

An Introduction to Clinical Trials

1.1. INTRODUCTION

Avicenna, an Arabian physician and philosopher (980–1037), in his encyclopedic *Canon of Medicine*, set down seven rules to evaluate the effect of drugs on diseases. He suggested that a remedy should be used in its natural state, with uncomplicated disease, and should be observed in two ‘contrary types of disease.’ His *Canon* also suggested that the time of action and reproducibility of the treatment effect should be studied (Crombie, 1952; Meinert, 1986).

But for several centuries Avicenna’s advice appears to have been largely ignored, with most ideas affecting choice of treatment depending largely on serendipity rather than planned experiments. Only in recent years (although see next section) has it become widely recognised that properly conducted *clinical trials*, which follow the principle of scientific experimentation provide the only reliable basis for evaluating the efficacy and safety of new treatments.

And just what constitutes a clinical trial? There are several possible definitions, but for our purposes the term will be used for any form of planned experiment designed to assess the most appropriate treatment of future patients with a particular medical condition, where the outcome in a group of patients treated with the test treat-

ment are compared with those observed in a similar group of patients receiving a control treatment, and patients in both groups are enrolled, treated and followed over the same time period. The groups may be established through randomisation or some other method of assignment. The outcome measure may be the result of a laboratory test, a quality of life assessment, a rating of some characteristic or, in some cases, the death of a patient.

As a consequence of this somewhat restricted definition, comparative studies involving animals, or studies that are carried out *in vitro* using biological substances from man do not qualify as clinical trials. The definition also rules out detailed consideration of investigations involving *historical controls*.

1.2. A BRIEF HISTORY OF CLINICAL TRIALS

It is almost *de rigueur* in books on clinical trials to include a section tracing their history. Our book is no exception! Table 1.1 (taken from Meinert, 1986) lists some important dates in the development of such trials, the first of which relates to the often described experiment of James Lind carried out in 1747 while at sea on board the *Salisbury*. Bradford Hill (1962) gives the following quotation from Lind's account.

On the 20th May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet in common to all, viz. water-gruel sweetened with sugar in the morning; fresh mutton broth often times for dinner; at other times puddings, boiled biscuit with sugar etc. And for

Table 1.1. Historical Events in the Development of Clinical Trials.

Date	Author	Event
1747	Lind	Experiment with untreated control group (Lind, 1753)
1799	Haygarth	Use of sham procedure (Haygarth, 1800)
1800	Waterhouse	U.S.-based smallpox trial (Waterhouse, 1800, 1802)
1863	Gull	Use of placebo treatment (Sutton, 1865)
1923	Fisher	Application of randomisation to experimentation (Fisher and MacKenzie, 1923)
1931	—	Special committee on clinical trial created by the Medical Research Council of Great Britain (Medical Research Council, 1931)
1931	Amberson	Random allocation of treatment to groups of patients (Amberson <i>et al.</i> , 1931)
1937	—	Start of NIH grant support with creation of the National Cancer Institute (National Institutes of Health, 1981b)
1944	—	Publication of multicenter trial on treatment for common cold (Patulin Clinical Trials Committee, 1944)
1946	—	Promulgation of Nuremberg Code for Human Experimentation (Curran and Shapiro, 1970)
1962	Hill	Publication of book on clinical trials (Hill, 1962)
1962	Kefauver and Harris	Amendments to the Food, Drug and Cosmetic Act of 1938 (United States Congress, 1962)
1966	—	Publication of U.S. Public Health Service regulations leading to creation of Institutional Review Boards for research involving humans (Levine, 1981)
1967	Chalmers	Structure for separating the treatment monitoring and treatment administration process (Coronary Drug Project Research Group, 1973a)
1979	—	Establishment of Society for Clinical Trials (Society for Clinical Trials, Inc., 1980)
1980	—	First issue of <i>Controlled Clinical Trials</i>

(Taken with permission from Meinert, 1986.)

supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of cider a day. Two others took twenty-five gutts of elixir vitriol three times a day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a day, upon an empty stomach: having

their gruels and their other food well acidulated with it, as also the gargle for their mouths. Two of the worst patients, with the tendons in the ham rigid (a symptom none of the rest had) were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of a gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with greediness, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a day of an electuary recommended by a hospital-surgeon, made of garlic, mustard-feed, rad. raphan, balsam of Peru, and gum myrr; using for common drink barley water well acidulated with tamarinds; by a decoction of which, with the addition of cremor tartar, they were greatly purged three or four times during the course. The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine, than a gargle of elixir vitriol, he became quite healthy before we came into Plymouth, which was on the 16th June. The other was the best recovered of any in his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick.

In spite of the relative clear-cut nature of his findings, Lind still advised that the best treatment for scurvy involved placing stricken patients in ‘pure dry air.’ No doubt the reluctance to accept oranges and lemons as treatment for the disease had something to do with their expense compared to the ‘dry air’ treatment. In fact it was a further 40 years before the British Navy supported lemon juice for the crews of its ships at sea; once again the question of cost quickly became an issue with lemons being substituted by limes, condemning the British sailor to be referred to for the next two hundred years as ‘limeys’.

Most of the early experiments involved arbitrary, nonsystematic schemes for assigning patients to treatments, such as that described by Lind. The concept of randomisation as a method for treatment

assignment was first introduced by Fisher and the first trial with a properly randomised control group was for streptomycin in the treatment of pulmonary tuberculosis (see Medical Research Council, 1948, and Armitage, 1983). But not all clinicians were convinced of the need for such trials — the following is taken from a letter published in a medical journal of the day, attacking a proposed trial for the treatment of depression:

There is no psychiatric illness in which bedside knowledge and long clinical experience pays better dividends; and we are never going to learn about how to treat depressions properly from double blind sampling in an MRC statistician's office.

Since World War II, the clinical trial has evolved into a standard procedure in the evaluation of new drugs. Its features include the use of a control group of patients that do not receive the experimental treatment, the random allocation of patients to the experimental or control group, and the use of blind or masked assessment so that neither the researchers nor the patients know which patients are in either group at the time the study is conducted. The clinical trial nicely illustrates the desire of modern democratic society to justify its medical choices on the basis of the objectivity inherent in statistical and quantitative data.

1.3. TYPES OF CLINICAL TRIAL

Clinical trials can take a variety of different forms. All however are *prospective* with observations being made over a period of time after treatment allocation. Perhaps the most common design for a clinical trial is the fixed sample size *parallel groups* design with random allocation of patients to treatment, rather than some larger randomisation unit such as family, hospital, ward, community, etc. One problem with such a design occurs when patients vary so much

in their initial disease state and in their response to therapy that large numbers of patients may be needed to estimate reliably the magnitude of any treatment difference. A more precise treatment comparison might be achieved by using a *cross-over* design in which each patient receives more than one treatment. A simple example is the 2×2 cross-over design in which one group of patients receive two treatments, A and B, in the order AB, another group in the order BA, with patients being randomly allocated to the two groups. Clearly such a design is only suitable for chronic conditions in which there is the limited objective of studying the patient's response to relatively short periods of therapy. The design and analysis of cross-over trials is more than adequately dealt with in Jones and Kenward (1989) and Senn (1993), and so will not be considered in any detail in this text.

The majority of randomised, placebo-controlled clinical trials have focussed on one drug at a time although this does not match up with clinical practice where it is rarely sufficient to consider only a single treatment for a condition. Questions about the effects of combinations of treatments can never be resolved by the simple parallel groups design in which an active treatment is compared with a placebo; consequently, some investigators have proposed *factorial designs* in which several treatments are considered simultaneously. Lubsen and Pocock (1994), for example, describe a trial in which patients were simultaneously randomised to each of three active treatments or their respective controls in a $2 \times 2 \times 2$ factorial arrangement. The claim made for the trial is that it provides three answers for the price of one (see Collins, 1993). As Lubsen and Pocock point out, this claim is only justified if it can safely be assumed that there is no evidence of any *interaction* between the three treatments. Lack of interaction implies that the effect of the treatments are additive on some particular scale expressing the effects of each treatment. Lubsen and Pocock are sceptical about whether interactions can often be dismissed *a priori*; if they cannot, then factorial designs will

require larger sample sizes to achieve the same power as a parallel groups design. Their conclusion is that such designs are most appropriate for assessing therapeutic combinations when possible interactions are actually of primary interest. Some consideration of such studies is given in Holtzmann (1987) and Berry (1990).

The pharmaceutical industry uses a well-established taxonomy of clinical trials involving drug therapy, in which the categories can, according to Pocock (1983), be described as follows:

Phase I Trials: Clinical Pharmacology and Toxicity

These first experiments in man are primarily concerned with drug safety, not efficacy, and hence are usually performed on healthy, human volunteers, often pharmaceutical company employees. The first objective is to determine an acceptable single drug dosage (i.e. how much drug can be given without causing serious side-effects). Such information is often obtained from *dose-escalation* experiments, whereby a volunteer is subjected to increasing doses of the drug according to a predetermined schedule. Phase I will also include studies of drug metabolism and bioavailability and later, studies of multiple doses will be undertaken to determine appropriate dose schedules for use in phase II. After studies in normal volunteers, the initial trials in patients will also be of phase I type. Typically, phase I studies might require a total of around 20–80 subjects or patients. The general aim of such studies is to provide a relatively clear picture of a drug, but one that will require refinement during phases II and III.

Phase II Trials: Initial Clinical Investigation for Treatment Effect

These are fairly small-scale investigations into the effectiveness and safety of a drug, and require close monitoring of each patient. Phase II trials can sometimes be set up as a screening process to select out those relatively few drugs of genuine potential from the

larger number of drugs which are inactive or over-toxic, so that the chosen drugs may proceed to phase III trials. Seldom will phase II go beyond 100–200 patients on a drug. The primary goals of phase II trials are:

- to identify accurately the patient population that can benefit from the drug,
- to verify and estimate the effectiveness of the dosing regimen determined in phase I.

Phase III Trials: Full-scale Evaluation of Treatment

After a drug is shown to be reasonably effective, it is essential to compare it with the current standard treatment(s) for the same condition in a large trial involving a substantial number of patients. To some people the term ‘clinical trial’ is synonymous with such a full-scale phase III trial, which is the most rigorous and extensive type of scientific clinical investigation of a new treatment.

Phase IV Trials: Postmarketing Surveillance

After the research programme leading to a drug being approved for marketing, there remain substantial enquiries still to be undertaken as regards monitoring for adverse effects and additional large-scale, long-term studies of morbidity and mortality.

This book will be largely concerned with phase III trials. In order to accumulate enough patients in a time short enough to make a trial viable, many such trials will involve recruiting patients at more than a single centre (for example, a clinic, a hospital, etc.); they will be *multicentre trials*. The principal advantage of carrying out a multicentre trial is that patient accrual is much quicker so that the trial can be made larger and the planned number of patients can be achieved more quickly. The end-result should be that a multi-

Table 1.2. Potential Problems with Multicentre Trials.

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- The planning and administration of any multicentre trial is considerably more complex than in a single centre,
 - Multicentre trials are very expensive to run,
 - Ensuring that all centres follow the study protocol may be difficult,
 - Consistency of measurements across centres needs very careful attention,
 - Motivating all participants in a large multicentre trial may be difficult,
 - Lack of clear leadership may lead to a degeneration in the quality of a multicentre trial.
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centre trial reaches more reliable conclusions at a faster rate, so that overall progress in the treatment of a given disease is enhanced.

Recommendations over the appropriate number of centres varies; on the one hand, rate of patient acquisition may be completely inadequate when dealing with a small number of centres, but with a large number (20 or more) potential practical problems (see Table 1.2) may quickly outweigh benefits. There also be other problems involving the *analysis* of multi-centre trials. It is likely, for example, that the true treatment effect will not be identical at each centre. Consequently there may be some degree of treatment-by-centre interaction and various methods have been suggested for dealing with this possibility. Details are available in Jones *et al.* (1998), Gould (1998) and Senn (1998).

1.4. ETHICS OF CLINICAL TRIALS

Since the time of Hippocrates, Western physicians have taken an oath in which they swear to protect their patients ‘from whatever is deleterious and mischievous.’ Unfortunately such an oath has not managed to stop many damaging therapies being given or to lessen the persistence of barbarous practices such as copious blood-letting. Even the most powerful members of society were vulnerable to the ill-informed, if well-intentioned physician, as the following account of

the treatment of the dying Charles II demonstrates:

At eight o'clock on Monday morning of February 2, 1685, King Charles II of England was being shaved in his bedroom. With a sudden cry he fell backward and had a violent convulsion. He became unconscious, rallied once or twice, and after a few days, died. Doctor Scarburgh, one of the twelve or fourteen physicians called to treat the stricken king, recorded the efforts made to cure the patient. As the first step in treatment the king was bled to the extent of a pint from a vein in his right arm. Next his shoulder was cut into and the incised area was 'cupped' to suck out an additional eight ounces of blood. After this, the drugging began. An emetic and purgative were administered, and soon after a second purgative. This was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beetroot, camomile flowers, fennel seed, linseed, cinnamon, cardamom seed, saffron, cochineal, and aloes. The enema was repeated in two hours and a purgative given. The king's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered and also a powder of cowslip flowers 'to strengthen his brain.' The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, liquorice, and sweet almond. Likewise white wine, absinthe, and anise were given, as also were extracts of thistle leaves, mint, rue, and angelica. For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the king's feet. The bleeding and purging continued, and to the medicaments were added melon seeds, manna, slippery elm, black cherry water, an extract of flowers of lime, lily of the valley, peony, lavender, and dissolved pearls. Later came gentian root, nutmeg, quinine and cloves. The king's condition did not improve, indeed it grew worse, and in the emergency forty drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the king's throat; this antidote contained an enormous number of herbs and animal extracts. Finally bezoar stone was given. "Then", said Scarburgh, "Alas! after an ill-fated night his serene majesty's strength seemed exhausted to such a degree that the whole assembly of physicians lost all hope and became despondent; still so as not to appear to fail in doing their duty in any detail, they brought into play the most active cordial." As a sort of grand summary to this pharmaceutical debauch, a mixture of Raleigh's antidote, pearl julep, and ammonia was forced down

the throat of the dying king.

Ethical issues in medicine in general and clinical trials in particular are clearly of great importance and present a potential minefield especially for two statisticians more involved and perhaps more interested in the pragmatic problems of the analysis of the data generated in such trials. Nonetheless, along with all staff involved in trials, the statistician must share in the general responsibility for the ethical conduct of a trial. And there are in addition some areas of trial conduct where the statistician needs to take particular responsibility for ensuring that both the proposed and actual conduct of the trial are appropriate.

A central ethical issue often identified with clinical trials is that of randomisation. Randomised controlled trials are now widely used in medical research. Two recent examples from the many trials undertaken each year include:

- A multicentre study of a low-protein diet on the progression of chronic renal failure in children (Wingen *et al.*; 1997),
- A study of immunotherapy for asthma in allergic children (Adkinson Jr. *et al.*, 1997).

Random allocation gives all subjects the same chance of receiving each possible treatment (although see Chapter 2). Randomisation serves several purposes; it provides an important method of allocating patients to treatments free from personal biases and it ensures a firm basis for the application of significance tests and most of the rest of the statistical methodology likely to be used in assessing the results of the trial. Most importantly, randomisation distributes the effects of concomitant variables, both measured and unobserved (and possibly unknown), in a chance, and therefore, impartial fashion amongst the groups to be compared. In this way, random allocation ensures a lack of bias, making the interpretation of an observed group difference largely unambiguous — its cause is very likely to be the different treatments received by the different groups.

Unfortunately, however, the idea that patients should be randomly assigned to treatments is often not appealing to many clinicians nor to many of the individuals who are prospective participants in a trial. The reasons for their concern are not difficult to identify. The clinician faced with the responsibility of restoring the patient to health and suspecting that any new treatment is likely to have advantages over the old, may be unhappy that many patients will be receiving, in her view, the less valuable treatment. The patient being recruited for a trial, having been made aware of the randomisation component, might be troubled by the possibility of receiving an ‘inferior’ treatment.

Few clinicians would argue against the need for the voluntary consent of subjects being asked to take part in a trial, but the amount of information given in obtaining such consent might be a matter for less agreement. Most clinicians would accept that the subject must be allowed to know about the randomisation aspect of the trial, but how many would want to go as far as Berry (1993) in advising the subject along the following lines?

I would like you to participate in a randomised trial. We will in effect flip a coin and give you therapy A if the coin comes up heads and therapy B if it comes up tails. Neither you or I will know what therapy you receive unless problems develop. [After presenting information about the therapies and their possible side-effects:] No one really knows what therapy is better and that is why we’re conducting this trial. However, we have had some experience with both therapies, including experience in the current trial. The available data suggest that you will live an average of five months longer on A than on B. But there is substantial variability in the data, and many people who have received B have lived longer than some patients on A. If I were you I would prefer A. My probability that you live longer on A is 25 per cent.

Your participation in this trial will help us treat other patients with this disease, so I ask you in their name. But if you choose not to participate, you will receive whichever therapy you choose, including A or B.

Berry's suggestion as to how to inform subjects considering taking part in a clinical trial highlights the main ethical problem in such a study, namely the possible conflict between trying to ensure that each individual patient receives the treatment most beneficial for his/her condition, and evaluating competing therapies as efficiently as possible so that all future patients might benefit from the superior treatment. The great dilemma of clinical trials is that if each patient is treated as well as possible, patients as a whole are not. Lellouch and Schwartz (1971) refer to the problem as competition between *individual* and *collective* ethics. Pocock (1983) suggests that each clinical trial requires a balance between the two. The prime motivation for conducting a trial involves future patients, but individuals involved in the trial have to be given as much attention as possible without the trial's validity being destroyed. Naturally the clinician's responsibility to patients during the course of a trial are clear; if the patient's condition deteriorates, the ethical obligation must always and entirely outweigh any experimental requirements. This obligation means that whenever a physician thinks that the interest of a patient are at stake, she must be allowed to treat the patient as she sees fit. This is an absolutely essential requirement for an ethically conducted trial, no matter what complications it may introduce into the final analysis of the resulting data.

Clearly the ethical issues will be of greater concern in trials where the condition being treated is extremely serious, possibly even life threatening, than when it is more mild. The problems that can arise in the former situation are well illustrated by the history of the trials of AZT as a therapy for AIDS. When such trials were first announced there was a large, vocal lobby against testing the drug in a controlled clinical trial where necessarily some patients would receive an 'inferior treatment'. Later, however, when the severity of some side effects was identified and the long term effectiveness of the drug in doubt, an equally vocal lobby called for AZT treatment to be abandoned. Expanding networks of 'support groups' makes these

problems increasingly likely.

If randomisation is the first priority in an acceptable clinical trial, *blinding* comes a close second. The fundamental idea of blinding is that the trial patients, the people involved with their management and those collecting clinical data from studies, should not be influenced by knowledge of the assigned treatment. Blinding is needed to prevent the possibility of bias arising from the patient, the physician and in evaluation. There are a number of levels of blinding of which the two most important are:

- *Single-blind*: Usually used for the situation in which the patient is unaware of which treatment he or she is receiving.
- *Double-blind*: Here both the patient and the investigator are kept blind to the patient's treatment. For many trials this is the arrangement of choice.

In drug trials blinding is usually relatively easy to arrange but the blinding of physical treatments, for example, surgical procedures, is often more difficult.

The randomised double-blind controlled trial is the 'gold-standard' against which to judge the quality of clinical trials in general. But such trials are still misunderstood by many clinicians and questions about whether or not they are ethical persist. One of the problems identified by Bracken (1987), is that doctors are frequently reluctant to accept their uncertainty about much of what they practice. Bracken concludes that when doctors *are* able to admit to themselves and their patients uncertainty about the best action, then no conflict exists between the roles of the doctor and the statistician. In such circumstances it cannot be less ethical to choose a treatment by random allocation within a controlled trial than to choose by what happens to be readily available, hunch, or what a drug company recommends. The most effective argument in favour of randomised clinical trials is that the alternative, practising in complacent uncertainty, is worse. All those points are nicely sum-

marised in the following quotation from Sir George Pickering, made when President of the Royal Society of Medicine in 1949, in response to the charge that the clinical trial constituted experimentation on patients:

All therapy is experimentation. Because what in fact we are doing is to alter one of the conditions, or perhaps more than one, under which our patient lives. This is the very nature of an experiment, because an experiment is a controlled observation in which one alters one or more variables at a time to try to see what happens. The difference between haphazard therapy and a controlled clinical trial is that in haphazard therapy we carry out our experiments without design on our patients and therefore our experiments are bad experiments from which it is impossible to learn. The controlled clinical trial merely means introducing the ordinary accepted criteria of a good scientific experiment.

Further convincing *empirical* arguments in favour of the double-blind controlled clinical trial are provided by the work of Chalmers *et al.* (1977) and Sacks *et al.* (1983) who provide evidence that nonrandomised studies yield larger estimates of treatment effects than studies using random allocation (see Table 1.3), estimates that are very likely biased; and Schulz *et al.* (1995), who demonstrate that trials in which concealment of treatment allocation was either inadequate or unclear (i.e., were not double-blind), also yielded larger (biased) estimates of treatment effects.

There are a number of other ethical issues in clinical trials which relate directly to one or the other of the statistical aspects of design and analysis; an example is determining the appropriate sample size by means of a power analysis — using too small or too large a sample would be unethical, a point that will be taken up in more detail in the next chapter.

Table 1.3. Results from Randomised and Historical Control Trials in Six Areas.

Therapy	Randomised Trials		Historical Control Trials	
	New treat. effective	New treat. ineffective	New treat. effective	New treat. ineffective
Coronary artery surgery.	1	7	16	5
Anticoagulants for acute myocardial infarction.	1	9	5	1
Surgery for oesophageal varices.	0	8	4	1
Flurouracil (5-FU) for colon cancer.	0	5	2	0
BCG immunotherapy for melanoma.	2	2	4	0
Diethylstilbesterol for habitual abortion.	0	3	5	0

(Taken from Sacks *et al.*, 1983.)

1.5. CLINICAL TRIAL PROTOCOLS

All clinical trials begin with a protocol which serves as a guide for the conduct of the trial. The protocol must describe in a clear and unambiguous manner how the trial is to be performed so that all the investigators are familiar with the procedures to be used. The protocol must summarise published work on the study topic and use the results from such work to justify the need for the trial. If drugs are involved, then pertinent pharmacological and toxicity data should be included. The purpose of the trial and its current importance need to be described in clear and concise terms; hypotheses that the trial is designed to test need to be clearly specified and the population of patients to be entered into the trial fully described. The protocol must specify the treatments to be used; in particular, for drug studies, the dose to be administered, the dosing regimen, and the

duration of dosing all need to be listed. Details of the randomisation scheme to be adopted must be made explicit in the protocol along with other aspects of design such as control groups, blinding, sample size determination and the number of interim analyses planned (if any). Although it is important that investigators adhere to the protocol, mechanisms need to be in place for making changes if the need arises. If changes are made, then they must be well documented.

1.6. SUMMARY

The controlled clinical trial has become one of the most important tools in medical research and investigators planning to undertake such a trial have no shortage of excellent books to which to turn for advice and information. But unlike the many other books dealing with clinical trials, this text is primarily concerned with the *statistical* issues of certain aspects of their design (Chapters 2 and 3) and, in particular, their analysis (Chapters 4 to 10), rather than their day-to-day organisation. This restriction will enable us to give fuller accounts of some recently developed methods that may be particularly useful for the type of data often generated from clinical trials. Some details of the software available that implements the methods described will be given in the Appendix.