MEDICO-PHARMACEUTICAL FORUM

A Report by the Forum's Working Party on Clinical Trials

1 WIMPOLE STREET
LONDON W1M 8AE
OCTOBER 1974

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PREFACE

The Forum was set up in 1968 to provide a setting for the discussion of problems of interest to both the medical profession and the pharmaceutical industry. At the two yearly Statutory Meetings such matters were discussed and debated as consultations between the industry and the profession before the withdrawal of medicines from the market by pharmaceutical firms, the obligations of the industry to the profession (and vice versa) and marketing as seen by the industry. As a result, certain subjects are identified for enquiry in depth; experts are asked to undertake these tasks; and their reports are then analysed and considered by the Forum. Three have now been published: the first on facilities for the early clinical studies of new medicine; the second on academic/industrial relationships; the third as now presented.

The Forum is greatly indebted to the distinguished chairmen and members of the respective committees of the Forum who have undertaken the task of producing these reports, and not least to Dr. Brian W. Cromie and the committee for Clinical Trials. Like all well-considered and concise reports, it raises supplementary questions which may well require separate study. It nevertheless stands firmly on its own as a clear and practical document, easy of reference and carrying the authority of a body made up equally of representatives of the major established medical institutions of the United Kingdom and members of the Association of the British Pharmaceutical Industry.

John Richardson
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The committee would like to acknowledge the assistance of The Medical Defence Union, The Medical and Dental Defence Union of Scotland and The Medical Protection Society in the preparation of Section 15 and of the C.S.M. medical staff in the preparation of Section 24.

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INTRODUCTION

In 1972, the National Economic Development Office published a report by the Pharmaceutical Working Party of the Chemicals E.D.C. (Focus on Pharmaceuticals, H.M.S.O. 1972), which included comments on clinical trials. The report pointed out that clinical trials in the United Kingdom have a world-wide reputation for quality but that there was room for improvement; in particular poor finishing and confusion on the ethics of payment to investigators.

With these and other problems in mind, the N.E.D.O. report welcomed the idea of a study by the Medico-Pharmaceutical Forum to evaluate and make recommendations upon the organisation of clinical trials.

The Executive Committee of the Medico-Pharmaceutical Forum considered this suggestion and appointed a working party with the following draft terms of reference:

> 'To evaluate and make recommendations upon the organization of clinical trials in the United Kingdom, with particular reference to areas of controversy and misunderstanding and to practical points, where errors frequently arise'

In order to facilitate progress, the working party divided into four sub-groups, each of which paid particular attention to certain aspects of clinical trials as well as to the general subject under consideration.

All members were requested to draw on the opinions and experience of their colleagues, where necessary and were reminded that the working party was not expected to write a text-book on clinical trials, as these were already available, but to give guidance and recommendations on those practical points and matters of principle, where there was doubt and confusion.

Each sub-group prepared a submission, which was amalgamated into a comprehensive draft that was later discussed, amended and agreed by the working party as a whole, resulting in this report on clinical trials.

Report

1. DEFINITIONS

(a) Clinical Pharmacology

There has been a tendency in the past to use the term Human Pharmacology for the study of drugs in healthy volunteers and the term Clinical Pharmacology for early trials in patients, while later studies in patients were referred to as Clinical Trials.

This terminology has caused considerable confusion, as "patients" are "human" and because other descriptions have been used.

In order to overcome any future confusion, it is recommended that the W.H.O. terminology be adopted (W.H.O. Tech. Rep. Ser. 1970, No. 446).

Thus, "Clinical Pharmacology is concerned with the scientific study of drugs in man".

Clinical Pharmacology, therefore, covers such studies whether in patients or not and includes early and later trials. Types of studies can be broadly differentiated into pharmacokinetic (absorption, distribution, metabolism and excretion), pharmacodynamic (mode of action, biological effect) and therapeutic. For convenience and traditional reasons, therapeutic studies therefore will continue to be generally referred to as Clinical Trials.

(b) Clinical Trial

A clinical trial is a scientific experiment in which a drug or procedure is applied with diagnostic, therapeutic or prophylactic intent to patients. It is part of clinical pharmacology but stresses the clinical benefit.

(c) Patient

A patient is a person who has sought medical attention because he desires medical help. This covers therapeutic, diagnostic or prophylactic help and includes referral on medical grounds.

(d) Volunteer

A volunteer is a person who agrees to enter a clinical pharmacological study. In addition to non-patient volunteers, this includes patients who have sought medical attention and who subsequently agree to enter a pharmacokinetic or pharmacodynamic study or a clinical trial.

The term "volunteer" is, however, commonly used as an abbreviation for "healthy or normal volunteer", to denote pharmaceutical staff or other non-patient groups that agree to take part in human pharmacological studies. "Healthy volunteer" is a poor definition, as it implies an interpretation of "healthy" and any group of subjects will include a percentage of anxious, allergic, hypertensive, insomniac, etc. people, as

exists in the normal non-patient population. "Normal volunteer" is a better definition, as the "normal" population includes people with all grades of minor abnormalities in a normal distribution about the mean, but has difficulties for some people and it is preferable to use the term "non-patient volunteer".

A "non-patient volunteer" is a person who has not been referred on medical grounds or come forward seeking medical attention and who agrees to enter a clinical pharmacological experiment, where a drug or procedure is applied. He or she may have minor abnormalities or disease, as would be expected in a representative sample of the normal population, but can still be accepted as a non-patient volunteer if the drug or procedure is not related to the specific treatment for the subject's condition and is not likely to influence it. (See also Section 9.)

(e) Controlled and Uncontrolled Trials

A *controlled* trial is a clinical trial where there is a "control" group, allowing valid comparisons to be drawn between the results of the different types of management of the different groups. This usually involves a more or less concurrent use of different "treatments".

Controlled trials should use the same reproducible methods or protocol and compare the therapy under investigation against a "control", which can be an active treatment, an inactive dummy or placebo, no treatment or any combination of these.

In trying to evaluate new treatments, diagnostic aids or procedures, it is clearly desirable to reduce variables of time, nursing care and other aspects of patient management between trial and control groups, so that differences in clinical results are likely to be due to differences in specific therapy and not to non-specific variables.

A trial making no explicit attempt at a valid comparison is an *uncontrolled trial.*

2. CONTROLLED TRIALS

Controlled trials are generally the preferred method of examining the effects of treatments but have some limitations in that the trial aspect tends to dominate the overall management of the patient and care must be taken in extrapolating results to more general clinical use.

A controlled trial includes a control group allowing comparisions to be drawn with a test group. Comparisons of drug therapy are more likely to be valid if other variables are balanced and one variable which must always be considered is the bias of clinical assessor and patient if treatments are recognised. Because of this, attempts should be made to prevent recognition or to "blind" both assessor and patient (double-blind) if this is feasible.

Conditions in some trials may make it undesirable or impossible to conduct a double-blind trial. In these circumstances, other forms of controlled trials (non-blind and single-blind) may yield useful information but, where it is appropriate, a double-blind should always be considered.

(a) DOUBLE-BLIND TRIALS

A double-blind trial must ensure that neither patient nor observer recognises a treatment and preferably does not identify a treatment as being the same that he or others receives or prescribes or has received or prescribed in the past. Such lack of recognition (blindness) avoids bias by either patient or clinical assessor.

All controlled trials attempt to balance variables, which may influence response to therapy. If they are also double-blind, then bias by patient or assessor and placebo responses are also balanced, so that any difference between test and control groups is due to the difference in active medication and it is this difference which controlled clinical trials normally set out to establish.

This need to overcome bias is frequently an overriding factor but there are certain aspects which must be considered when designing or conducting double-blind clinical trials.

(i) *Recognition of Medicaments*

It is common to alter shape and colour of a medicament to prevent recognition but to forget about smell and taste. This might be important if the trial involves repeated cross-overs, allowing patients to differentiate one treatment from another.

It must be remembered, however, that major changes in formulations, including taste, could alter patient acceptance or bioavailability of medicaments.

(ii) *Bioavailability*

Alterations of medicaments to prevent identification may alter bioavailability and possibly clinical performance of test or control therapy. Changes may only be noted after specially prepared trial formulations have been stored, so checks should be made with this in mind for long-term trials.

(iii) *"Identical" Medicaments*

The simplest way of preventing recognition of medicaments is to make them appear identical for both test and control groups. While this is an established method, it may involve some risk of an increased carry-over effect in cross-over trials from an active treatment to a matching dummy or vice versa, resulting in a potential loss of sensitivity.

(iv) *Double-dummy*

On occasions, measures needed to produce identical medications or other forms incapable of separate recognition alter a treatment so drastically that patient acceptance is changed and a realistic assessment of that treatment is not obtained. On other occasions, treatments are so completely different in appearance, route of administration, taste, etc. that they cannot readily be made

unrecognisable and in both of these situations, the double-dummy technique may be used, whereby each patient always gets both treatments but one of the treatments is always a dummy (placebo), allowing the active agents to be compared. It must be accepted, however, that this rather complicated system and apparent double treatment may increase the artificiality of trials and also reduce patient co-operation.

(v) *Labelling*

As with appearance and taste, every effort must be made to prevent identification of a form of therapy and labelling should always be of individual patient-courses of treatment and not of types of therapy. The optimum system utilises separate packs labelled with the individual patient number, the duration and identification of the treatment course and dosage instructions.

However, many modifications are acceptable, as long as neither clinical assessor nor patients can recognise treatments.

(vi) *Compromise*

Many factors have to be considered in the design of a double blind trial and it is always necessary to make decisions between the ideal and the practicable solution. Because of this, there is an element of compromise in the design of all such trials.

Whatever decisions are made, it is wise to record the reasons for the decisions at the time and to include this rationale later in any subsequent publication.

(b) Single-blind Controlled Trials

This is a confusing term, as either investigator or patient could be the "blind" party.

(i) *Single-blind (Patient) Controlled Trial –*

is rarely used, except where the medication is well known and distinctive and where the investigator must know the therapy given for reasons of safety or to adjust the dosage immediately according to response. An example might be the investigation of new anti-coagulants.

(ii) *Single-blind (Observer) Controlled Trial –*

is more common. When the test and control treatments are dissimilar in appearance, taste, route of administration, etc., it may be impossible (or misleading) to try and make the trial double-blind. In such cases, the patients appreciate that two different treatments are being given (by the pharmacist or other third party) and may recognise the treatments but the observer remains blind.

A modification of these techniques may be useful for dose-ranging studies, where one medical investigator makes an initial

assessment and alters the dosage, if necessary, while another observer, who remains blind, completes the final evaluation of the treatment.

3. UNCONTROLLED TRIALS

After initial pharmacokinetic and pharmacodynamic studies, new drugs are often used without any attempt to make a valid comparison or to overcome possible bias in patient or assessor. Such studies examine tolerance, first side-effects, drug interactions, biochemical changes with longer-term therapy, etc. Uncontrolled trials also have a place in the first examination of new indications for both new and established drugs.

This report includes within the term "uncontrolled trials", those studies that have some comparative or control group but which make no attempt to overcome bias, so that valid comparisons cannot be made.

Although valid comparisons cannot be made from these uncontrolled trials, they may allow clinical observations of value, which contribute to the knowledge of the drug and point the way to confirmatory controlled trials. In addition, intelligent use of uncontrolled trials can prevent the trial wastage that occurs if double-blind trials are started at too early a stage, when clear guidance on optimum dosage and clinical indication has not yet been determined.

4. CLINICAL TRIAL PHASES

Attempts to simplify trial phases into early and late or short-term and long-term resulted in increased confusion and it is recommended that the guide-lines of the U.S. Food and Drug Administration (F.D.A.) be universally accepted.

Phase I is intended to include the initial introduction of a drug into man. It may be in non-patient volunteer subjects to determine levels of tolerance, followed by early dose-ranging studies for safety and, in some cases, early efficacy studies in patients. Alternatively, with some new drugs, the initial introductions into man may ethically or scientifically more properly be done in selected patients. When non-patient volunteers are the initial recipients of a drug, the very early trials in patients, which follow, are also considered part of Phase I.

The number of subjects and patients in Phase I will, of course, vary with the drug but may generally be stated to be in the range of 20–50 receiving the new agent.

Pharmacodynamic and metabolic studies, in whichever stage of investigation they are performed, are considered to be Phase I clinical pharmacologic studies. While some, such as absorption studies, are performed in the early stages, others, such as efforts to identify metabolites, may not be performed until later in the investigations.

Phase II is intended to include early controlled clinical trials designed to demonstrate efficacy and relative safety. Normally, these are performed on closely monitored patients of limited number and scope. This Phase will

seldom go beyond 100–200 patients on the drug, all under rigidly controlled protocols.

Phase III are the expanded controlled and uncontrolled trials. These are performed after efficacy has been basically established, at least to a certain degree and are intended to gather additional evidence of efficacy, plus further evidence of safety, tolerance and definition of adverse effects.

Phase IV are post-marketing clinical trials. They include additional studies to investigate the incidence of adverse reactions, specific pharmacological effects or similar information. Also large-scale, long-term studies to determine the effect of a drug on morbidity and mortality or trials intended to supplement and confirm pre-marketing data.

Trials with a marketed drug for a new clinical indication are not included in Phase IV.

5. PHASE I TRIALS

Standard methodology has been covered in other texts [1,2,3] but some uncertainty remains on the first administration of a new drug to humans. Points to be considered are as follows:

(a) Subjects

Non-patient volunteers should normally be used. On rare occasions the specific action of the drug, as shown by animal studies, would suggest the choice of patients who might benefit rather than non-patient volunteers. One such example might be a powerful antimitotic agent, which could be toxic to healthy people but beneficial to leukæmic patients. Further examples might be trials of hypotensive agents and relaxants of skeletal muscle.

(b) Location

In addition to the facilities necessary to conduct the investigation, appropriate resuscitation facilities with trained staff must be immediately available. The main criterion is that there is no geographical risk with consequent delay in applying resuscitation measures, if required. Such facilities normally exist only in special hospital units but it is possible that industrial laboratories could be used if the same full facilities were available.

(c) Route of Administration

No route of administration should be used that has not been previously tested in animal species. The route of intended final administration should normally be utilised in these first trials but it might be considered advisable to give drugs intravenously, where a systemic

[1] *Principles and Practice of Clinical Trials.* E. & S. Livingstone. Edited by E. L. Harris and J. D. Fitzgerald. 1970.

[2] *Clinical Research for all.* C. Maxwell. Cambridge Medical Publications Limited. 1973.

[3] *Lectures on the Methodology of Clinical Research.* M. Hamilton. 2nd Edition. Churchill Livingstone. 1974.

action is envisaged. The effects of maximum absorption can then be predicted at an early stage.

(d) DOSE

No definitive advice can be given on first dosage, which will vary from case to case. Discussions between pharmacologists, toxicologists and clinicians should enable an estimate to be made concerning the human-effective dose[4]. First administration is commonly taken as a tenth of this estimate and subsequent doses (in different individuals) increased with careful monitoring of all systems.

(e) PRESENTATION

First studies usually employ the simplest presentations suitable for the route of administration selected. It is rare for the presentation to remain unchanged and further studies will have to be conducted with each presentation or with different conditions of administration (before and after meals, etc.). Determination of bioavailability in successive formulations and presentations will give guidance on the degree of trial repetition that is needed.

6. PHASE II TRIALS

Phase II trials incorporate all the problems of clinical trials generally, many of which are covered separately. Considerations which apply particularly to Phase II studies are as follows:

(a) PATIENT SELECTION

It is important to set criteria for patient selection, which will allow sufficient numbers to be included to give impetus to a proposed trial.

Such relatively wide selection might, however, dilute the result and prevent demonstration of a therapeutic effect. This can often be overcome by careful stratification of patients on entry into the trial, giving reasonably homogenous sub-groups. It is usual to randomise therapy within each sub-group but care must be taken not to have a system of treatment allocation which is too complicated to succeed.

(b) LOCATION

Phase II trials need careful supervision and control and it is recommended that they are carried out in hospitals.

However, some conditions are principally seen in general practice and, for these, it may be necessary to conduct the trials in general practice.

(c) ROUTE OF ADMINISTRATION –

will be that intended for normal clinical use.

(d) DOSAGE

It cannot be stressed too often that more effort is probably wasted in clinical trials by inadequate early dose-response studies than by any-

[4] World Hlth. Org. Techn. Rep. Ser. 1966, **341**, 18.

thing else. Also, estimations of optimum dosage in a hospital ward must be confirmed in conditions of routine practice, before undertaking lengthy double-blind, comparative trials outside of hospital.

(e) Presentation

The dosage form used in Phase II trials should approximate as closely as possible to that anticipated for general clinical use. As stated previously, any change in formulation or other alteration of test or control medication, could alter bioavailability and this should be determined to avoid invalid conclusions.

7. PHASE III TRIALS

In addition to the many general aspects of clinical trials, some of the following problems apply particularly to Phase III trials:

(a) Multi-centre Trials

Multi-centre trials involving many hospitals or practices are often needed in Phase III to provide sufficient patients. Such trials have particular difficulties, which must be considered and avoided by adequate planning.

During initial planning, each centre must have a delegate who discusses and then accepts the final protocol and who must ensure that all others involved in the trial at his centre understand and accept the protocol. The trial must not call on facilities that are not available to all investigating units and must not include treatment methods or diagnostic criteria that are not accepted by all participating clinicians.

As it is important in multi-centre trials, that those assessing results should accept uniform definitions and criteria, one needs to know the "inter-rater performance correlation" for both the objective and subjective assessment and it is desirable that there should be a high positive correlation. Examples of assessments, where this correlation is of particular importance, are the interpretation of X-rays and ECG's, the classification of histological specimens, the use of psychiatric ratings, and the assessment of physical performance. If this poses particular problems, they may be overcome by referring all results of certain investigations to a single expert.

(b) Staff Involvement

With all trials, it is important to inform all staff that are likely to be involved, but this is vital for longer trials, such as Phase III, where months of work can be lost due to the unintentional action of a receptionist, nurse, pharmacist or other member of staff, who has not received adequate explanation or instruction. The need to inform ancillary staff applies equally to hospitals and to general practice and particular attention must be paid to staff changes or locums.

(c) Continued Enthusiasm

Even though all appropriate personnel have been involved, so that they understand the details and the importance of a study, it is inevitable that some waning of enthusiasm occurs in doctors, patients and attendant staff during the course of longer trials. In order to overcome this problem, it may be helpful to conduct periodical reviews of progress particularly for multi-centre trials. It may also be necessary to organise a follow-up system for patients who fail to keep appointments, otherwise the drop-out rate could become too high to allow meaningful analysis.

(d) Long-term Toxicology

Even though it is not vital to the conduct of the trial, it is foolish not to include routine tests, such as hæmatology, liver function tests, etc., in a sample of patients in any long-term trial, so that evidence of long-term tolerance and toxicity can be accumulated.

(e) Control Therapy

Once therapeutic activity has been demonstrated in Phase II, it may be considered reasonable to use standard therapy as a control for further comparative trials. This is acceptable, if the standard therapy has itself been proven as efficacious and if the investigators are repeating previous trials and have proved the sensitivity of the method. If, however, there is any controversy over the standard treatment or any doubts on the sensitivity of the method, it will be necessary to include a placebo or two doses of standard drug to show that the trial is capable of differentiating standard therapy from placebo or from a reduced dose, before assuming that it is suitable to test a new drug. The sensitivity of a trial method is, probably, always in doubt when an investigator or group of investigators is using a protocol for the first time.

8. CLINICAL TRIAL ETHICS

Clinical trials must have the basic aim of testing a concept that could produce ultimate benefit to man.[5,6] This could be a major breakthrough in therapy, an improvement in tolerance, an extension of therapeutic range, an improvement in patient acceptance, an attempt to identify drug-responders, a confirmation of earlier work to help disseminate information on the optimum use of a therapeutically active substance or even disproving the value of some established regimens. A safeguard that trials comply with this basic aim is given by Ethics (often called Ethical) Committees[7] or their equivalent. The protocols of all trials and the rationale for them should be cleared by such committees.

[5] M.R.C. (1963) Responsibility in Investigations on Human Subjects. H.M.S.O. Cmnd. 2382, July 1964, reprinted in Brit. med. J., 1964, **2**, 178.

[6] R.C.P. (1967) Supervision of the Ethics of Clinical Investigations in Institutions. Brit. med. J., 1967, **3**, 429.

[7] R.C.P. (1973) Report of the Committee on the Supervision of the Ethics of Clinical Research Investigations in Institutions. Roy. Coll. Phys., July 1973.

9. NON-PATIENT VOLUNTEER CONSENT

A non-patient volunteer taking part in a clinical pharmacology study or an experimental study of a procedure or prophylactic agent, must do so of his own free will after giving fully informed consent.[8] This necessitates a written statement, which allows a volunteer or his adviser to understand the hazards involved.

10. PATIENT CONSENT

No-one doubts the frequent need for patients taking part in clinical trials of new products to give informed consent to the trial, whenever possible in writing. The patients thereby acknowledge that they have been made aware of the broad objectives of the trial, the likely benefits and, most important, the possible side effects of treatment. The need for informed consent is particularly strong when a new drug is involved or when unusual doses or methods of administration of standard drugs are employed. A full understanding of all the considerations is, however, impossible and patients are often inclined to give consent out of respect for their doctor believing that he will always act in their best interests. A full explanation of all the aspects may furthermore so alter the trial conditions that realistic assessments become impossible. This, as well as the degree of possible risk, must be taken into account by the investigator before he decides how much explanation is needed to obtain patient consent. No patient who declines to take part in a clinical trial must be included. In trials of marketed drugs at standard dosages (including placebos under some circumstances), which do not differ materially from standard practice, specific explanation and patient consent is not required,[9] although it may be preferred as a safeguard to justify additional visits or tests.

The whole subject of ethics and consent is well covered in the "Statement by the M.R.C. on Responsibilities in Investigations on Human Subjects".[10]

11. TRIALS IN PATIENTS UNABLE TO GIVE VALID CONSENT

At the moment, it is considered to be unwise to investigate in children the pharmacokinetics and pharmacodynamics of a new drug in a well-ordered way, since new drugs can only be recommended (with parental consent) if therapeutic benefit is expected.[11,12,13] Consequently, trials are rarely conducted in children, with the grave risk that, as new drugs become

[8] The Report of the Committee to Investigate Medical Experiments on Staff Volunteers. June 1970. Report issued by A.B.P.I., 162 Regent Street, London W1R 6DD.

[9] *Principles and Practice of Clinical Trials.* E. & S. Livingstone. Edited by E. L. Harris and J. D. Fitzgerald. 1970.

[10] Report of the M.R.C. for the year 1962-63. H.M.S.O. Comnd. 2382, July 1964. Reprinted in Brit. Med. J., 1964, **2**, 178.

[11] H.M.S.O., Cmnd. 2382, July 1964, reprinted in Brit. med. J., 1964, **2**, 178.

[12] Porter, A. M. W., Brit. med. J., 1973, **1**, 46.

[13] Tulloch, A. E., Brit. med. J., 1973, **4**, 485.

generally available, they are used for the first time in children in normal clinical practice instead of under carefully supervised conditions.

A similar situation relates to subnormals and to the foetus in utero, and the committee recommends that further consideration be given to investigating this matter fully and making appropriate recommendations.

12. PRE-TRIAL ORGANISATION

(a) Team Involvement

Although a trial may be originated by a co-ordinator, the final design must be accepted by the whole team. This will not normally include all nurses, receptionists, porters, etc., who might come into contact with the trial but, if possible, they should be informed of the study and of the medical benefit, which could accrue from a well-conducted investigation, as misdirected patients or discarded specimens could ruin a trial.

(b) Trial Protocol

Full explanations of protocols and basic trial procedures have been given elsewhere (see Section 5 for suggested reading). Each protocol is unique for the situation and conditions of each individual trial. Producing a "Master Protocol" for all drugs or even for different trials of one drug is pointless. This is sometimes attempted but, unless all centres are involved in planning (see Multi-centre Trials, Section 7 (a)), it is unlikely that assessment data will be sufficiently uniform to allow pooling.

Valid data from a few carefully conducted studies are better than masses of information collected in different ways, utilising slightly different criteria and often diluting good observations, so that a therapeutic effect or adverse reaction is lost.

(c) Description

In addition to recording the ideas and rationale behind a trial design (see conclusion to Double-blind Trial, Section 2 (a) (vi) above), all intentions and decisions about patients selection, exclusion, stratification, method of assessment, interpretation of results, etc., should be accurately recorded. Such recording ensures consistency of selection and interpretation as time passes during the trial and assists in the final writing up of the trial.

(d) Payment

Decisions on payment are part of pre-trial organisation and are dealt with more fully in Section 14.

13. MEASUREMENTS AND ASSESSMENTS

(a) Simplicity

Measurements should be as relevant and non-invasive as possible. Simple measurements, frequently repeated, can often yield more information than a few complex ones.

(b) Symptoms

A considerable proportion of medical time in clinical practice is devoted to attempts at relieving symptoms. These are subjective phenomena, which cannot be assessed objectively but their assessment can be an important part of clinical trials.

(c) Assessment by Patients

Apart from subjective assessments of specific symptoms, patients can usually make pertinent and useful observations on treatment received, benefit obtained and side-effects suffered, if they are asked. Some of this information may be collected by record cards held and completed by patients but most will come from careful questioning. Whenever possible any such questions should be posed in the same way and by the same person to all patients and an additional request for general observations should always be included.

(d) Rating Scales

Rating scales are used in two ways: self-rating scales by the patient or rating scales completed by an assessor.

The use of well-accepted and proven rating scales adds to the value of trials, makes comparisons easier and facilitates confirmation by other workers. Treatments differ, however, even when they are of the same basic type and minor differences, which could be of eventual therapeutic importance, might be missed by the inappropriate use of such standard scales. The incorporation of a global assessment, in addition to standard rating scales, is essential. Particularly when a new type of drug is being investigated, reliance should not be placed solely on standard rating scales, which could allow a novel therapeutic (or toxic) effect to be missed. For this reason, the value of intelligent clinical observation should never be minimised and trials should never be allowed to become routine matters.

(e) Unwanted Effects

The detection and assessment of unwanted effects of the treatments being tested is an important part of clinical trials. Investigators need to be alert for unpredicted effects as well as predicted ones.

The possibility of drug interactions must be considered and it is desirable to record all drugs (if possible with dose and frequency) taken by each patient in the period just before and during a trial. Tobacco, alcohol and caffeine-containing drinks deserve inclusion in the record.

In the detection of unwanted effects, non-specific questions to the patient are especially valuable in bringing to light unexpected effects, but it appears probable that only direct questions about specific effects can yield a reliable estimate of their prevalence. This is particularly true of subjective effects; objective drug effects should be detected by appropriate observation.

14. PAYMENTS

Payments for studies (including pathological investigations) may be made to the department(s) and the monies used for a variety of purposes, e.g. overheads, apparatus, salaries for research fellows, technicians, etc., according to local circumstances. Payment may be on a contract basis for a given trial or the trial supported indirectly by a general research grant.

(a) Clinicians

Personal payment to clinicians involved in a clinical trial poses problems. There is no doubt that trials frequently involve clinicians in a large amount of extra work but the influence of personal payment on the normal patient/doctor relationship must be considered. Because of this concern, unrestricted personal payment might be regarded as unethical but it is equally wrong for a clinician to be out of pocket due to lost sessions or be inconvenienced by extra work without compensation.[14] The level of payment is relevant and should realistically relate to the time lost and work done and be approved by the ethics committee or equivalent. All decisions relating to financial support, whether by direct payment for completing reports, grants for time spent or indirect aid, such as equipment or books, should be settled and recorded before the trial starts and be honoured, irrespective of the result of the trial.

The payment of travelling and hotel expenses to attend Scientific Meetings in order to report the findings of the trial should be considered a normal part of the expenses of the trial.

(b) Other Staff

The same policy should apply to paying technicians, secretaries, etc. Such people are often forgotten and trials can fail due to inadequate motivation and reward for ancillary staff.

(c) Volunteers

Volunteers should be offered out-of-pocket expenses and a reasonable fee or equivalent reward for the time and trouble involved.

(d) Patients

Patients should be offered out-of-pocket expenses, such as loss of earnings, fares for additional out-patient attendances, etc., but this should only be reimbursement and give no inducement to participate in clinical trials.

15. PROFESSIONAL INDEMNITY

When patients are recruited for entry to a clinical trial they should be warned of any known adverse effects of the treatment and given some idea of their known or estimated incidence and severity. They should also be informed of the possibility of unknown effects.

[14] Wld. Hlth. Org. Techn. Rep. Ser., 1968, **403**, 19.

In spite of the most meticulous planning and design of a clinical trial, unpredicted and unpredictable effects of the drug under test are occasionally encountered. If such effects are adverse to the health of the patient by causing him discomfort, pain or disability, temporary or permanent, he may wish to sue the doctor in charge of the trial for financial compensation.

If the clinician should be sued in negligence he would doubtless consult his medical defence or protection society who would handle the matter in precisely the same way as they would in the case of a therapeutic mishap. Where a patient suffers harm and no negligence is alleged this falls outside the province of the medical defence or protection society.

Pharmaceutical companies may have insurance arrangements for clinical trials. Sometimes, the company's insurance cover relates to a specific trial and sometimes to clinical trials in general. Clinical trials in this context are usually defined as studies for which a Clinical Trials Certificate has been issued by the D.H.S.S., but may include studies of medicines, which are already approved by issue of a Product Licence (or Product Licence of Right), but which are being used in a clinical trial in a way not covered by the Product Licence (e.g. in a higher dosage).

If pharmaceutical companies are not covered by insurance for clinical trials, they must guarantee to give the investigator indemnity against any subsequent claim based on a drug effect, as opposed to professional negligence. From the clinician's point of view, it is very important that the design and method of conduct of the trial be clearly agreed with the sponsoring pharmaceutical manufacturer, since the insurance cover may be prejudiced by any significant departure from the protocol.

Claims due to reactions with marketed products, where no special trial risk was present, would be covered by a company's public liability insurance, if any legal liability existed.

16. STATISTICS

Statistical analysis is an important aspect of clinical trials but the majority of unacceptable trials fail for other reasons, as good statistics cannot rescue a poor clinical trial.

Nevertheless, many poor trials could be prevented or put on the right path by advice from a statistician on the proposed protocol.

Some points, relating to statistical analysis, should be considered:

(a) Variations not due to Drugs

As already stressed, a statistician should be involved at the planning stage of a trial. He should be informed about variations due to the natural history of the disease being studied and the degree of change likely to be clinically significant. He must also be told of other changes, such as seasonal variations, visits of relatives, nursing staff changes, alterations in diet or ward routine, etc., which could influence the patient's condition, irrespective of drug therapy.

(b) Long-term Effects

If there is the theoretical possibility of a cumulative effect with long-term therapy or a diminished action for reasons such as enzyme induction or development of tolerance, the statistician should be told, so that the trial design can allow these aspects to be specifically studied.

(c) Carry-over Effects

In cross-over trials, there is always a tendency towards a carry-over effect due to residual action of the drug or to bias from the previous drug (or placebo) effect; this latter being more likely in trials with medicaments of identical appearance. The statistician must be aware of this risk and advise accordingly on trial design. In some cases, it is possible to have a non-treatment period between each therapy to allow return to base-line levels, but often this cannot be achieved. In such situations, the carry-over effect reduces the value of within-patient comparisons in a cross-over study and it might be better to conduct only between-patient comparisons, where no carry-over problems exist.

(d) Record Forms

Final analysis of data may be simplified by using patient record forms that are suitable for immediate computer analysis or, at least, suitable for easy transcription to computer tapes or cards. This must be considered for all trials with many patients and test parameters and is almost mandatory for multi-centre trials.

For practical reasons, record forms should be sufficiently robust to withstand the frequent handling that takes place during the trial and it is usually preferable for them to be made of card rather than paper.

(e) Drop-outs

The longer the trial, the greater the number of patients dropping out. Some will drop out after allocation to a trial group but before receiving therapy, some during a run-in period and others at later stages of a trial.

The management of drop-outs at these various stages must be considered in the planning phase of the trial and the decision made adhered to, irrespective of the numbers of drop-outs. Every effort must be made to find the reason for dropping out but this will be impossible in some cases and the groups must be analysed in the same way, whether or not the reason for failure is known.

One must also consider whether unreliable drug-takers should be regarded as drop-outs and this is discussed further in Section 17.

(f) Clinicians' Opinions

As stated earlier, there is much confusion between clinical value and statistical significance, particularly among statisticians.

Declarations on statistical significance must not be allowed to confuse clinical common sense and it is always advisable for the clinician

to give an overall opinion regarding clinical value and relevance in the light of the statistical analysis of the results.

(g) Details Supplied

This will be discussed further under "Publications" but it is important that sufficient data and statistical methodology is given to allow other workers and readers to analyse the data themselves and come to their own conclusions on the trial result and on the suitability of the statistical analysis used.

17. PATIENT NON-CO-OPERATION

Surveys have shown that up to 50% patients do not take medication as directed. The errors increase with the complexity of the regimen, a point which must be borne in mind when considering the double-dummy technique.

Apart from reducing to a minimum the actual number of medicaments prescribed, the rate of failure to take drugs can be reduced by the use of calendar-type packs, which constantly remind patients of the medicaments to be taken and their timing. Such packs will usually result in greater patient co-operation than simple bottles of bulk tablets with instructions on the label. Even so, it must be accepted that some patients will take fewer than the recommended doses or will take none at all. Some will admit their failure but others will not. Every effort must be made to encourage patients to take their medications regularly and to identify drug-defaulters.

A decision must be taken before the trial begins whether the primary aim is to evaluate a "total treatment regimen" or the pharmacological and therapeutic properties of a drug. If the "total treatment regimen" is under consideration, then it should be possible to accept the test and control groups as being representative of patients under normal conditions and to include them in the results, irrespective of the reliability of drug taking. When the assessment of the drug itself is the primary aim of evaluation, it is necessary to check on drug-taking routinely in all pateints and to analyse the patients taking the drug and the drug-defaulters separately. Even when the most careful precautions are taken, it must be recognised that drug-defaulting is likely to remain an undetected bias in a substantial minority of patients. This applies to in-patients as well as out-patients or patients in general practice.

The methods of checking the reliability of patients in taking drugs as prescribed include:

(a) Asking the Patient

(b) Counting Residual Tablets

This is easier with calendar-type blister packs. If medicaments are supplied in bottles, the controls and checks are less obvious if the patient is always given more tablets than are actually required and the residue above this known excess represents tablets which the patient has forgotten to take.

(c) Drug Markers –

such as riboflavine, quinine, methylene blue, etc. This has limitations, as the addition of dyes can alter the formulation and consequent bioavailability. Also, patients who are not co-operating are likely to take tablets just before clinic attendances, so that their urine will contain the marker on that day.

(d) Drug Levels in Serum or Urine

This has some of the limitations of (c) but drug levels are less likely to be at the correct maintenance level, if only a single tablet has been taken. Again, spot checks are of greater value than routine examinations.

Unfortunately, these methods give no indication of the exact dose taken by the patient over time and cannot ensure that full therapeutic doses have been taken regularly, particularly as some patients are determined to mislead.

18. COMBINATIONS

As a corollary from the evidence that patients' failure to take medicaments is proportional to the complexity of the regimen, there are strong arguments in favour of combination products for those patients who need to take more than one medicament at standard dosages and which can appropriately be taken together. Combinations must, however, undergo trials, as they are new formulations. In addition, such trials ensure that any risk of drug interaction occurs under the supervised conditions of clinical trials, rather than the relatively unsupervised conditions of normal clinical practice.

Trials of combinations should start with assessment of the individual ingredients to find the optimum dosage of each active agent alone and in combination. For these studies, a factorial design is desirable and it should be possible to vary the dose of each great independently from the other by using the double-dummy approach. An alternative, but pharmaceutically more cumbersome, method is to make individual formulations with the different dosage ratios for each group of patients in the trial. If individual medicaments have been used in trials for a proposed combination product, the finally preferred ratio of active agents must be subjected to confirmatory clinical trial, using the actual pharmaceutical formulation of the combination product.

19. "ROUTINE" TRIALS

While there may be no difficulties in finding investigators for a new drug of considerable therapeutic potential, it is often hard to set up studies with old products or with drugs similar in type to existing therapies; often referred to as "routine" as opposed to novel trials. However, major advances are sometimes made by a series of minor steps and qualitative differences in similar drugs can point the way to valuable new research. Examples include the diuretic effects noted in early hypoglycæmic agents, leading to the

thiazides and the anti-depressive effect of I.N.A.H. when used in the treatment of tuberculosis. Such observations can only be made by continued scientific assessments of well-known drugs or groups of drugs, so the importance of these should not be underestimated by investigators. In addition, minor changes in formulations (tablet form of chloral hydrate; long-acting injections of fluphenazine; palatable, stable, pædiatric penicillin suspension, etc.) can improve patient acceptance and therapeutic success, which are just as important in practical therapeutics as new chemical entities.

20. MEDICAL ADVISER PARTICIPATION IN TRIALS

Doctors who work as medical advisers in the pharmaceutical industry not only have an interest in clinical trial methodology but, by their experience, have special knowledge, which deserves to be used.

Apart from their knowledge and experience, they also have a personal interest in encouraging clinical colleagues to adhere to the protocol and to complete the trial, an important point in avoiding waste of effort.

When a medical adviser participates in a hospital trial, he should preferably hold an honorary clinical appointment and the hospital ethics committee should be informed and approve. The independent clinician in charge of the trial retains overall responsibility for the trial, for the selection of patients taking part in the trial and for their withdrawal from it. In practice, he will frequently delegate or share this responsibility with others, only insisting on personal referral in cases of doubt.

21. PUBLICATION

Most clinical trials are conducted in the expectation that the final report will be published. The facilities for such publications in the U.K. are considered to be adequate but a number of points relating to publications must be considered:

(a) Ownership of Data

If work is carried out on a contract basis (e.g. toxicology by a commercial laboratory), the data belong to the person or organisation that has ordered the investigation.

With clinical trials, the resultant data belong to the clinical investigator and he must decide, usually in consultation with the co-ordinating medical adviser, whether to publish and in what form. He may, however, be limited by previous agreement, which should be in written form, on the timing of publication for patent or other reasons of confidentiality. In any case, the clinician should give full information to the pharmaceutical company before publishing clinical trial results with a new compound.

(b) Acknowledgements

Authors must declare grants, fellowships or other assistance, which they have received for the trial, when presenting the final report for publication.

(c) Negative Results

Trials with negative results must be accepted on their merits in the same way as trials with positive results. In such cases, however, editors must take particular care that conclusions drawn are valid, as the tendency towards insensitivity and inflexibility of controlled trials make false negatives much more likely than false positives. This is particularly important in small trials, where it is possible to produce the misleading suggestion that there is no difference between a new product and an established treatment.

(d) Incomplete Data

It is preferable for all meaningful data to be included but limitation of space often makes it impossible to publish all information collected in a trial or all details of the formulations, the test procedures and the statistical methods employed. In these circumstances, editors of journals publishing trials may be prepared to keep such unpublished information on file and to make copies available to interested parties or to review these additional data as part of their editorial responsibility and to inform readers that copies can be obtained from the author, the company or some independent source.

(e) Correspondence Columns

The Committee recommends that no journal should accept clinical trials for publication if it does not also have a correspondence column to allow comment on the trials.

(f) Uncontrolled or Non-blind Trials

Uncontrolled or non-blind trials often include valuable clinical information, which points to the need for confirmatory controlled, double-blind trials.

Nevertheless, such uncontrolled trials should not give the impression of being controlled confirmatory studies and they should be published under the clear heading of "Clinical Notes" or "Clinical Observations".

(g) Editorial Responsibility

Editors of medical journals that publish clinical trials should accept that they have a considerable responsibility in guiding therapeutic opinion. Every effort should be made to ensure that phrases and definitions used are clearly understood (confusion over the words "controlled trials", "single-blind", etc.) and that the trial is referred to an independent referee to ensure that it comes up to an acceptable standard. It is also important that conclusions drawn do not go beyond the scope of the data presented. For example, it is still commonplace for trials with a fixed dosage of a drug administered for a short period of time to a highly selected group of subjects to conclude that the drug is to be (or not to be) recommended on the basis of these results for

widespread use in normal clinical practice. Editors have the responsibility to see that this does not occur.

(h) Formulation Details

While it may be impossible to give all details of formulations used in trials because of confidentiality, the basic data on the characteristics of the formulation should be given. This is particularly important where a non-standard formulation of a marketed product is being employed and it is inferred that the results obtained are relevant to the use of the marketed preparation, without evidence of comparability having been given.

(i) Summaries and Abstracts

With the expansion of medical and scientific literature, summaries are of increasing importance, as they are often the only part of an article which is read. The same is true for translated abstracts. The accuracy of these summaries and abstracts is, therefore, of great importance and they should include all the main facts consistent with the space available and ensure that a balanced and valid view of the trial and its results is presented.

22. INVESTIGATOR PANELS

Suggestions have been made at different times for panels of investigators, so that everybody involved in trials would know which clinicians were interested in conducting such studies. Unfortunately, doctors fear that the inclusion of their name on such panels might mean that they were allocated trials in subjects that did not interest them. Others would be prepared to help in some type of clinical research but not be prepared to conduct long-term or difficult trials. These and other reservations prevent general investigator panels from becoming a practical reality.

There is a place for panels of specialised interests, such as those organised by the British Tuberculosis & Thoracic Association or the Royal College of General Practitioners, who not only collect people with common interests but who have evidence of the reliability of their investigations and who can impose some degree of discipline on the panels. Even here, there is a potential danger in such panels achieving a near-monopoly status and eventually allowing the organising committee of the speciality panel to go beyond advice and guidance and establish an unwanted degree of control.

In general, we believe that the present system in the U.K. of informing and selecting investigators without the use of panels works reasonably well.

23. TRIAL WASTAGE

The National Economic Development Office report (Focus on Pharmaceuticals H.M.S.O. 1972) stressed the wastage that occurs in clinical trial effort, due to poor finishing. There is a shortage of investigators who are capable and prepared to conduct clinical trials, so it is particularly important that attention be paid to all factors that waste this limited capacity.

(a) Calibre of Investigator

Investigators must be interested in the project and have the tenacity of purpose to follow a trial through. This is particularly important for longer trials and those where staff changes occur, so that new people are constantly having to be involved. A successful trial is unlikely if an investigator does not show evidence of basic interest or determination.

(b) Calibre of Co-ordinator

The medical adviser or other co-ordinator has a difficult task in understanding, explaining, persuading, following up, assisting and using his diplomatic skill to achieve the right balance between assisting and occasionally bullying from the day of the first planning meeting to the final publication.

If he is not of sufficiently high calibre to perform these functions and does not have the drive and determination to continue, the trial may well fail (Section 20).

(c) Confusion over Ethics

Some investigators are uncertain of ethical considerations involved in trials, worried about their responsibility to patients in trials and unhappy about payment to themselves or their staff (see Section 14). Such doubts can reduce motivation and allow a trial to fail. It is hoped that this report will clarify such uncertainties and remove that particular reason for trial failure.

(d) Poor Planning

As had been stated earlier, many trials fail because the preliminary planning was inadequate. The basic concept of the trial must be clearly defined and all details considered (Section 12).

In addition, the trial must be capable of answering the question that is being posed. An "immediate double-blind trial" can give misleading information and the mistake of going into such a trial before adequate dose response studies are completed has already been stressed (Section 3 and Section 6 (d)).

(e) Lack of Facilities

Some trials fail from lack of facilities or personnel. The adequacy of facilities should have been assessed in the preliminary planning and may be a deciding factor in abandoning the trial before it starts. Shortage of personnel may, however, be rectified in certain circumstances by the appointment of a research fellow or by instituting GP out-patient sessions to help the investigator.

(f) Loss of Information

Trials can fail because a junior ancillary worker discards vital samples or loses record cards. All people involved in a trial, at whatever level, must be made aware of the study to ensure understanding and prevent unnecessary accidents (Sections 7(b) and 12(a)).

(g) Lack of Responsibility

A consultant has ultimate responsibility for patients under his care but trials are often carried out more satisfactorily by junior personnel with more time and more intimate patient contact. The consultant must, however, agree to the study and be kept fully informed.

Trials have failed when negotiations have been limited to junior staff who do not have the final responsibility for the patients involved.

(h) Lack of Co-worker Support

Some degree of stimulation and motivation can often be achieved by the sharing of information on trial progress between different centres involved in a major trial or series of trials. This is particularly useful for multi-centre trials but can also be applied in other circumstances on occasions.

(i) Inadequate Motivation

The best motivation is an interest in the study but this might not apply to all people involved in the trial, particularly those at a technical level. For such personnel, individual explanation of the aims of the trial can be helpful and payment for extra work done or overtime is essential (see Section 14).

(j) Patient Shortage

There are always fewer suitable patients available than appears to be the case from original estimates, but trials should not be allowed to fail because patients present themselves so irregularly and so infrequently that the staff involved forget the details of the protocol. As suggested earlier (Section 6(a)), it is better to widen the criteria for entry and to stratify into patient groups than to fail from lack of patients.

It has been suggested that patient panels could be set up for certain diseases but this might lead to an undue level of selectivity and it would probably be better to keep a record of centres who tend to see many cases of certain diseases and who would be willing to take part in trials. This might be extended to certain general practices, as well as hospital centres.

(k) Failing Trials

Despite careful planning, some trials will fail in practice for a variety of reasons. The commonest causes are probably patient shortage or staff changes with lesser interest by the new staff.

When it becomes obvious that a trial is not progressing satisfactorily, it should be reviewed. If the study is failing from loss of enthusiasm or similar cause, it is better to admit it frankly and stop the trial. More trial effort will be wasted by trying to continue with a failing trial than by stopping and making a completely fresh start.

24. COMMITTEE ON SAFETY OF MEDICINES

The Medicines Commission is a statutory body (Medicines Act, 1968) on which lay members serve in addition to those drawn from professional

and industrial interests and which gives guidance on the general execution of the Act and the establishment of Committees. The Committee relating to Clinical trials is the Committee on Safety of Medicines which is composed of independent experts in medicine, pharmacology and allied interests but which is administered by the Department of Health and Social Security. The issue of Certificates and Product Licenses is undertaken by the Department in the name of the Licensing Authority and according to advice received from the Committee on Safety of Medicines, which evaluates the technical data and bases its recommendations on a consideration of any potential hazards in the proposal. When applicants disagree with advice given by the Committee on Safety of Medicines, an appeal procedure entitles them to a hearing before the Medicines Commission.

The Act allows a doctor or dentist to undertake a trial on his own initiative provided he uses licensed medicinal products available through normal channels of supply. In general, if the materials are to be supplied from any other source, then the protocol must comply with the terms of a valid Clinical Trials Certificate held by the supplier. Alternatively, the investigator must notify the Licensing Authority of his intention to obtain exemption from the requirement to hold a Certificate before he can lawfully be supplied.

Any trial arranged by a person or organisation, other than the practitioner having clinical responsibility for the patient, must comply with a Clinical Trial Certificate unless the intention is merely to evaluate the performance of one or more marketed preparations which are to be used in accordance with licensed indications.

The address of the Licensing Authority is:

Licensing Authority,
Medicines Division,
Department of Health & Social Security,
Finsbury Square House,
33/37A Finsbury Square,
London EC2A 1PP.

25. CONCLUSION

This report represents the views and experience of the working party composed of clinicians in hospitals, in general practice and in the pharmaceutical industry. Their experience has selected the topics where there appears to be misunderstanding and confusion or where practical problems exist that can be corrected. Their opinions on the selected topics often differed but discussion, research and sharing of previous experience allowed suggestions to be made and conclusions to be drawn, which were agreed by all.

We hope that, although many of the points made are straight-forward and relatively obvious, their clear statement will be welcomed and assist workers in clinical pharmacology in the future.

Previously published reports by the Forum include:

Clinical Pharmacology on Facilities for Early Clinical Studies of New Medicines;

Academic/Industrial Relationships;

and, jointly with the Library and Lay Section of the Royal Society of Medicine:

The problems arising from the growing public interest in medicine and therapeutics.

Copies may be obtained from

The Medico-Pharmaceutical Forum,
1 Wimpole Street, London, W1M 8AE