LOGISTICS AND MANAGEMENT OF CLINICAL TRIALS

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This chapter is concerned with some of the more mundane aspects of the day to day design, planning, documentation, and management of clinical trials, rather than with the finer points of trial design which are dealt with in detail elsewhere. The points considered here, taken individually, seem obvious and trivial but it is hoped that some may be helpful in obtaining the maximum return for the work invested in running a trial.

Trial design

(i) Preliminary discussion

Brief notes of all discussions, from the earliest stage at which it is decided that the study is both necessary and ethical, are useful when formulating the design. Once the underlying hypothesis has been precisely stated, and the question which the trial has been designed to answer is specified, the design will be defined in the course of discussions with medical colleagues and the biostatistician. It is essential to include the biostatistician at the earliest stage of planning; as well as advising on matters where his expert knowledge is obviously relevant, such as the numbers needed, the significance level and power of the study, and the methods of analysis, of sampling, of allocating patients to the different treatment regimes, and of selecting controls, he will also be able to give valuable help on matters less obviously his concern, including the precise comparisons to be made, the degree of blindness, the number of treatment groups needed, and the duration of follow-up, and quality control of the data.

(ii) Preliminary documentation

It is also useful to begin drafting the two basic documents, the trial protocol and the operating manual, at a very early stage. This is a helpful method of identifying problems or weaknesses in design which may otherwise not become apparent until too late. Even a small study, in which nearly all the work will be done by one investigator, needs both these documents. The protocol may be needed for submission to the grant awarding body and the ethics committee; the operating manual, though used only by the people involved in the daily work of the trial, is equally

necessary. Several check-lists are available which may help protocol design (Clinical Trials Unit, 1977; Friedman *et al.*, 1981). The work of revising and updating trial documents has become considerably easier since word processors became more widely available.

(iii) Source of patients

The availability of patients will largely decide whether a study must be multicentre or can be carried out in one centre only. The most usual sources are hospital out- or in-patients, general practice lists, or registers of employees. Suitable subjects may be identified by screening, by case-finding, or by referral. Not all patients from any source, with any given pathology, will be available for study, and this has important implications for the applicability of results. For instance, a hospital-based study of the management of myocardial infarction will provide information about hospitalised cases only; with no data for patients treated at home. On the other hand, a trial based in general practice may have available for study only patients not needing consultant referral; and people in an industrial medical department available for inclusion in a trial may be only those who are fit enough to go to work.

In studies based on hospital populations, the admission or out-patients lists of people under the care of the consultants concerned form — permission having been obtained — the register from which to select patients. When a study based in general practice is designed, it is more difficult to ensure that no eligible people are missed. The age-sex register, or attendance records for previous years help to determine the numbers likely to be available; the help of the practice nurse or manager will probably be essential.

(iv) Treatment and control groups

So far as is possible, of course, the only difference between these groups should be in the composition of the tablets taken; it may however be very difficult to achieve this. For instance, in a recent American study (Hypertension Detection and Follow-up/Program Co-operative Group, 1979) of carefully graduated ('stepped') care in the treatment of hypertension, patients randomised to the stepped care

regime not only received prescriptions according to this precisely regulated schedule, but were given their drugs, and medical advice, free of charge. Those randomised to the control group were referred back, after screening, to their usual source of medical care for the treatment of their hypertension and had to meet the bills in the usual way: thus there were differences between the management of the two groups in addition to the drug regimes followed. Of course, this does not invalidate the result of the trial, which showed a marked reduction in all-cause death rate in the stepped care group; but it does mean that it is uncertain whether or not all the benefit was due to the superior control of blood pressure in this group in comparison with the other.

(v) *Entry and exclusion criteria*

The definition of entry criteria is useful in two ways. First, patients not meeting trial criteria, or unsuitable on ethical grounds, can be excluded; second, it is implicit that patients not deviating from these criteria may be included ethically in the study, and this may facilitate the decision to enter some patients about whose suitability the doctor may have been concerned. For instance, in the Medical Research Council's randomised placebo-controlled trial of treatment in mild hypertension (Report of Medical Research Council Working Party on Mild to Moderate Hypertension, 1977) participating general practitioners agree to enter all patients with blood pressure in the trial range (unless exclusion criteria apply). However, a doctor seeing a prospective patient who is at the lower end of the age range, but whose blood pressure is towards the upper limit, may be concerned initially lest it would be unethical to enter this person to the study. The entry criteria, particularly when supported by a brief account of the more important published work which may usefully be included in the protocol, should be reassuring.

Grounds for exclusion will include, together with such pathological or psychological factors as would make participation unethical, failure to obtain the general practitioner's or consultant's consent.

Entry criteria invariably restrict the sorts of patients in whom the treatment effects will be studied. This in turn affects not only the ease of recruiting suitable patients but the nature of the population to whom the eventual results will be applicable. Having decided the entry criteria it is useful to restate the primary trial questions in terms of how the trial sample is now defined.

(vi) *Follow-up visits*

An exact timetable of the follow-up visits required, listing the examinations and investigations which are to be performed at each, should be drawn up when

the trial is being formulated. This will be helpful to colleagues deciding whether or not to collaborate, to members of the ethical committee who need to be sure that painful or inconvenient procedures are only to be carried out when absolutely necessary, and to grant awarding bodies who wish to see that the calculations for this aspect of the estimated expenditure are reasonable. It may be helpful to specify which visits are essential and which can, if absolutely necessary, be omitted.

(vii) *Drugs and treatment changes*

At the planning stage, the source and specification of the drugs, and measures to be taken to ensure the maintenance of quality, can usefully be explored. Restriction and standardisation of non-trial medication should also be considered.

The reasons for altering the treatment of any patient in the study defined usually fall into three groups: progression or regression of the underlying condition to a stage at which randomly allocated trial management is unethical, development of suspected adverse drug reactions and patient default due to any cause.

(viii) *Termination of participation*

Events necessitating termination usually fall into two groups: death from any cause or development of a feature which forms one of the end points of the study, as for instance if a patient in a trial of a drug designed to reduce the incidence of myocardial infarctions experiences such an attack.

A number of other patients may withdraw from the trial during its course. Ideally the possible reasons (e.g. pregnancy, adverse drug reaction) should be foreseen in advance, stated in the protocol and, if possible prevented. The operating manual should contain explicit directions on the procedure in case of suspected drug toxicity, interaction, concurrent disease or other occurrences which might jeopardise the patient's health or the integrity of the trial. Careful and imaginative planning in this way will maximise patient safety and minimise losses to the trial.

(ix) *Quality control*

Regular routine quality control of the data is an essential feature of the monitoring of results, and is usefully considered in detail when trial design is planned. It should, within appropriate confidence intervals, measure possible bias, include checks on 'blindness' and patient compliance, and identity within—and between—observer and within—and between—centre variations.

An important aspect of quality control, especially in multi-centre studies, is the maintenance of morale and enthusiasm, particularly amongst participants

involved with tedious and routine trial tasks. Personal visits from the co-ordinating team and feed-back about recruitment and data quality will all help to maintain the sense of urgency necessary for an efficient contribution from each centre.

(x) *Subsidiary analyses*

So far as possible, it is necessary to plan all such analyses before the study begins, and it is wise to resist pressure to introduce subsidiary studies, however interesting, once the final design has been established. Unless these extra projects are very valuable indeed they may well be more nuisance than they are worth, for they may reduce the size of the final comparison groups and can even make it impossible to answer the main trial question. Further, if the number of comparisons to be made becomes large enough, some will, as a result of chance, show significant differences between treated and control groups (Simon, 1982).

(xi) *Liaison between centres*

Single-centre trials have a number of advantages over multi-centre trials when recruitment is adequate. Often considerable resources have to be spent maintaining contact between geographically, and often intellectually, distant collaborators for the sake of the additional patients they will supply to the trial. Without some effort the increased power of the trial attributable to the extra patients is more than offset by the increase in variance due to differences between centres. Paradoxically inter-centre differences have the advantage of representing the heterogeneous population to whom the trial results will be applied more closely than a single centre can. The difficulties of multi-centre trials are helpfully discussed elsewhere (Friedman *et al.*, 1981; Klimt, 1979).

In any multi-centre study, it is essential to have one person at each centre who takes the responsibility for running the study and for liaison with the co-ordinator. A list of participating centres, identifying these people by title and by name (for example, the cardiology consultant, with the senior registrar in cardiology acting as his deputy) is helpful, and should also give the name, address, and telephone number of the trial co-ordinator.

The trial co-ordinator, in his turn, must make himself known to all participants including the pharmacists at each centre. This is important whether or not trial drugs are being dispensed by them; their help will often be sought by patients taking trial medication who may get inappropriate advice unless the pharmacist knows about the trial. Trial personnel may vary, but their essential duties are to ensure that everyone is doing what they have agreed to do, and to monitor

the progress of the trial, advising the participants to proceed or to stop depending on statistical and/or ethical decision rules to which all parties are agreed. It helps if these two rules are embodied in two people; if not blindness may suffer. If the study is a long-term one, it is important to emphasise this at the beginning, for deterioration in the quality of the data is to be expected unless those participating appreciate at the outset that they are undertaking a prolonged commitment. All participating doctors understandably become impatient for information about results, and it may be helpful to explain at an early stage that, even if sequential methods of analysis are employed, on-going results cannot usually be disclosed. Regular quality control visits to peripheral centres are very useful, as a method of maintaining both the quality of the data and good communication with the co-ordinating centre.

Supervisory bodies

(i) *Working party*

A working party of experts in relevant fields is helpful, and may be set up at the planning stage of any sizeable study; they will advise on design and on scientific problems which are identified while the trial is in progress. The members of this working party will need to be familiar with the main points of trial design and procedure, but should be ignorant of results lest these make it difficult for them to exercise their scientific judgment without bias.

(ii) *Monitoring Committee*

However, it places too great a burden of responsibility on the trial co-ordinator if he, immersed as he is with day to day detail, is the only person aware of results as these accrue; it is helpful to him to have access to a small group, distinct from the working party, with whom he can discuss in confidence the ongoing results.

(iii) *Ethics Committee*

The monitoring committee may decide that problems have arisen necessitating discussion with an ethics committee. This committee should be made up of totally independent people, to whom the start or the continuation of the trial are matters of academic interest only. If in the opinion of the ethics committee, changes in the protocol, or even the termination of the trial, are necessary, they will make appropriate recommendations to the working party.

Documentation

(i) *Protocol*

The protocol should describe the background to the study and the trial design in sufficient detail for the reader to arrive at a reasonably informed decision on the usefulness and ethics of the plan, and to have a clear idea in principle of how it will be carried out. Precise detail of day to day running is unnecessary.

(ii) *Operating manual*

In contrast to the protocol, the operating manual should include every detail of trial management. Even if the triallist expects to control all aspects of the work himself he will find it helpful to write such a manual.

The degree of detail needed will be appreciated by anyone who has tried to take over the running of an inadequately documented trial; it must be possible for a triallist to hand a study over in emergency, without waste of the time and money already invested.

(iii) *Forms, questionnaires, cards, and notes*

Examples of each of these may usefully be appended to the protocol and included in the text of the operating manual.

Wherever possible, information should be recorded directly onto a document from which it can be punched. Transferring information from one document to another wastes time, and increases errors. Two copies of the document will probably be needed, one for the punch card operators, and one for medical records. If the documents are in the form of a booklet or a pad so that the alignment of the pages is preserved, carbon paper may be used to make copies; if not, NCR paper probably gives better results, though it is a little more expensive.

The boxes provided for recording the information should be at least 0.5 cm square, otherwise the entries may be difficult to read. This wastes the time of the punch card operators, who are expected to work at speed, and of course may lead to errors.

Transcription of participants' names requires precise instructions to be given. Some surnames may contain more letters than the number of boxes: state that the recording should start with the left-hand box, and the name be truncated where necessary. Give instructions for the recording of an apostrophe such as that in O'Kelly; for dealing with the prefixes Mac, Mc, or St; and for whether or not hyphens are to be recorded. Where numerical values are concerned, give instructions about rounding up or down, and use of decimal points.

Even apparently simple questions need to be

formulated precisely. For instance, if a patient's height is to be recorded, specify 'height without shoes': women automatically remove their shoes before being measured, but men do not unless they are asked to do so. Patients and doctors commonly use different units of measurement and forget to say which they are using.

Do not ask for information which will not be used. Such questions are worse than useless, for the more the interviewer and the interviewee are fatigued the less accurate will be the data which will eventually be used. Unless a participant's occupation is relevant, do not ask about it; but if information is needed, make sure that the recorded data actually contain this. To record that a person works as a 'civil servant', or as an 'engineer', is useless, for these terms cover a wide variety of jobs, are of no value even as guides to social class, and certainly do not indicate occupational hazards. Information is likely to be even less precise when women are asked about their husband's work.

If self-completed questionnaires are to be used, limit the number of questions to be asked, for participants will answer less accurately the greater the number of questions there are. Not only should the number of questions be stringently restricted, preferably to fewer than ten, but the number of times the questionnaire is to be completed by each patient should be limited, for as people become familiar with the form they may automatically repeat their previous answer. Replies may be validated by interviewing a random sample of the participants.

It is always useful to ask several colleagues to complete—not just to read through—some sample questionnaires, to ensure that what seem to the designer to be clear questions and instructions are in fact unambiguous and easy to follow.

Reasons for changing from the original randomly allocated treatment, or for terminating a patient's participation altogether, may usefully be tabulated on forms which can be used as card-punching documents. The form listing terminating events may also include space for the name and address of a doctor who can provide the detailed information which the triallist is certain to need.

Coloured stickers should be provided for easy identification of notes if NHS folders or hospital documents are to be used. Each page of all trial forms, X-rays, ECGs, and pathology results should show the patient's name, the date, and his trial identification number. In a multi-centre study, forms may be labelled with patient's names and numbers before being sent to the individual clinics; this saves work and time at the periphery, but has the disadvantage that it makes it possible for forms to be used for the wrong person.

Trial participants should each be given a card to carry, stating that they are trial subjects, listing the trial drugs, and giving the address and telephone

number of a doctor who is not blind to the treatment and who can, if necessary, disclose this information.

A system for identifying the notes of patients who have lapsed, or whose follow-up forms have not been received, or about whom there is unanswered correspondence, will be useful. Coloured tags, or a separate filing system, may be used. For further discussion the reader is referred to Friedman *et al.* (1981), Good (1976), and Wright & Haybittle (1979).

Interpretation and quality of data

(i) Interviewing technique

The element of interpretation can never be eliminated where an interviewer is employed. With care, bias introduced by interviewer interpretation can be reduced: measures taken to achieve this include moving interviewers from one centre to another in a multicentre study; splitting up teams of investigators so that any bias is distributed evenly; and tape recording interviews so that a tendency to incorrect questioning technique can be observed and corrected.

(ii) Individual judgment

If a trial involves interpretative assessment, for example of X-rays, or of histopathology, or of ECGs, a further possible source of bias is introduced. A panel of readers, blind and reading independently of one another, may be employed. Where there is an element of possible progression to be considered, the material may be looked at in randomised or in date order. Consensus opinion may be based on either a majority opinion or on an arithmetical mean of the scores.

Films and slides should be recirculated at intervals so that an assessment of within-, as well as between-observer variation, may be obtained. A set of previously classified examples may be used for comparison with readers' assessments of the actual trial material. These points should be discussed with the statistician.

If more than one laboratory is to be involved, comparability of results must be ensured as far as possible. A measure of comparability can be obtained by each laboratory analysing part of the same sample; many laboratories participate in national quality control schemes, such as the National Quality Control Scheme for Clinical Chemistry or the UK National Quality Control Scheme for Haematology. Participating laboratories will know how their results compare with those of others, and discussion with the medical director of the laboratory will enable the trial co-ordinator to assess to what extent results may be pooled.

Supplies, equipment, and stores

Training should be provided in the use of any special equipment which will be provided, and arrangements made for regular calibration and maintenance of this equipment, for provision of substitutes should machinery fail, and for emergency servicing. The peripheral centres should be told that organisation of stores, and stock control, will be the responsibility of the co-ordinating centre.

Tablets will usually be sent to the individual clinics from the co-ordinating centre, rather than being supplied to the individual centres directly from source. The triallist, often in collaboration with his local pharmacy, is responsible for stock control of tablets as of equipment, and for labelling of containers for the peripheral clinics; the clinics however are responsible for requisitioning further supplies from the centre. In a single-blind study, the system of labelling should be explained to the staff at the peripheral clinics.

Pilot study

Before attempting a study of any size, a pilot study will be found to be very helpful. The planning and documentation must be as precise as for the full trial: if, for instance, the expense of clerical work is not costed at the pilot stage, an opportunity to estimate the clerical cost of the trial as a whole will have been wasted. As well as helping to define details for the full-scale trial, the pilot study will identify weaknesses in the trial design, and the protocol may be substantially improved. The pilot phase is probably the first opportunity to see how patients will react to the proposals, so it is useful in assessing the percentage who will agree to participate, and possibly in identifying those who will participate for the whole of the planned length of the study. Refusal or default may occur if follow-up visits are too much trouble, or fares too expensive, or time off work too costly; investigations may take too long or be too painful; or involvement in any trial, with the degree of uncertainty which that involves, may be too worrying. The protocol may be amended at this stage so that the lapse rate for these and other avoidable reasons may be reduced. The results from the pilot trial will give some idea of the variance of the observed effects under trial conditions. This, in its turn, will improve the original 'guesstimate' of the number of patients needed and hence the necessary recruitment rate. Once the full scale trial has begun, the protocol may be altered only if there is urgent necessity. The pilot phase represents an excellent opportunity, and the last convenient chance, to get the trial design right.

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