THERAPEUTIC TRIALS AND SOCIETY

Making the best use of resources

A discussion paper based on a multi-disciplinary seminar held by the *Drug and Therapeutics Bulletin*

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Preface

In 1984 the Drug and Therapeutics Bulletin hosted a multi-disciplinary seminar on therapeutic trials in their widest context. We considered whether the ways in which trials are now commissioned, performed and reported meet the many purposes for which they are used in medicine.

Although clinical trials have improved both in scientific and technical standards in recent years, they have still not tackled many important questions that they could; conversely many clinical trials are performed to answer unimportant or irrelevant questions.

One reason for this is that many trials are funded by the pharmaceutical industry. These naturally address commercially but not necessarily medically important questions. For example, trials of reduplicative drugs tend to waste scarce resources such as skilled investigators, specialised facilities and suitable patients.

In the seminar we first examined how to encourage better use of resources in commissioning trials. The construction of 'shopping lists' of problems most needing clinical trials to solve them seemed most promising. We suggested that each specialty could draw up its own list through the relevant specialty society and publish it for the information of all funding bodies.

We then discussed how to improve the way the profession uses the results of clinical trials in improving the practice of medicine. It seems to take many years for the profession to recognise and use knowledge gained from clinical trials. Trial reports are often, in effect, inaccessible to most practising doctors but no one seems to be concerned about this. We made many practical suggestions for bringing trial findings to the prescriber.

The *Drug and Therapeutics Bulletin* is publishing this edited summary of the outcome of the Seminar in the hope that the issues raised will be widely discussed, and that many of our recommendations may be tried and improved upon.

The Contributors

This discussion paper arose from a seminar organised around three papers specially written for it by Drs Michael Orme, Andrew Herxheimer and Linda Beeley. The first draft of the present document was prepared from these papers, and from the discussion at the seminar. The draft was then sent for comment and amplification to all who had been invited, though some had not been able to attend the seminar. All those who contributed at the seminar or subsequently are listed below. Except in the few places where it is indicated in the text, none of them is to be held responsible for the views expressed, which may not reflect their opinion, nor, of course, do the views reflect those of any organisation with which contributors are associated.

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1 *Introduction*

High quality clinical trials of drugs and other treatments are the cornerstone of the scientific assessment of how best to treat patients.

The resources needed to perform trials are skilled investigators, with access to the necessary clinical and technical facilities, to adequate numbers of suitable patients and to money. These resources are scarce and will be wasted if used on trials that offer little prospect of improving treatment.

The great majority of trials in medicine are funded by the pharmaceutical industry. They are needed primarily to furnish data to justify product licence applications and support marketing efforts. Although some of these trials are medically important, others are not. Trials of little or no direct commercial value but of greater scientific and medical importance are by comparison few, and are generally funded from non-commercial sources.

A related problem is that many doctors do not regard therapeutic trials as a normal and integral part of their work, although to assess whether one's treatment is satisfactory or not is self-evidently part of any professional activity. A further problem is that even clear findings from trials which show a therapeutic advance are often haphazardly translated into practice.

These important issues involve many disciplines, making them all the more difficult to deal with coherently. The *Drug and Therapeutics Bulletin* held a seminar in May 1984 with the aim of bringing various disciplines together to examine the problems from all perspectives and suggest proposals as a basis for wider and fuller discussion.

2 *The nature of clinical trials*

To find out whether a new drug or treatment is of value, it is necessary to compare what happens when it is used and when it is not used. This comparison is planned as a clinical trial. To make it more reliable and to exclude possible bias by the patient or doctor in judging the response, some patients are given a matching inactive 'dummy' or placebo preparation. Treatment with active drug or placebo is arranged randomly without the patient or doctor knowing which it is. This is the basis of the placebo-controlled clinical trial. It may be ethical to withhold an active remedy for a time in some clinical situations, but in many it is not. In general where an effective treatment already exists the new treatment must be compared with it. Placebo-controlled trials are intended to show efficacy, especially when the assessment of efficacy is subjective; comparisons with other treatments assess the relative benefits and risks of new and existing treatments.

The decision whether any trial is justified requires a rigorous ethical review independent of those proposing the trial. In most institutions an ethics committee for human research is charged with this responsibility. Since much has been written about the work of these committees (Royal College of Physicians 1984) this report does not discuss the subject further.

Clinical trials fall into two somewhat overlapping categories. In the first, the main questions concern *the drug or treatment*. How effective is it? How is it best used? Such trials are an essential part of the development of new drugs. They include the earliest studies, usually in healthy volunteers (Phase I; 25–50 subjects), the first studies in patients (Phase II; 50–250 patients), trials in larger groups before the drug is marketed (Phase III; 500–2000 patients), and studies after marketing (Phase IV) to explore, for example, further uses of the drug.

Trials in the second category examine *the management of a disease or condition*, for example comparing different regimens consisting of several drugs and/or other measures such as diet, surgery, meditation training, and often assessing long-term outcome as well as short-term effects.

Although most clinical trials investigate drug treatment, non-drug treatments can also be tested by the same scientific methods. At present this is seldom done and more such trials are sorely needed. Although this report is illustrated mainly by examples from drug trials, it is also applicable to non-drug trials.

Trials should answer important questions that have not been adequately answered. They should be scientifically valid, their results should be generalisable and the findings should be worth the cost of the trial (Sackett 1980).

The many requirements for scientific validity have been outlined recently (*Drug & Therapeutics Bulletin* 1985). The requirement most relevant here is that the ability of a trial to detect differences between treatments depends on the number of patients included. Most trials in which no difference between

treatments was found are too small to be likely to detect even a 25% difference (Freiman *et al* 1978). Trials comparing new treatments with existing treatments (where differences may be small) require far more patients than the less clinically useful trials comparing a treatment with placebo. The second most important requirement is that the patients in the trial should be a representative sample so that the results will be generally applicable, and this also is determined by sample size. Although large trials cost more, they may be more effective than small trials since they are more likely to answer questions reliably. A fortune is wasted on small trials.

2.1 THE ORGANISATION OF TRIALS

Most doctors do not regard therapeutic trials as part of their normal work and may be reluctant to get involved. Important trials may not get off the ground at all if clinicians see no need to alter their practice. For example, the Department of Health and Social Security (DHSS) and the Medical Research Council (MRC) began a trial to confirm or refute American evidence that oral hypoglycaemic drugs were harmful. After two years, only 12 patients had been entered into the trial, apparently because the physicians concerned did not believe that the trial was necessary. It is only recently that another better designed trial has been set up to answer this question among many others.

The way in which patients are distributed among doctors also influences the organisation of trials. It is much easier to mount trials if the patients are concentrated in the hands of a few specialists in regional centres than if they are cared for by a large number of practitioners, each having only a few suitable patients (mal-uniting fractures, for example).

Multi-centre trials Large trials need to recruit patients from many centres. Such multi-centre trials are difficult to organise. Although they may be more reliable they are often unpopular with doctors, because the individual doctor cannot identify with the trial, and because he or she gains less kudos if there are many contributors.

Multi-centre studies do, however, allow the rapid recruitment of large numbers of patients, and thus a speedy conclusion. Mobile skilled coordinators can stimulate participants. Data can be standardised and analysed in a way that is impossible in a series of small studies, potentially improving statistical validity. Clinicians in small hospitals or rural areas who lack the technological facilities (eg for data collection) for effective single-centre trials might be especially motivated to participate in a larger centrally controlled trial.

Multi-centre trials may cost no more per patient than single-centre trials. A recent US review reported a cost of $523 per head for a multi-centre trial compared with $587 for a single-centre study (Meinert 1982). The same is probably true in Britain although the costs are generally lower. More money is probably wasted on hopeless small trials than is spent on potentially powerful multi-centre trials.

On the other hand, trials that are centrally controlled tend to be more intellectually conventional. Lack of personal involvement tends to reduce interest in the study and weaken adherence to the protocol. To counteract flagging motivation, one pharmaceutical company is experimenting with a viewdata system. Doctors type in information for each patient at the time of consultation via the telephone and the information goes into a central computer. Individual doctors can then obtain information about the current number of patients in the trial, how long they have been participating, adverse reactions, etc, at any time – stimulating them to carry on. However, it is essential to prevent 'peeping' at the actual results as this jeopardises the validity of the whole trial.

Trials in general practice Many trials are most appropriately conducted in general practice, where most disease is managed. Many general practitioners (GPs) are not keen to participate because they feel that they have too little time, that the extra work is not adequately paid or that some industry-sponsored trials are covert drug promotions. Many doctors become cynical about the value of trials because those they read seem to give conflicting results – although the reasons for the conflicting results are poor design, performance and analysis. Some doctors are inhibited simply because they do not know how to do a trial.

There are many reasons why trials may be worth doing in general practice. In the UK, the GP keeps in one place almost all information about a patient's use of the National Health Service (NHS), in and out of hospital. GPs do most of the prescribing in the country and see many conditions which never reach hospital at all. The GP, whom patients are more likely to consult than anyone else, is also in a better position to detect side effects or adverse reactions, particularly when these develop after the trial has been completed. However, compliance with treatment is often more difficult to guarantee or measure than it is in trials in hospital in-patients. Trials based on one or a few general practices may yield ungeneralisable results because of the differences between the patient populations in different practices – particularly in their behavioural, attitudinal and cultural characteristics.

Long-term research programmes based on multi-practice controlled trials may be attractive and rewarding to GPs if they see their personal part as vital – as for example in the MRC mild/moderate hypertension study (1977) and the Royal College of General Practitioners' study of oral contraception (RCGP 1974). These large studies involving many GPs in a disciplined protocol are also likely to create a more discerning attitude to treatment among participants.

Trials of routine care Routine care can be studied in controlled comparative trials without expensive technology and with a relevance clear to both patient and doctor. In countries with a national health service, the performance of trials as a part of normal health care can reduce their cost. In one part of Italy, for instance, GPs have engaged in a simple trial to document any differences among

themselves in treating high blood pressure in elderly patients: to date, 4500 patients have been recruited by GPs simply selecting ten patients at random (Avanzini *et al* 1984). More specialised treatments in out-patients and in hospital can also be studied. A pioneering trial in the treatment of tuberculosis in East Africa and Hong Kong was performed by the doctors running the local clinics (Fox 1983). A current example is a randomised open multi-drug trial in Italy to compare the efficacy of three drugs for severe cardiac arrhythmias (Gianni *et al* 1985). A hospital study has examined the value of streptokinase in the treatment of acute myocardial infarction; 176 Italian coronary care units participated (GISSI 1986). The estimated cost was low: *ca* £400,000 for about 11,500 patients. In all these studies the doctors providing the service are doing the research, and this makes the findings directly relevant to their own population of patients. It is valuable to establish such networks of doctors and units experienced in clinical trials.

2.2 SOME INFLUENCES UPON INVESTIGATORS

There are many motivations for doctors to take part in a trial. Many trials clearly spring from the needs of clinical practice (see above examples). Some are stimulated by an investigator's enthusiasm for a new idea – particularly if clinical trials are already part of a local programme of research activity. Enthusiasm is, however, no guarantee of relevance or validity.

Others are stimulated by the investigator's need to publish or to gain a higher degree – for the sake of career rather than scientific interest. This is also no guarantee of relevance, although the trials are more likely to be well performed.

Other trials are initiated by a drug firm asking a particular doctor or unit to do a trial, usually because of local expertise. For example, a unit interested in peripheral vascular disease and equipped to study limb blood flow may be asked to test new drugs. Some units may undertake trials of little medical interest because they can use the fee for more interesting research. These 'pot-boiling' studies may be poorly performed if they do not interest the investigators.

Patients now want to take more responsibility for their health care and to ask doctors about the comparative benefits of different treatments. They understand the need for trials and are often willing to participate in them. This deserves an active response from doctors.

2.3 FUNDING OF CLINICAL TRIALS

The cost of funding trials increases continually. Some multi-centre studies already cost millions of pounds. At a time when resources are shrinking in universities, in the MRC and in the NHS, investigators will need to cost their clinical trials more realistically. In the past it was common to do a particularly interesting trial for an unrealistically low sum. Nowadays, most trials are more accurately costed and include, for example, travel, the extra work in the local pharmacy and in the hospital laboratory, and institutional overheads such as

heating, lighting, telephone, typing, stationery, computer time, etc.

In addition, some trials entail consequential expenses which may be crippling if not foreseen. For instance, a trial of a new cancer chemotherapy may result in greater use of very expensive antibiotics in patients developing agranulocytosis. If a trial shows a drug to be effective, the patient may need to continue taking it, perhaps for life, at public expense once the trial has stopped.

Clinical trials may be commissioned or funded by a number of different agencies.

Pharmaceutical companies tend to be most interested in funding short-term trials of new drugs in common diseases designed to show their superiority over an older treatment (sometimes an obsolete Aunt Sally) or placebo. Doctors are more concerned with comparisons between the best current treatments and with long-term outcomes of treatment.

Companies rarely wish to fund a trial for an orphan drug or disease where the financial reward is likely to be small. In the USA this problem has been mitigated by the 1983 Orphan Drugs Act, which provides financial incentives for developing drugs for rare diseases (Finkel 1984). They may also be reluctant to fund a study on an old drug whose patent has long expired, however important the potential advantages from the outcome of the trial. Similarly it is difficult to raise funds to study drugs intended primarily for treating diseases confined to the Third World. In such cases the WHO or a development agency may provide initial funding.

Companies may also hesitate to fund comparisons between competing drugs, when the comparison might be disadvantageous for the sponsoring company's product; studies comparing different durations of treatment with the same drug – since, if brief treatment is found as effective as prolonged treatment, the manufacturer's sales will fall; and studies measuring long-term outcome, which are often too costly and uncertain to be commercially justifiable.

The MRC may fund a trial through one of its own units, a long-term programme grant or a special project grant. Some trials are also set up because of a pressing social need and may be stimulated by the DHSS or by individual members of Council Boards or committees. The MRC has been responsible for a broad programme of trials in cardiovascular and neurological diseases, cancer and the leukaemias and other haematological disorders.

Charitable research trusts may fund clinical trials but their resources for this purpose are usually small. They may occasionally approach an investigator, but usually respond to a valid protocol application and subject this to peer review.

Their policy over capital expenses for equipment may lead to problems. Often charities do not like to pay for the purchase or maintenance of a necessary piece of equipment, perhaps because it is not clear who owns it once the study is completed. Annual maintenance may be as much as 10% of the capital cost and this may be difficult to include in the overall running costs of a department.

The DHSS will occasionally approach a unit to ask for a trial on a particular problem. The DHSS will then review the subsequent protocol and fund the study if the protocol is approved. The NHS honours its role to initiate work more in the breach than in the observance.

Most grant-giving bodies expect therapeutic research to be funded commercially. The MRC has, however, collaborated with several industrial companies in organising trials. For example, pharmaceutical companies have contributed by supplying drugs (often in special formulations) for trials in cancer, hypertension and tuberculosis.

The funding body has to decide whether the trial is worth the cost. This involves accurate costing and difficult value judgements. Such decisions are rarely made explicitly, but they should be and can be (Hammond & Adelman 1976; Teeling-Smith *et al* 1983; Leu 1984).

Distrust between the providers of funds and researchers adds to the difficulty of mounting trials. Clinicians and research workers may think industry influences the final reporting of results, and occasionally distorts or suppresses information. Companies may think that researchers are failing to keep adequate records, to divulge information or to adhere to the protocol. The DHSS is accused of being slow and mean. The MRC has been criticised for not carrying out a number of important studies.

Defining and meeting research needs should be seen as a cooperative responsibility and information flow needs to be open. At present market research and prescribing statistics are confidential and geared mainly to the needs of industry and the financial administrators of the DHSS, rather than those of doctors and scientists.

Cooperation between clinicians and pharmaceutical companies sponsoring research could be improved if all trial protocols spelt out their respective rights and responsibilities. For example, they should specify when and how the decision will be made to end the trial, and who will have final responsibility for the report.

2.4 PERSONAL PAYMENT OF INVESTIGATORS

It is fair to pay investigators a fee which recognises the extra time and expertise they provide; larger payments are unethical and unacceptable. Doctors need to be wary of accepting gifts or payments offered in a way that could be open to question. There have been many promotional trials in which the doctor is given a gift as an inducement to prescribe a drug that he might not otherwise use. In many cases the design of the study is such that no useful information can be obtained and this type of trial is then clearly unethical. Recent correspondence in the *British Medical Journal* (Smith 1984; Diamond & Robinson 1984; Cousins 1984) and the RCP Guidelines (1984) suggest that it may be improper to accept payments that have not been described explicitly in the protocol, and thus have not been reviewed by the ethics committee.

3 *Can we use our resources more rationally?*

Having discussed the disadvantages of current ways of instigating therapeutic trials, we now consider how the situation could be improved. This involves a systematic approach aimed at making clinical needs, rather than the less relevant needs already described, the moving force.

3.1 EPIDEMIOLOGICAL APPROACH

Illnesses differ greatly in importance, both as perceived by the patients who suffer them and as manifested by the disability, death and economic losses they cause. Some conditions affect millions of people, others only hundreds. The first major attempt to assess the relative importance of different diseases in the UK was made by Black and Pole (1975) who examined five indices of the burden of diseases on the health service: in-patient days, out-patient attendances, GP consultations, days of sickness benefit and causes of death. When these indices of burden were given equal weight, 11 conditions out of the 54 broad categories studied accounted for just under 70% of the total burden. These were mental illness and handicap, respiratory disease, myocardial infarction, bone and joint disease, accidents/suicides, neoplasms, digestive, neurological and cerebrovascular disorders, skin diseases and urogenital disorders.

Another method of judging the relative importance of different health problems is to list those that require treatment and to estimate the number of people in the country with each problem. National morbidity data such as those produced by the Research Units of the RCGP are crude and incomplete. They do not, for instance, provide the incidence, prevalence, treatment, diagnostic criteria and natural history of polymyalgia rheumatica and giant-cell arteritis. The National British Cohort Studies provide more detailed data on common illnesses of children and adolescents, including their duration and the degree of disability they cause (Davie *et al* 1974; Wadsworth *et al* 1984). They also document the natural history of diseases from childhood to adult life.

It is then necessary to estimate the danger to life, and the degree and duration of disability and suffering each disorder causes, by using measurements of health status, for example, scales of disability and distress (Rosser & Kind 1978; Hurst 1984; Holland 1985).

3.2 THERAPEUTIC APPROACH

The next step is to list, for each problem, the existing and anticipated treatments, and to estimate their efficacy, their hazards and how much they contribute to the patient's quality of life, and whether they are worth the cost (ie 'therapeutic value for money'). The reliability of such estimates will vary widely and would be one important factor determining the need for further trials. To take an extreme case, an estimate may be based on a single uncontrolled study

in which the treatment appeared to give excellent results: there is then a good case for mounting a rigorous trial. Inevitably this process will raise further questions; for example, which treatment leads to better quality of life? What is the best dosage and length of treatment? Which patients are most likely to respond? The relative importance of these questions is probably best assessed by doctors with special experience of the particular problem, and where possible by representatives of patient groups or the public.

The listing of problems would best be done separately for the different areas of medicine, by specialty and probably even by subspecialty. For example, gastroenterology would be too large a field for one group: separate groups would concentrate on peptic ulcer, inflammatory bowel disease, gall-bladder disease, etc. A recent paper attempted to list problems which need trials in the treatment of whooping cough, and suggested a rough order of priorities (Broomhall & Herxheimer 1984). Such a process requires expert knowledge, both of the resources available for performing trials – investigators, clinical facilities and patients, and of the likelihood of trials in that area solving the problems listed. GPs would also be essential members of assessment groups.

Each assessment group would need to consider both drug and non-drug therapies, such as surgery or adjustment of lifestyle, and management strategies.

Inevitably, constructing a list of soluble priorities would involve the reassessment of criteria which are used to judge the effectiveness and benefits of treatment.

Another factor determining priority would be the feasibility of funding trials unattractive to industry: multi-drug comparisons; trials specifically to assess risks and unwanted effects of treatment already established as beneficial; trials of methods of managing chronic or terminal conditions which are commercially unattractive but socially essential; trials in fields such as perinatal care, where drugs play a smaller part than in other specialties; assessment of alternative medical practices such as osteopathy.

This approach is not new, but is broader than previous attempts. A few noteworthy clinical research programmes have incorporated a similar idea and carried it forward over many years. Examples are the MRC's trials in pulmonary tuberculosis, the UK Acute Lymphoblastic Leukaemia (UKALL) trials, the European Organisation for Research and Treatment in Cancer (EORTC) cancer trials, the Breast Cancer Trials Coordinating Committee and some parts of the WHO Research Programmes in Tropical Disease and Human Reproduction (eg World Health Organization 1983). These examples show that the approach can be made to work.

3.3 THE SHOPPING LIST

This approach would produce a 'shopping list' of trials deserving priority either by industry, by public or charitable funding, for each therapeutic area.

The nature of each problem would determine its likely funding. For instance,

if a drug treatment were likely to produce a big improvement only a small study would be needed and funding would not be a problem. If the likely improvement were smaller but the treatment was new, industry could be expected to provide funds. If the difference were likely to be small and the drug was an old one, but the disorder is common, public funding would be necessary. If the disorder were rare an appropriate charity might fund the study. There would be a strong case for increasing funding for clinical studies of the problems on the lists; the existence of the lists would also facilitate the rational use of public funds, increased or not. This might best be done through a central body (perhaps associated with the MRC) which could commission work in areas identified by the lists.

Decisions on the relative weight which public funding should give the lists in different specialties would be partly influenced by the community burden of disease in each specialty. The shopping lists would be of equal value to other providers of funds such as philanthropists, charities, the pharmaceutical industry, the insurance industry (Kahn 1984) and international organisations. In sponsoring or supporting work on a list, any one of these would be publicly seen to be spending money to good effect. This would be so even if a trial had negative results, because a definite answer to an important question is a victory over ignorance.

The lists would also encourage clinical investigators to commit their time and energy more profitably. But they should in no way constrain private funding agencies or individual investigators from sponsoring or undertaking any therapeutic trial which they consider worthwhile. This would safeguard the vital innovative element in research – the individual with the right idea at the right time. Many creative researchers want to pursue their own ideas, do their own work and be identified with it, rather than participate as an anonymous member of a group.

3.4 DIFFERENCES FROM THE ROTHSCHILD PROPOSAL

This proposal in one way resembles Rothschild's for the government funding of research in the United Kingdom. In relation to medicine, the intention was to concentrate spending on research on the numerically and socially important diseases. However, the application of the Rothschild principle to research commissioned by the Health Departments was unsatisfactory as it imposed the role of 'customer' on administrative civil servants who could not fully appreciate the scientific issues, in contrast with the MRC which had long and successful experience of making decisions of this kind (Black 1980). The membership of the MRC and of its Boards is drawn from practising clinicians and research workers who in turn seek the advice of independent scientific and medical experts.

The present proposal differs from the Rothschild approach in two important ways. Firstly, the scope is much narrower: here we deal only with clinical trials concerned with treatment. Secondly, the 'shopping lists' would be compiled by clinicians and scientists independent of the funding agencies.

3.5 PRACTICAL DETAILS

The practical work of constructing the lists requires scientific and clinical experience, independence and continuity. It might be best done under the auspices of the relevant scientific or specialty society, such as the British Society of Gastroenterology, the British Diabetic Association etc.

The search of the literature and the production of 'state of the art' summaries of existing knowledge necessary for constructing a list entails much work. Few academic units are likely to have the staff, time or funds to undertake it. It might therefore be desirable to fund fellowships or possibly a unit in a Royal College or in an academic department specifically for this purpose. Such a unit might also be able to carry out feasibility studies where necessary to decide whether an expensive trial is warranted.

Eventually, were such an enterprise to be shown to work on a modest scale, the Royal Colleges might be able to help by facilitating cooperation and fertilisation between disciplines.

Since most therapeutic problems are not confined to one country, collaboration between similar specialties in different countries would be a natural and fruitful development. As the facilities, and therefore the approaches that can be tried vary from country to country, studies of related problems are often complementary and illuminate each other.

3.6 REGISTER OF TRIALS

A valuable by-product of the construction of shopping lists could be a register of all trials in progress or planned in each specialty. These registers could reduce needless duplication of work and facilitate the referral of suitable patients.

Only a few such registers now exist, and many clinicians do not know of them. For example the MRC holds a register of UK cancer trials. There are also international registers of trials in cancer chemotherapy and a European register of anti-thrombotic trials. The National Perinatal Epidemiology Unit has set up a register of all trials published so far in the perinatal field (Grant & Chalmers 1981) and this is to be expanded to include unpublished and ongoing trials (Chalmers & Sinclair 1985).

It might be useful if a central resource office held all registers, as well as unpublished trial results. The same office could usefully house published trial results as well, which are not now systematically retrieved. It would help if every trial report were to incorporate the term 'clinical trial' in the title or the list of keywords.

Much of the trial data collected by industry is not published. They might be made accessible if each company were to deposit them with the central resource office.

4 *Narrowing the gap between trial and prescriber*

The results of a clinical trial cannot affect practice until they have been published, the report read and its conclusions understood by at least some prescribers, and the implications broadcast effectively to the majority of prescribers who may have read neither the original report nor any discussion of it.

Clinical trials are ultimately pointless if their findings are not translated into clinical practice. At present valid trial findings affect clinical practice haphazardly and often after great delay. One simple example is the treatment of babies with simple diarrhoea. It has been known for 15 years that correct treatment is with fluids, glucose and electrolyte solutions, not with drugs. This has been verified in clinical trials and published repeatedly, yet a survey undertaken five years ago showed that the vast majority of babies with diarrhoea were still being treated with drugs instead of fluids (Morrison & Little 1981). Why doesn't the message get through?

There seem to be three main reasons: poor trials, poor communication and poor understanding.

4.1 POOR TRIALS

So many trials are now published that it is difficult, if not impossible for even full-time researchers, let alone practising clinicians, to read all the trials in their specialty. Many published clinical trials are either irrelevant to clinical needs, or unhelpful because of poor design or execution. This plethora of unremarkable – if not misleading – trials wastes researchers' time, and obscures important advances. It may even discourage clinicians from reading or heeding trials in general. Such trials would be less common if they were not published. It is up to the editor of the journal to which the report is submitted to ensure that it is relevant and valid. The editor is usually assisted by referees but their advice is often inadequate or tempered by a mistaken sense of 'generosity'. Some journals seem to exist only to satisfy the aspirations of national medical societies or schools, or of sponsoring pharmaceutical companies. Their pages are filled with worthless material whose titles and keywords fatten the print-outs of computerised literature searches and misleadingly dignify uncritical review articles and drug advertisements.

The most insidious consequence of poor trials is that they often give conflicting results which confuse the reader and arouse cynicism. There cannot be several different versions of scientific truth and the existence of conflicting trial results can usually be attributed to subtle and often inexplicit differences in the question being asked, or in the population being studied, or to invalid design, performance or analysis.

The most common reason for conflict between similar trials is too small a sample size and the consequent risk of random variation. Pooling of the results

from several trials, using appropriate statistical techniques, can often help a clearer conclusion to emerge. The reliability of pooled results depends on several factors such as the homogeneity of the populations from which data have been collected, the number of subjects in the different trials and the compatibility of the study designs. The shopping list would help to achieve conformity in trial designs, facilitating their comparison or pooling.

Sometimes problems arise from an apparent *lack* of conflict. Major journals are unfortunately biased towards the publication of 'positive' trials (in which the treatment difference reaches conventional statistical significance) and are reluctant to publish negative ones (in which it does not). For example, some years ago a trial of thioproline (Norgamen) for head and neck cancer was published, reporting highly positive results (Brugarolas & Gosalvez 1980). Another trial report from the EORTC of totally negative results with the drug was rejected, though a letter summarising other negative results with it was printed some months later (Sappino & Smith 1980). Such 'publication bias' is dangerous because it produces an excess of false positive findings or exaggerated estimates of benefit (Pocock 1983, 1985).

To aid the assessment of clinical trials and to improve their quality in all countries, their design, performance and analysis need thorough discussion in the scientific literature. Two new journals, *Controlled Clinical Trials* and *Statistics in Medicine* are now publishing in this area. Another, *Ricerca & Pratica* (published by the Mario Negri Institute, Milan), in each issue examines one important trial. One need is still unfilled: that for a clinical trials digest which can bring together a variety of trials in the same therapeutic field, and discuss their limitations and imperfections in the context of constructive criticism.

4.2 POOR COMMUNICATION

The title and summary of a paper tend to determine its impact but often over- or under-state the contents. Statisticians, editors and referees, as well as the authors, could play an active part in composing them. Journal reports might also mean more to prescribers if they contained a clearly identified action paragraph indicating how, in the author's view, the findings of the trial should be applied.

Few prescribers have the time to study more than a few of the trials relevant to their practice. They therefore need independent summaries and assessments of trial findings which evaluate the trial itself, and its implications in the context of existing knowledge. Such reviews may be provided in an editorial in the journal which published the trial, by reviews and editorials in other medical journals or by publications which specifically assess drug therapy such as the *Drug & Therapeutics Bulletin, Prescribers' Journal* and regional drug newsletters. Therapeutic advances are in due course incorporated into the *British National Formulary.*

More systematic dissemination of important trial findings is also needed and could be achieved by producing a regular, say quarterly, listing of newly published reports in each special field.

A most effective form of communication is person-to-person by word of mouth. The form of persuasion traditionally used by the pharmaceutical industry to great effect has been the representative who visits individual doctors or groups of doctors. This might be a technique which could effectively be applied in the health service, provided it is controlled professionally rather than administratively. Any element of an authoritarian or dogmatic approach must be avoided.

The experience of Avorn & Southeria (1983) in New England shows the potential of education by personal contact. In a four-state trial to reduce excessive use of cerebral and peripheral vasodilators, an oral cephalosporin and propoxyphene, physicians were offered either printed information alone or personal visits from a non-commercial educator as well. Those who received the personal visits significantly reduced their inappropriate prescribing, whereas those receiving just conventional printed material did not. A similar finding was made in Tennessee (Schaffner 1983) where the prescribing of three inappropriate antibiotics fell significantly after doctors had been counselled by physician colleagues.

Other avenues also need to be explored. At a local level, clinical pharmacologists and pharmacists could exchange information with GPs and other doctors. Course organisers at postgraduate medical centres and local drug and therapeutics committees could also have a role in the running of regular group seminars. Suitable material could be specifically designed nationally for use in local continuing education, as was done in the Open University pilot course 'Topics in Drug Therapy' (1982).

Planned specific efforts are needed to achieve specific goals. An impressive example was the campaign in the Royal Melbourne Hospital to persuade the medical staff to treat streptococcal pneumonia with benzylpenicillin instead of amoxycillin (Harvey 1983; Keenan 1983).

In printed material the important factors are clarity, simplicity and trust in the source. These are elements which make advertising successful. Advertising also depends heavily on the use of pictures and colour but this has hardly been tried in non-commercial material for prescribers. What data exist (Avorn & Southeria 1983; Harvey 1983) support their potential, when used either alone or else in conjunction with a personal visit from a non-commercial medical representative.

4.3 POOR UNDERSTANDING AND MOTIVATION

Prescribers often lack the ability to understand trials because they tend to be reported in a form usable only by the experienced few. Although commentators may pick out trials which indicate the need for some change in treatment practice, the information is rarely conveyed with sufficient strength. Even if it is, many prescribers find it difficult to make that change, partly because they lack clear information about their own prescribing practice and partly because comments in a journal often seem remote and impersonal. Of existing publications in the UK, the *Drug & Therapeutics Bulletin*, *Prescribers' Journal* and *British*

National Formulary perhaps influence therapeutic decisions most directly.

For change in treatment practice, strong motivation is therefore needed, especially since audit by peers and self-audit play little part in doctors' training and practice. Information about one's prescribing practice is essential for self-audit and would usefully be accompanied by selected findings from appropriate clinical trials or other relevant material (Hamley *et al* 1981 a and b). When the Prescription Pricing Authority has been fully computerised and can produce the necessary material, audit could more easily become a regular activity for GPs. A one-year controlled study of audit among London GPs indicates that it can change prescribing habits (Harris *et al* 1984), but follow up showed that within two years doctors had mostly reverted to their previous pattern of prescribing and it seems that 'more sustained intervention is needed to bring about more lasting change' (Harris *et al* 1985).

5 *Conclusions: Main recommendations for discussion*

MORE RATIONAL USE OF RESOURCES

1 **Shopping lists of needs** Expert groups should be set up to produce shopping lists of trial needs for all areas of activity in the health service (para 3.3). These should include not only drug trials but others which now attract little or no funding.

These shopping lists should be published so that funding bodies (including industry) and the scientific community can make use of them.

2 **Funding of trials** Public funds available for therapeutic trials on the lists might most effectively be allocated by a central medical commissioning body. More public funding is required for trials deemed to be of major potential benefit for the NHS. It should be possible for the DHSS to provide such funds from savings achieved in the national drugs bill by the introduction of new policies (para 3.6).

3 **Cooperation between funding bodies and investigators** A closer and more trusting relationship needs to be built up between funding bodies, such as the DHSS, the MRC and industry, and between them and academic departments (para 2.3). It would be useful to create an open forum where all parties can discuss research needs.

4 **The role of general practitioners** GPs must be encouraged to participate in clinical trials. This will be easier if they are paid for their time and if the trials address the problems they see in their own practice. This will then help convince them that trials are essential for treatment, especially if emphasis is given to comparative trials based on routine care, or local trials whose findings will be directly relevant to their patient population (para 2.1).

5 **Register of trials** For each specialty there should be a register of trials currently in progress or planned. The registers might best be kept by a central resource office and the data made freely available (para 3.6).

6 **Feasibility studies** Fellowships or a unit should be funded for the purpose of organising and performing occasional feasibility studies for major proposals of merit (para 3.5).

NARROWING THE GAP

7 **Standardised data** Trial results could be more readily translated into action if data were collected and presented in a standardised way that would allow a pooling of results from different trials (para 4.1). This would require agreement on general principles of data collection – perhaps initially within specialties – and better technological back-up, eg in statistics. Properly pooled results from several randomised trials are more reliable than those of one trial alone.

8 **Quarterly listing** A quarterly listing of newly published clinically relevant trials should be introduced, classified according to the therapeutic categories used in the British National Formulary. Such a listing should be linked as closely as possible to the prescribing information which doctors use frequently (para 4.1).

9 **Clinical trials digest** One or more clinical trials digests should be introduced, to aid assessment and analysis and improve the quality of clinical trials in all countries (para 4.2).

10 **Personal contact** Health authorities should set up pilot projects to train suitable professionals whose role would be to visit doctors, individually or in groups, to discuss current treatment and to up-date ideas, and to promote communication and contact between hospital and general practice (para 4.2).

11 **Training in evaluation of trials** Doctors need early and continuing training in the critical evaluation of published studies if they are to make use of the findings (para 4.3).

12 **Self-audit** Systematic training is needed in the process and practice of self-audit, in particular as it applies to changing prescribing habits (para 4.3).

Most of the above recommendations require resources from the health service, as nothing can be achieved by merely wishing for the best. Provision of resources along the lines proposed will be cost-effective for the health service in the long term and will raise standards of health care, not only in Britain.

Summary

Clinical trials are essential to identify the best treatments for patients. This report first considers the resources required for their performance – skilled investigators with appropriate facilities, enough suitable patients, and money. These resources are scarce and should not be wasted on trials unlikely to give useful information, either because they are asking therapeutically trivial questions or because their design is incapable of yielding decisive answers.

Resources could be used more rationally than hitherto if trials that are clearly needed were instigated and encouraged. The clinical need for trials can be assessed through systematic consideration of what health problems in the population require treatment, what treatments for them exist or are anticipated, and the estimated usefulness of these treatments. An approach is outlined for constructing 'shopping lists' of trials needed to answer important clinical questions.

A separate shopping list would be required for each specialty. The lists would clearly identify trials which deserve funding, whether from industry, charities or public funds. They might thus facilitate funding.

Another problem concerns the translation of important trial results into clinical practice. This translation is often haphazard and slow, probably for three main reasons – the large number of poor or irrelevant trials, poor communication of the message, and insufficient understanding of trial methods. So many trials reports are published that few clinicians can pick out those that are both relevant to their practice and of good quality. Furthermore reports are usually expressed in a form which makes it hard to apply the results directly to practice. Independent reviews of important trial findings should therefore be more widely circulated. Lastly, most doctors are not trained to dissect trials. They lack the experience and time to work out the implications for themselves, and find it difficult to change their prescribing in response to a rather impersonal publication.

The report concludes with 12 recommendations for discussion on the more rational use of resources and on ways of narrowing the gap between trial and prescriber.

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