THE CLINICAL TRIAL IN GENERAL PRACTICE

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FEW should (though some, regrettably, will) lament the passing of subjective clinical impressions as a valid basis for the evaluation of new drugs; but we still have a long way to go in improving alternative methods.

The properly conducted clinical trial has become indispensable as the number of pharmaceutical compounds, especially synthetic compounds, requiring urgent therapeutic evaluation continues to increase. Too many trials involve considerable work on the part of the clinician, the pharmaceutical supplier, the statistician and, in some cases, the patient, yet provide no useful information when the results have been analysed.

I believe that useful clinical trials can be carried out in general practice, provided the general practitioner understands the objectives and pitfalls. It is too easy to be misled into thinking that clinical trials pose so many problems that only the polymath expert could hope to find his way through the labyrinth of organic chemistry, experimental pharmacology, ethics, logic and statistics that sometimes seem to be given more weight than medical experience and acumen.

The truth, as always, lies between the extremes. A clinical trial that is designed and executed without thought and care will be utterly valueless. The general practitioner, however, has a unique and valuable contribution to make in clinical trials: his part in their design and analysis may be limited, but his opportunities and capacities to make pertinent observations are often infinitely superior to any other.

The definition of a valid clinical trial

The clinical trial has been defined by Bradford Hill (1955) as "a carefully and ethically designed experiment with the aim of answering some precisely framed question".

The published report of a good clinical trial will provide accurate data (preferably in a form which permits comparison with the

results obtained by previous investigators) and informative conclusions that will stand up to critical scrutiny.

The simpler and more clearly defined the objective of the trial, the more meaningful and valuable will be the result. If the main objective becomes obscured by side issues, the whole trial can easily lose its validity and its value.

The stages of a clinical trial

It is easier to define a valid clinical trial than to carry one out without falling into one or more of the various pitfalls. Ross (1951) surveyed 100 published papers on therapeutic trials in which control procedures were adopted, and concluded that 73 per cent of them failed to show a definite result.

Laites and Weiss (1958) were even more discouraging. In a ciritical review of the efficacy of meprobamate they analysed 18 trials, and concluded that all 18 suffered from fatal defects in design or execution.

It may be useful to divide a clinical trial into nine phases:

Interest
Reading
Preliminary design
Decision
Final design
Execution
Analysis
Assessment
Report writing

Preliminary phases

It is unnecessary to elaborate that any investigator must familiarize himself with the drug to be assessed, past experience with the compound and the various methods available for carrying out the clinical evaluation. He should review the whole question and ask himself whether to continue with the trial, or to scrap the idea. His decision will depend on practicability, scientific value, and ethics. Does his practice offer sufficient patients, and does the proposed trial involve work which he and his staff can perform without detriment to the normal running of the practice? Are the proposed results worth obtaining? And can they be obtained without contravening the ethical requirements? This last question has received considerable publicity in recent years (Witts 1960; Medical Research Council 1964; *British Medical Journal* 1964), and I need not dwell on it in this paper.

In general, the clinician may rely on the assurance of others on the safety of the test and control drugs to be used. In the United Kingdom submission must be made (almost always by the pharma-

ceutical manufacturer) to the Committee on Safety of Drugs (Dunlop Committee) for sanction to carry out clinical trials, and sanction for a trial in general practice would normally be given only if the safety of the drug had previously been evaluated, for example in a hospital with the facilities for continuous observation and specialist investigation.

Having decided that the proposed trial is worth carrying out, and offers no ethical problems, the clinician enters the fifth phase, the final design of the trial.

Final design

In producing the final design of the trial, the clinician must consider the exact question to be answered, and the known characteristics of the drug under investigation. In the light of this, he must first decide what control procedures are called for; and it is at this early stage that he should seek the help of a statistician (for even those doctors who remember from their schooldays the difference between the arithmetic mean, the mode and the median, rarely have sufficient knowledge of this specialization to avoid drawing ' significant ' wrong conclusions). As Bailey (1959) puts it, " it is important for the statistician to be in on the whole project from the start and not merely to be called in at the end to make some rather doubtful arithmetic look respectable ".

Adequate control procedures are essential if a trial is to produce evidence of any scientific value. No *built-in* controls were required in the first Medical Research Council trials of streptomycin in tuberculosis meningitis, for the disease was accepted as a fatal one; but the use of controls is necessary to show whether any alternative treatment is superior.

A control group is introduced in order that one may be able to analyse the results obtained in the two groups and make a valid comparison between the test drug and a placebo, or between two drugs. In dividing patients into a test group and a control group every effort must be made to ensure that the groups are strictly comparable. One has only to postulate a study in which all the severely-ill patients were given an established drug, and only the moderately-ill received the test drug, for the fallacy to be apparent. Random allocation of patients to one group or the other will ensure an acceptable control procedure, if statistical advice is taken on the means of randomization and the numbers involved.

Another useful control procedure is the ' cross-over study ', in which each patient acts as his own control. He receives one drug for a period, then a drug-free control period, and then the alternative drug. The period chosen must take account of such

characteristics as a latent period or persistence of action (as in Rauwolfia derivatives and monoamine oxidase inhibitors). Clearly the cross-over study cannot be used in short-lived or fluctuating conditions, but may be used in, for example, hypertension, Parkinsonism, migraine, or in a study of the actions, rather than the therapeutic efficacy, of the drug. Absorption studies are a case in point. Where its use is apt, then, the cross-over study has much to recommend it.

The control procedures must also be designed to protect the results from the effects of bias, whether by patient or clinician. The placebo reactor is too well known to need more than a mention but it is perhaps not well enough appreciated that the investigator must not be emotionally involved (Hart, 1958), for an expectant attitude will affect results. Wolf (1959) reports a case where an oral placebo was administered to two groups of subjects under identical conditions, and gastric acidity studied. The group treated by one doctor showed a 12 per cent increase in acidity, and the group treated by the other an 18 per cent decrease. There is evidence in surgery, too, that the enthusiast gets better results than the sceptic. Beecher (1961) compared the incidence of complete pain relief in two groups of patients with angina pectoris in whom the internal mammary arteries were ligated. The enthusiasts obtained a 38 per cent success rate, while the sceptics obtained only ten per cent. See also Loranger *et al.* (1961).

One of the better ways of eliminating bias is the double-blind trial. There has been much confusion over the term ' blind '. A trial is blind when the patient does not know whether he is receiving placebo, control or test drug. When the clinician (i.e. the doctor evaluating response) is also ignorant of the drug being given, the trial is double-blind. Such terms as ' triple-blind ' are, strictly speaking, meaningless.

As far as possible neither doctor nor patient should be able to distinguish the test drug from the control by any physical characteristic—or by simple deduction. If the dosage of the test drug has to be adjusted to response, the same procedure must be gone through with the placebo or (if this is practicable) with the standard drug being used for comparison. Abruzzi (1964), in an article on the treatment of anxiety, attacked published clinical reports on tranquillizers for lack of adequate control, yet himself fell into one of the obvious traps. He claimed to compare in a ' double-blind ' trial pentobarbitone sodium in a long-release form with meprobamate; but the one was given b.i.d. and the other q.i.d.

Moving on from control procedures, we come to the selection of patients. A clear definition of the patients to be included in the

trial must be made at the outset, and published in the final report to inform readers how far the results may be extrapolated to the population at risk. According to circumstances, one might wish to exclude pregnant women, or women of childbearing age and children, or patients already treated with other drugs. The contra-indications of the drug must be scrupulously observed. In certain cases age, sex or even ethnic group might be relevant.

Rigorous diagnostic criteria are vital to proper selection. Although control procedures will reduce error, they cannot prevent errors from occurring if slipshod diagnosis is permitted. Even in well-conducted trials errors of diagnosis do happen. In an MRC trial (Medical Research Council, 1955) to assess ACTH and cortisone in acquired haemolytic anaemia, one of the patients failing to respond was subsequently found to have haemolytic anaemia of congenital origin.

From the selection of patients, one turns to the detailed planning of the regime to be followed. Drawing on his knowledge of the characteristics of the drug(s) under study, the clinician must decide the dose (or dosage range), the frequency and diurnal pattern of dosage, the route and the duration of therapy. (Apropos of this last, be sure that adequate supplies of the drug are available to complete treatment for the number of patients.) When a standard drug is used as a control, it is important to give the correct dosage, or conclusions can be misleading. For example, in a trial (*Practitioner* 1962) comparing two long-acting coronary vasodilators, pentaerythritol tetranitrate was administered in half the usual dose; but this was not taken into account when the authors compared the incidence of side effects. With placebo control, too low a dose of the test drug will not reveal a difference between a drug and a placebo, whereas too high a dose may obscure therapeutic value by exaggerated toxic effects (Medell and Houde 1958).

The effects of other drugs must be borne in mind, and the decision taken to prohibit all other medication, including self-medication; or to record carefully all other drugs.

Side effects pose a real problem: to ask, or to wait to be told. Asking may produce a crop of varied compliants which have no relevance to the drug, but to wait may perhaps obscure a genuine hitherto-unrecorded side effect—especially if it is somewhat bizarre, or offensive to the patient's modesty. Whichever decision the doctor comes to, he should stick to it if his data on the incidence of side effects are to be capable of analysis.

Precautions are less of a problem, for a clinical trial of a comparatively new drug there can be no excuse for failing to observe the recommended precautions. These may include certain signs

to be watched for—even inquired after—special investigations (blood urine, liver function, etc.). The doctor should also have available an antidote, in case of accidental or suicidal overdosage, and should know the recommended methods of treatment. The criteria for discontinuation should also be decided.

All the preparations so far described go for nothing if no data, or the wrong data, are recorded. In Kipling's words,

> " I keep six honest serving-men
> (They taught me all I knew);
> Their names are What and Why and When
> And How and Where and Who
> *The Just-So Stories*—The Elephant's Child

What and *Why* are inseparable: together they ensure that relevant data are not omitted, and that irrelevant data are not allowed to interfere with relevant. For it is worth repeating that a simple study designed to answer a specific and limited question is more likely to be of genuine value than a discursive study from which no conclusions can be drawn.

Data obtained in a trial of one presentation of a drug may be quite irrelevant to another presentation of the same drug. " Formulation of drugs into various dosage forms may modify profoundly the onset, intensity, and duration of physiological response, the correct dosage for the patient, the incidence and intensity of side effects, and the stability of the drugs ". (Levy and Nelson 1961). More recently Lees (1964) has shown the very wide variation in rectal prednisolone absorption from suppositories made up from five different bases; and Venning (1964) reported a fourfold improvement in absorption of spironolactone by a simple alteration in tablet preparation.

However relevant, observations easily become uninterpretable. The effects of many drugs (analgesics come immediately to mind) do not lend themselves to true measurement, and must be recorded subjectively. However, even subjective results must be brought into a meaningful form. Faced with a choice between Good, Moderate and Poor, either doctor or patient will often take the line of least resistance and record Moderate. The various responses should be specifically described in language that the patient can understand—for example, No pain, Pain much improved, Pain somewhat improved, No difference, Pain somewhat worse, Pain much worse.

To come back to Kipling's serving-men, we ask *When* to determine how often and for how long data should be recorded—six times daily for a week, once a fortnight for twelve months, etc. As always, the answer will depend upon the characteristics of the disease and of the drug.

How is of special interest to the statistician. To analyse responses, they must be in a standard form, either numerical or such that they can be coded numerically. A special printed or duplicated report form will be a help, and if a parameter cannot be accurately measured, a system should be devised to reduce variability to the minimum. It is essential that report forms should be filled in legibly and accurately, and should be unambiguously intelligible to someone who has never seen the patient.

Where is of little importance in this study—in the surgery, clearly, is the most efficient, but regrettably will not always be practicable.

Who is to record the data is more important. To observe and record requires skills which must not be under-estimated, and which can be perfected only with a training that does not form part of the present medical curriculum.

Execution

In general terms the execution is the conscientious application of the plans so far described, but it often involves other people.

Following on the general practitioner's duty to brief himself is his duty to brief anyone else involved in the trial—his partner or assistant, and his patients. There must be clear instructions on dosage, route, frequency of administration, possible toxicities etc. I remember a trial to assess the value of a peripheral vasodilator in varicose ulcers, in which an assistant applied the liquid preparation to the ulcers instead of administering it orally. Small wonder that he and the patients complained bitterly that the dressings were sticking to the wounds!

It is even more important to take special care in briefing the patient, who may well have difficulty in fully understanding complex instructions on a strange subject. A *Lancet* (1965) annotation commented on the staggering degree of error (> 30 per cent) in the Census returns of 1961, as revealed by a post-enumeration survey of 6,500 householders. Whether these people were lying about their lack of hygienic amenities, or were truly unable to comprehend carefully written explanations of the questions, *The Lancet's* words remain: " Whoever employs statistical techniques should bear in mind the lessons of the post-enumeration survey. . . . It is less easy for doctors, trained in other disciplines, to realize that even what appears to be a sensible question may yield a misleading answer ". For a report of an outright fraud (deliberate invention of data), see Lasanga (1964).

The clinician in charge of the trial must make every effort to see that observations are made and recorded accurately, which will usually involve the difficult task of defining symptoms with greater

exactness than is necessary for normal practice. If the data are to have scientific value it may also be necessary (quite apart from ethical requirements) to take the patient into one's confidence: full follow-up of cases is necessary if aims of random allocation are not to be jeopardized: and the patient may better appreciate the need to follow instructions. It is, of course, the clinician's job to make sure that his instructions are properly understood.

Analysis and assessment

The raw data comprising a number of individual results in detail must be analysed and summarized to produce proper conclusions. This normally involves the use of statistics, and raises a warning. In the words attributed to Andrew Lang, " He uses statistics as a drunken man uses lamp-posts—for support rather than illumination ". The doctor is therefore advised to have his data processed by an expert (properly briefed on the medical criteria of significance), and confine himself to assessing the results of this analysis.

The assessment must be strictly related to the ' precisely framed question ' that the trial was designed to answer. A trial designed to answer a more complex question would involve many more patients than the individual general practitioner could muster, though he might usefully take part in multi-centre trails of the type organized by the General Practitioners Research Group or the College of General Practitioners.

The clinician (preferably in co-operation with the statistician) should take a retrospective look at the validity of the trial, comparing results with those of other investigators.

If he is satisfied that the trial has been valid, the clinician should decide whether to report his findings. If he has added something to the state of knowledge on the therapeutic usefulness of a drug or the treatment of a disease he should naturally write up the trial and submit it to a medical journal. The results do not, however, have to be revolutionary to justify publication. It can be valuable to confirm other people's results, and especially valuable to provide a rational basis for conclusions that others have arrived at by guess-work and asserveration. For remember, it is entirely possible to arrive at a true conclusion by a series of false or fallacious steps: it still remains for someone to conduct a valid clinical trial to demonstrate the truth of the conclusion.

Writing the report

Data supplied should give all the information necessary for a critical assessment by the reader of the validity of the trial. Glaring examples abound where no difference is shown between two drugs while the author states that one is to be preferred.

The general practitioner's part in clinical trials

As I said earlier, the general practitioner has opportunities for clinical trial that are denied his hospital colleagues. Hodgkin (1963) has very clearly described the different disease spectra that he experienced in hospital and later in general practice. Many of the conditions the general practitioner deals with are never seen in hospitals, while others, seen at an earlier stage, present problems that are quite different from those facing the hospital staff.

In hospitals it is very difficult to collect sufficient numbers of patients with the whole range of acute upper respiratory infections, acute gastroenteritis, the acute infectious diseases of childhood, dysmenorrhoea, morning sickness, etc. These are the stuff of general practice, and the general practitioner has made, and will increasingly make, substantial contributions to medical knowledge by assessing therapies in his own particular field. One may mention, in particular, the report published by the College of General Practitioners (1957) on the prophylactic use of antibiotics in measles, and that of the General Practitioners Research Group (*Practitioner*, 1963) on " Drugs in Pregnancy ".

The general practitioner has an advantage over his hospital colleague, too, in having an established personal relationship with his patient, so that he has fewer barriers to overcome.

The problems facing the general practitioner when it comes to carrying out a clinical trial have been enumerated (Fry 1964) as follows: lack of training, lack of time, lack of staff, lack of equipment and lack of finance.

None of these problems, I would suggest, need deter the general practitioner who is interested in such work. While it is true that the medical student does not get enough training in clinical pharmacology and drug assessment and that the academic facilities in these fields are inadequate, it is still possible to get advice and guidance. The College of General Practitioners has a Research Advisor for this purpose, and the great majority of hospital consultants will willingly give advice, as will the Medical Research Council, the Arthritis and Rheumatism Council for Research, the British Tuberculosis Association and other specialized bodies. In this country most pharmaceutical firms have medical departments, one of whose functions is to provide aid to clinicians wishing to carry out investigations. These departments will help design the trial, and supply the test drug, control drugs and report forms. The majority will also provide or arrange for expert statistical advice, and will if necessary arrange for the results to be analysed.

On the whole the execution of a clinical trial is not a time-consum-

ing business, and can usually be incorporated into the routine running of the practice without much difficulty. If the general practitioner is conducting a trial of special interest to a pharmaceutical firm he may well be recompensed for any extra work to himself or his staff.

It is true that the doctor who literally runs his practice single-handed could be deterred from many clinical trials by lack of staff; but this will surely apply to very few.

I would submit that lack of equipment is even less important. Many trials do not require any specialized equipment. Either the investigations can be done within the existing framework of the practice, or suitable arrangements can be made with the local hospital and laboratories. If equipment is needed, it can often be borrowed, hired or in some cases received as a gift.

Finance to cover extra secretarial aid or such simple items as stationery and filing cabinets might be obtained as a research grant, or such expenses might be paid by a pharmaceutical firm willing to support the investigation.

Summary

The general practitioner should be encouraged to take part in clinical trials, since he has a unique contribution to make. The superficial difficulties in his way can usually be overcome by specialist help from hospitals and laboratories, from research bodies or from the pharmaceutical industry. This article provides the general practitioner with an introduction to the design and execution of a valid clinical trial, with notes on some of the pitfalls to be avoided.

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Deafness in acute otitis media. J. F. NEIL *et al. Brit. med. J.* 1966. **1**, 75.

This paper reports an audiometric follow-up (for three years) on 121 children with acute otitis media. Nearly all cases were treated with oral penicillin by their general practitioner.

Only two children (1.5 per cent) suffered permanent damage to hearing in both ears and a further six (5 per cent) had permanent loss in one ear. A further 15 per cent had a minor hearing loss of between 10 and 20 decibels. Twenty per cent of the children had a hearing loss of over 20 decibels at the first testing, and although most of these recovered the average time between the attack and a final normal hearing test was 23 months.

The only factor which appeared to increase the risk of permanent deafness was recurrent attacks of otitis media.

Cytology and the general practitioner. T. R. CULLINAN and B. A. MONTGOMERY. *Brit. med. J.* 1965. **2**, 1525.

Facilities for cervical smear tests were offered to patients in a mixed urban and rural practice near London. One hundred and ninety patients had the test performed five of whom had " doubtful " smears.

The most surprising finding was that of about 1,100 women who saw the posters offering the service only 40 (3.7 per cent) asked for a test. The remaining patients tested were either done as part of a gynaecological or obstetrical examination, because they were considered specially at risk, or were taking oral contraceptives.