain from participation in the studyand that he or she is at liberty towithdraw his or her consent to participation at any time. The doctor should obtain thc subject's frcely-given informed consent, preferably in writing. There should be no modification of this basic right to information and consent. The doctor may advise and suggest, but in an informed situation".

This declaration introduced the concept of "informed consent" as a basic right of the patient.

Development of the treatment Introduction of a new treatment into the community must pass through three phases.

Phase I. Determination of the effectiveness of a therapy by animal experimentation.

Phase II. Lack of toxicity (no mortality, minimum morbidity) by animal experiments.
Phase III. Comparison of the therapy with the modalities available for establishment of possible therapeutic superiority (comparative clinical trials).

What is a Clinical trial

In its simplest form a therapeutic trial is an administration of a treatment to a patient and observing its results. Any conclusions reached can be confirmed by repetition of the same therapy. However, evaluation of new treatment methods is infinitely more complex particularly in the introduction of new surgical therapies.

Regardless of the magnitude of brain-work and animal screening, a time is reached when the new therapy must be administered to the first patient. This is the beginning of a clinical trial. Every conscientious surgeon will admit that his own experience results in the adoption of more critical attitude towards clinical problems. This is an example of ongoing clinical research which improves the overall surgical care. Putting this attitude of mind under discipline is the foundation of clinical trials.

To get maximum information from a trial, the results may be compared with an already established "gold standard", (comparative trials). Comparative studies may be blind (when the patient does not know the treatment, or double blind (when even the observer does not know the treatment) to get away with any bias influencing the results.

Types of Clinical trials

Analysis of the result of various therapies may be prospective or retrospective. Prospective evaluations are most informative because the study is conducted with definite aims in mind. Retrospective evaluations are not that perfect as some valuable information may not have been recorded carefully.

Prospective trials may be simple or comparative. Comparative trials may be randomised when the allocation of therapies (control or trial) is just pick and choose or may be non- randomised when the groups are made according to predetermined criteria. Comparative studies may be of three types. Standard A vs Standard B,. StandardAvs New therapy, Standard Avs StandardA plus adjuvant therapy (Figure)

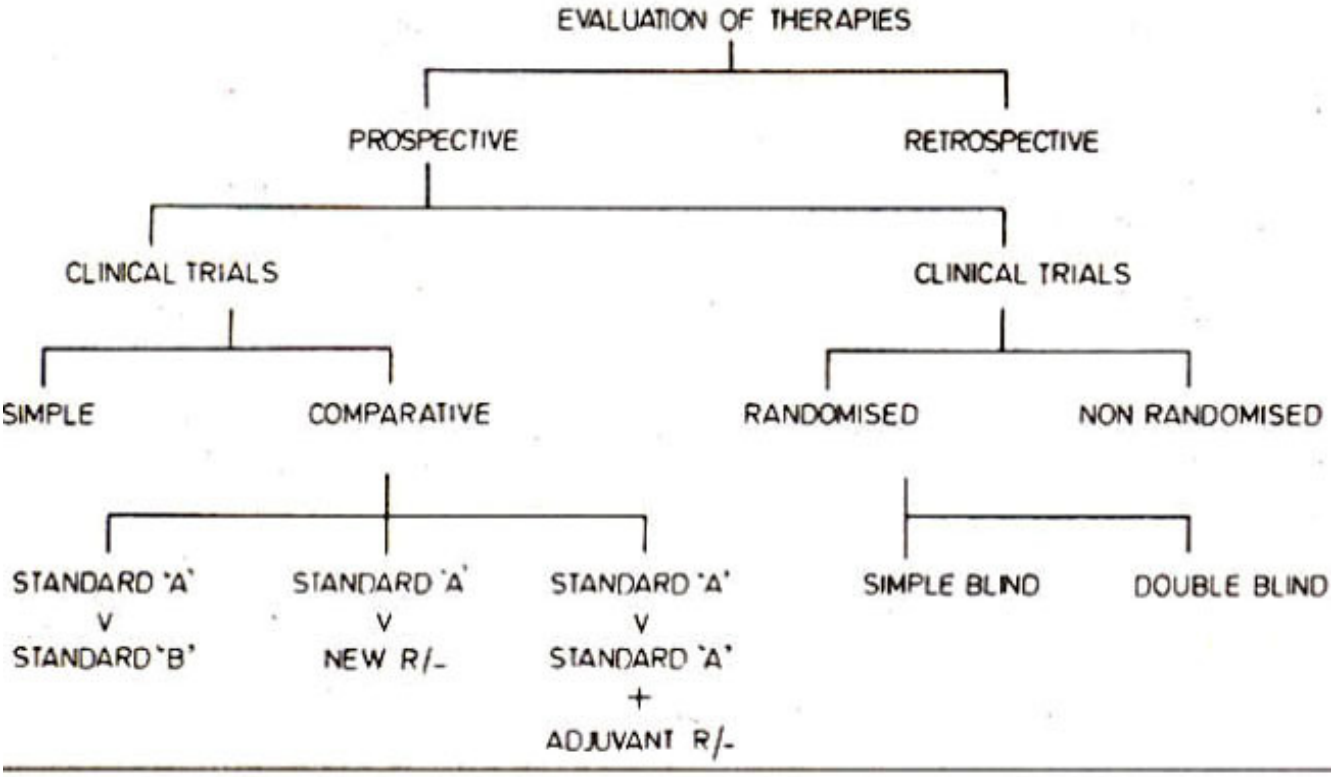

Figure. Schematic representation of various types of clinical trials.

When there are two different approaches to the same problem, the comparative study is labelled as standard A vs standard B. The classical example of such a trial is comparison of Bassini's repair with darning for inguinal herniorrhaphy[5].

In second types of trials a new treatment is compared with an already established therapy. If a surgeon decides to treat all patients of acute cholecystitis by urgent operation (a new concept), it ought to be compared with the classical conservative treatment followed by elective cholecystectomy[6].

On occasion a trial may be conducted to compare an established treatment with the same treatment and an adjuvant therapy like chemo, radio, or immunotherapy. A classical example is comparison of standard treatment (extirpation) of colon for malignant disease[7] vs same treatment followed by chemotherapy[8]. This is a particularly worrying situation because one has to balance the advantages of protecting a proportion of patients against the disadvantage of subjecting a fraction of patients to a dangerous therapy which will be of no avail but may induce a number of serious side effects. Trials of the last two nature must be planned with caution and thorough deliberation. A discussion with other colleagues may be worthwhile. It is further suggested that every hospital should have a local ethical committee which should approve such trials and supervise their conduct.

Trial disciplines

Clinical trials should be conducted in precise and careful manner. Following outlines will help in carrying them out with meaningful results.

The objects of the trial should be clear. It is no use administering a therapy haphazardly and trying to analyse the results. They donot yield worthwhile conclusions.

2. The study design should be carefully chalked out Decision about the nature of trial i.e., blind or double blind should be made from the outset. The proforma must contain all the relevant information. It should neither be unduely brief nor should contain unnecessary details. One should adopt a practical and flexible approach which combines generality with comprehensiveness.

3. Check all the references and read the relevant literature. It is futile to enter into a clinical trial without thorough understanding of the disease process and various types of therapies effective against it.

4. It is much better to carry out a pilot study on a small number of patients before starting the main trial. It will reveal the shortcomings of the design and unmask practical difficulties which must be overcome before launching the trial.

5. The studies should invariably be comparative. Non comparative trials may help drug companies promote their products but do not yield useful information. The use of historical controls may give erroneous results because of difficulties in matching the stage of disease.

6. The problem of informed consent has attained much importance in developed countries though it is not very serious over here. Most of the patients are not interested in hearing about the alternative forms of standard therapy and really prefer to rely upon the doctor's discretion. Most of the patients ask, "can operation be avoided". If the answer is "no", they are not bothered the type and extent of surgery except perhaps for the size of the scar. The only aim in their mind being a cure in one go.

7. The staging of disease process is very important. Newer screening and diagnostic techniques reveal the spread of disease beyond the visible confines and treatment model for a stage may be inappropriate for another stage of the same disease. This has been proved for carcinoma of breast[9] and various types of lymphomas[10].

8. All the variables in the protocol should be standardised to get the best matching pairs for comparison. For example two members of a pair should match in age, sex, weight, stage of disease, competence of surgeon, antibiotic cover and postoperative care if the efficacy of a particular operation is being assessed. Comparisons based on dissimilar groups of patients will give erroneous results[11].

9. It should be decided in drug trials as to use a fixed or variable dose, tailored to the needs of the patient. Use of a fixed dose facilitates double blind comparisons of the treatments and will give maxi-

mum information about the efficacy and toxicity of the drug but is fraught with the danger of administering suboptimal and possibly harmful treatment to a fraction of patients. This temptation should be resisted when a considerable variation in the dosage between patients is required to produce a pharmacological effect. For example, in diabetes mellitus dose is tailored according to the patient's needs[12] and so it should also be in a clinical trial. In such circumstances double blind comparisons must be abandoned in favour of patient's safety.

10. The use of placebo in a clinical trial seems tempting but will keep a group of patients without any treatment. Deliberate denial of an available treatment is ethically wrong and unjustified. The pragmatic view of a clinical trial is that the control arm should be an accepted treatment for disease in question. The use of a placebo or sham or inactive treatment is justified only when there is no recognised and proved management for the disease. This will obviate any psychological or psychophysiological effect on the patient and make the observations unbiased[13].

11. Accurate observations is the key note of any clinical trial. The use of objective measures and numerical expressions give the most reliable results. Preconceived notions may influence the results and invalidate the conclusions. A trial should not be stopped prematurely if the results arc not according to the wishes, The trial must be continued till the truth is fully revealed.

12. Medical statistics has emerged as an integral part of tabulation of results. Everybody involved in the conduct of trials should be familiar with common methods of statistical analysis. One should understand the standard 'P' value, logs, antilogs, linear curves, pie diagrams and their various presentations. In long term follow-up, additional variables like subtraction of death which arc expected to occur in the people of similar age in the normal population and deaths due to unrelated causes must be incorporated. Alternative methods of measurement of therapeutic efficacy such as disease free interval, recurrence rate and appearance of metastatic disease will need be considered as well. In such complicated situations, it is much better to obtain the help of a medical statistician[14].

13. One of the latest developments in clinical medicine is the application of computer for data processing. Recording and retrieving informations has been facilitated tremendously by its use. This also helps in accurate tabulations of results and extraction of inferences. Its routine use will widen the potentials of information technology[15].

Ethical consideration

The committee on controlled therapeutic trials of the International Union Against Cancer (IUAC), has proposed following guidelines for prospective clinical trials[2].

1. It is unethical to attempt to analyse the effects of a treatment by haphazard and uncontrolled administration of that treatment.
2. It is unethical not to carry out a clinical trial when there is doubt whether a new treatment is better than an established one.
3. It is unethical to conduct a trial without an appropriate clinical and statistical design.
4. It is unethical to carry out a clinical trial without due responsibility for the patient's care and if the procedures do not contribute to the benefit of the patients without their understanding and permission.
5. It is unethical to terminate a trial unless a meaningful result has been obtained.

While these considerations may be difficult to follow and may even be debatable, they provide solid guidelines and determine the responsibilities of the trial conducting team.

A number of other ethical considerations may be added to these. A therapeutic trial should be started only if animal experiments or previous experience has established its safety. It should not impose financial burden on the patient. The trial conducting personnel should have no prior commitments to ensure validity of results.

Problems faced

A number of problems may frustrate the smooth conduct of a trial. Some of these are mentioned below.

1. Exclusion of certain patients from the very begin-fling may make a trial less representative. For ex-

ample, exclusion of diabetics in trials on antibiotic therapy will limit their usefulness for general public.
2. Financial constraints regarding provision of necessary equipment, laboratory animals, investigation work, drugs, threads and secretarial service may pose unsurmountable difficulties. Sponsorship by the pharmaceutical industry is tempting but is fraught with ethical problems mentioned already. It is much better if the government sponsors such research activities.
3. Lack of compliance by the patients will give erroneous results. Simplifying the instructions, use of calendar packs, diary cords as reminder or a request to return unused drugs may enhance compliance. For strict control spot checking of blood or urine samples for particular drug may be carried out.
4. Loss of follow-up and withdrawal of patients from a clinical trial may be minimised by a careful checking on the eligibility of the patient to enter the trial before registration both physically and domestically. One may need to issue reminders when the appointments are missed. Stressing the patients to report back to the surgeon in case of a complication will also improve follow-up.
5. A trial may have to be terminated prematurely if its safety cannot be established beyond doubt[16].

Special problems in surgical trials

Trials in surgery should generally be conducted on the protocols given above. The ability to audit and criticise techniques though useful in all branches of medicines, is particularly desirable for surgical practice. Because of the irreversibility of process, surgical trials demand greater care.

Preoperatively, the study model should be designed carefully and patients should be selected meticulously. All relevant investigations should be carried out and stage of disease should be accurately defined.

During operation competence of the surgeon must be ensured and only the specified procedures carried out. If it is not possible, the limitations of the procedures should be highlighted indicating the reasons as well.

Postoperative management should be as uniform as possible. Most of the patients who have undergone trials, surgery will need long term follow-up to assess the quality of life, for decades after any procedures.

Trials in surgery are demanding, time consuming and difficult to conduct. They create pressure upon a busy surgeon to ensure that all aspects of the protocol have been met with. A constant quest for better management and maintenance of enthusiasm are vital for their successful execution. Only by putting surgery on trial can we be confident that the tremendous progress initiated by the surgical giants of the past will be maintained for the benefit of the patients in the future[17].

CONCLUSION

It is vital that the clinical trials, be it small and compact, of moderate proportion or be it large and multi disciplinary continue as a vital and valuable instrument in the conquest of disease. This is the only means of eliminating useless and harmful treatments and selecting the most appropriate therapy for a given ailment. Surgeons must join hands to conduct them carefully and methodically.

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