

IN BRIEF

- Justification of the use of 'controls' and 'blinding' in a clinical trial
- An explanation of the need for and the process of randomisation
- A discussion of the ethical problems in a clinical trial
- An understanding of an intention-to-treat analysis

Further statistics in dentistry Part 3: Clinical trials 1

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The **clinical trial** is a planned experiment, strictly on human subjects, which is conducted with a view to investigating the efficacy of one or more treatments for a given condition. It is possible to use statistical techniques to make inferences about the population of patients who will present to the practitioner in the future using information obtained from the sample of patients in the trial. Consequently, the results of the trial may be expected to influence the way in which patients with the condition are treated in the future.

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This paper discusses some of the more important design and analysis considerations underlying clinical trials. In particular, the comparative nature of clinical trials, the need for randomisation and blinding techniques, the ethical problems inherent in 'experimenting' on human subjects and analysis by intention-to-treat are discussed in some depth. The following paper in the series concentrates on sample size estimation with some discussion of sequential and interim analyses. More details of all aspects of clinical trials can be obtained from Pocock,¹ whilst the considerations which govern the quality of reporting of clinical trials are described in the CONSORT statement (www.consort-statement.org).

TRIAL DESIGN

It is crucial that the clinical trial be designed and analysed so that its results are unbiased and any conclusions drawn from it are valid. Bias is present when the trial results are systematically distorted and so are consistently above (or below) what they should be. Various sources of bias were briefly discussed in an earlier paper (Research Designs 1) in this series. Design considerations are particularly important because, although it is possible to correct an inappropriate analysis or weak presentation, it is often impossible to rectify the situation once the data have been collected in a trial which has deficiencies in design. A well-designed trial is one which, at the very least, is comparative in nature and incorporates ran-

domisation of patients to treatments; it is then called a **randomised controlled trial (RCT)**.

Use of a 'control' treatment

An essential feature of a clinical trial is that it is *comparative* in nature. This means that it is necessary to compare the results of a group of patients who are receiving the new treatment under investigation with another group of similar patients under some different treatment regime. This other treatment regime, the **control** treatment, may be an active treatment (a *positive* control) such as a standard treatment that has been shown previously to be effective. Alternatively, if ethical considerations permit, the other treatment regime may be the absence of active treatment or else a dummy treatment, called a **placebo**, both of which are *negative* controls. A placebo is an inert substance which looks just like the active treatment. Its purpose is to separate the act of being treated from the real effect of the active treatment. Many individuals are influenced by suggestion and respond to the act of receiving treatment, producing what is often called the 'placebo-effect'.

A clinical trial which includes a comparative group is called a **controlled** clinical trial. The reason for making the trial controlled is to ensure that, provided the composition of the treatment groups is similar, any conclusions drawn from the trial as to the effectiveness of the new treatment under consideration can be

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attributed solely to the administration of that treatment and not to any other factors.

There are some researchers who advocate the use of **historical controls** instead of or, sometimes, in addition to concurrent controls. Historical controls are individuals who have received the standard treatment in a previous trial so that the results of the current patients on the new treatment under investigation can be compared to these historical controls. This obviates the need for randomisation as all patients in the trial can be assigned to the new treatment.

Some researchers prefer this retrospective approach for two reasons. Firstly, fewer patients are required in the current trial. Secondly, it overcomes the ethical problem the practitioner faces when obliged to put as many patients on the standard treatment as on the new treatment which the practitioner believes (intuitively) to be superior. Similarly, the patients may well have convictions about the advantages of the new treatment, and they will only consent to being included in a trial which ensures that this is what they will receive. However, there is always the danger that the results from the historical controls are not strictly comparable to those of the current patients. This may be a consequence of differences in the type of patient, the severity of the illness, the ancillary treatment, the criteria for evaluating response, the quality of recorded data and the intensity of monitoring of the patients. The overall effect of such a retrospective comparison is that the efficacy of the new treatment is usually overestimated which leads to a biased result. The controversy rages on but the policy of not using historical controls, except in the situation in which the condition is rare and there are few patients available for the trial, is invariably promoted.

Randomisation

It may be that the clinician has a preconceived notion as to the effectiveness of the new treatment and this will influence the way in which the patients are allocated to various treatments, if given the freedom of choice. This might result in the more severely ill patients being allocated the standard treatment, or *vice-versa*, even if the clinician's intention is to be fair, and this in turn would result in a biased estimate of the treatment effect. In order to avoid the possibility of this happening, the patients are *randomly* assigned treatments. This means that the method of determining which treatment each patient receives relies on chance rather than on personal judgement so that the potential for allocation bias is obviated.

Random allocation (ie randomisation) can be achieved by some mechanical method such as tossing a coin, but is more usually accomplished by using random number tables or computer generated random numbers. To illustrate randomisation, consider a trial in which there are two treatments, A and B, for a given condition. One 'random number' approach to allocating a patient one of the two treatments is to refer to a

random number table (found in many statistical texts as well as in books of statistical tables). The table consists quite simply of blocks of the digits 0-9 which have been generated in a random manner. Each block usually consists of five numbers by five, for example:

69373
95662
97758
12154
25583

A complete table, with all digits equally represented, will consist of a grid of these blocks. To use the table, a starting point is selected at random, and then the sequence of digits is followed along a row or up or down a column. Suppose, that the starting point is the top left hand '6' in the above section of the table, and the decision has been made previously to follow the sequence down the columns, and to allocate the next patient presenting to the clinic to 'A' if the digit is even, and to 'B' if the digit is odd (including zeros which are regarded as even). Thus the sequence 6, 9, 9, 1 and 2 would result in the first five patients successively receiving A, B, B, B and A. Starting at the top of the next column, the sequence 9, 5, 7, 2 and 5 would result in the next five patients successively receiving B, B, B, A and B; and so on. It can be seen, in this particular allocation sequence, that if the trial consisted only of 10 patients, three patients would be allocated to 'A' and seven patients would be allocated to 'B'. Such an imbalance is undesirable and yet is not uncommon if the sample size is small.

Fortunately, the simple random allocation procedure can be modified, for example, to allow each patient to be allocated one of three or more treatments, or, using a process called **balanced** or **blocked randomisation**, to achieve approximately equal numbers of patients in the different treatments groups. Suppose two treatments, A and B, are to be compared, and it is decided that balance is required after every group or block of k patients, where k is some multiple of two (the number of treatments). For illustrative purposes, let $k = 8$. Using the randomisation technique described in the previous paragraph on the first block of 8 patients, each successive patient is randomly allocated either A or B depending on whether the next random number in the sequence is odd or even. However, as soon as $k/2 = 4$ patients have been allocated one treatment, say A, the remaining patients in the group of 8 patients who have not yet been allocated a treatment have to be allocated the other treatment, B. This will result in 4 patients in each treatment group in the first block of 8 patients. If this process is repeated for the next block of 8 patients, then of the 16 patients in the two blocks, 8 patients will be in each treatment group. If this process is repeated a number of times, exactly half the patients will receive A and the other half will receive B if the total sample size is a multiple of 8. If the total sample size is not a multiple of 8, then approximately half the

Randomisation

Randomisation, the process of using a method based on chance to allocate patients to different treatment groups, is used to avoid bias



patients will be in each treatment group, and this is usually satisfactory for purposes of analysis.

Clearly, randomisation promotes comparability of the treatment groups with respect to the effects of extraneous variables which might influence the response to treatment, such as the age or sex of the patient or the severity of the disease. Although the researchers may believe they are aware of which variables are likely to influence response, and may attempt to ensure that the treatment groups are similar with respect to these variables (using *stratified* randomization), it may be that there are other relevant extraneous variables about whose effects they are unaware. By randomising the patients to the different treatments, it is possible to ensure that the treatment groups are balanced, on average, for all extraneous variables of consequence.

Two factors should be noted in relation to randomisation. Firstly, *randomisation* (or *random allocation*) should be distinguished from *random sampling*.² The former is concerned with deciding which patients should receive the different treatments. The latter is concerned with deciding which patients to select from the population for inclusion in the trial. In randomisation, the patients are *given* treatments; in random sampling, the patients are *taken* from the population. Both, however, rely on chance to achieve their ends. Secondly, it can be shown that random allocation obviates the need for strict random sampling from larger populations, one of the assumptions underlying statistical hypothesis testing which is an important component in the analysis of clinical trials.

Blinding

Another source of potential bias arises from the assessment of the response to treatment. Both the patient receiving treatment and the assessor of the response to treatment may have preconceived notions about the superiority of one treatment over another. If either was aware of which treatment the patient was receiving, this might influence the assessor's assessment of response and lead to a biased result. Such a biased assessment may be intentional or, more usually, subconscious or unintentional, and is more likely to occur when the response to treatment is subjective rather than objective.

One way of controlling this assessment bias is to conduct the trial in such a way that the clinician, the support staff, the patient and the assessor of the response to treatment are unaware of which treatment the patient is receiving. Such a trial is called a **double-blind trial**. In order to make the trial double-blind, it is important that the treatments that are being compared look, taste and feel identical. If one of the treatments is a non-active control treatment, this can only be achieved by introducing a dummy or placebo as the negative control. If the form of administration of the different treatments differ, for example if one treatment comprises a toothpaste and a second treatment comprises a mouthwash,

then it is possible to make the treatments appear identical by having one group receive the active toothpaste with a dummy mouthwash and the other group receive the dummy toothpaste with an active mouthwash.

It is not always possible, either because of ethical considerations or because of practical difficulties, to make the trial double-blind. For example, it would hardly be ethical to mimic an invasive procedure such as surgery in order to facilitate blindness, and it would be impossible for a surgeon to be blind to the particular treatment that a patient is receiving. In such circumstances, the aim should be to make the trial **single-blind** so that the assessor of the response to treatment is unaware of the treatment that the patient has received. If the response to treatment is objective rather than subjective in nature, then concerns regarding assessment bias, provided that the trial is at least single-blind, are substantially alleviated.

ETHICAL PROBLEMS

The most serious objection to randomised controlled trials arises because of the ethical dilemma facing the researcher. There is a conflict between what might be termed *individual* and *collective* ethics. On the one hand, the practitioner would like to administer the treatment which is regarded as most beneficial for the particular patient; on the other hand, he or she is attempting to evaluate different treatments with a view to establishing, for a future population of hypothetical patients, the most effective treatment for a given condition.

There is no easy solution to this ethical dilemma. A balance has to be struck between concern for the individual and human experimentation for the advancement of science. At no stage should the former be sacrificed for the latter. To achieve this balance, it is important to employ safeguards for the individual patient and also to design and conduct the trial so that high scientific and organisational standards are attained throughout.

Guidelines for the ethical requirements of clinical research are outlined in the World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects which was adopted in Finland in 1964 and revised most recently in Edinburgh, Scotland, in 2000. Details may be found at www.wma.net/e/policy/17-c_e.html. These guidelines provide a basis for 'protecting' the individual. Included in them is a requirement that 'informed consent' is obtained from every patient (or legal guardian, if necessary) to be included in the trial. Informed consent implies that the patient is aware of and understands all the implications involved in the study which are known to the researchers, and is willing to accept these as a condition of his/her involvement in the study. An additional safeguard adopted in the UK is the requirement that all proposals come before local ethical committees

Ethical problems



The ethical dilemma in a clinical trial is the conflict between achieving the greatest benefit for the individual patient and determining the most effective treatment for future patients

Intention-to-treat analysis



Patients who do not conform to the protocol are retained in the treatment groups to which they were assigned in an intention-to-treat analysis

whose members, comprising both lay individuals and clinicians, discuss the ethical implications of the proposed trial.

All aspects of the trial, including its rationale, patient selection criteria, treatment schedules and methods of evaluation, design, study size, proposed statistical analysis, patient consent, forms, withdrawals and administrative responsibilities, must be specified in a document called a **protocol**. The protocol is produced before the trial is undertaken. It ensures that all relevant and important considerations which lead to a scientifically worthwhile study are considered at the outset whilst, at the same time, an indication is given of the procedure to be adopted for each individual patient.

INTENTION-TO-TREAT ANALYSIS

One of the major difficulties when analysing clinical trials is knowing how best to handle what are termed **protocol violations**. These are patients who fail, for any one of a number of reasons, to complete the intended course of treatment; they are called **withdrawals**.

Sometimes a withdrawal results in there being incomplete data for evaluation for that patient, and it is unrelated to the condition or treatment of the patient. It may be that the patient fails to turn up to the clinic because of moving out of the area or simply because the patient is tired of the commitment. Alternatively, the incomplete information may be caused by administrative errors so that some measurements are missing. One has to hope that the number of missing observations is not too great in these circumstances, establish that their omission does not create any biases, and then analyse the data without them.

From time to time, however, a protocol violation occurs when a patient is evaluated through the length of the trial but that patient is no longer receiving the treatment that was originally assigned. For example, the patient

may be switched to the alternative treatment because of side-effects or may get bored with taking a prescribed medication in a trial for a non-acute condition over a prolonged period of investigation. These protocol violations are also called withdrawals and one has to decide how best to deal with them. Should the results from these withdrawals be analysed according to what should have happened to the patients or to what actually happened to them or should they be omitted?

Although it may at first appear to go against the grain, the approach generally adopted is, wherever possible, to include all withdrawals in the statistical analysis, and analyse the results for these patients as if they were still in the treatment groups to which they were originally assigned. This approach is termed **analysis by intention-to-treat**. The rationalisation for this type of analysis is that it avoids the biases that would be introduced by the alternatives of either omitting the results or analysing the results according to the treatments that these patients actually received. Such biases could arise if the comparison groups were no longer comparable with respect to any variables likely to affect the measure of response, or if withdrawals exacerbated the efficacy of a particular treatment by excluding patients who suffered ill-effects from that treatment.

The intention-to-treat approach to analysing the results of clinical trials is often called the **pragmatic approach** because its aim is to make inferences about the effectiveness of a particular treatment regime as it is adopted in practice. The alternative **explanatory approach**, that of analysing the results only for the compliers who conform to the protocol specification, is very occasionally adopted but the aim, then, is geared to understanding the processes involved rather than to making decisions about how to treat future patients. A fuller discussion may be obtained from Schwartz, Flamart and Lellouch.³

1. Pocock S J. *Clinical Trials: a practical approach*. Chichester and New York: John Wiley and Sons, 1983.
2. Kish L. *Survey Sampling*. New York, John Wiley and Sons, 1995.
3. Schwartz D, Flamart R, Lellouch J. *Clinical Trials*. London: Academic Press, 1980.