PROFESSIONAL DEVELOPMENT

Clinical Trials

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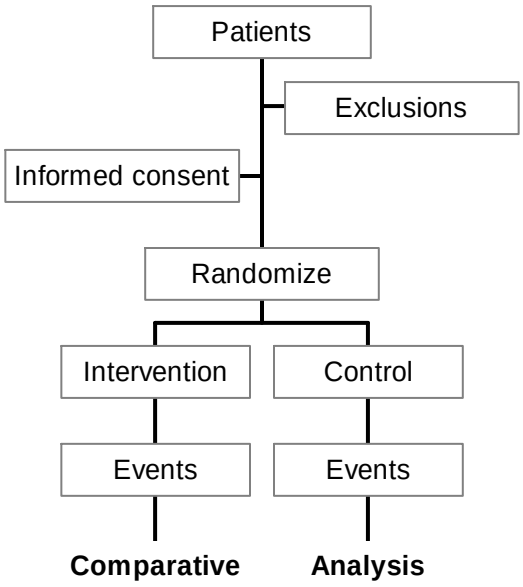
INTRODUCTION

A **clinical trial** (randomized controlled trial) is a trial (experiment) in which subjects are randomly assigned to one of two groups: one (the experimental group) receiving the intervention that is being tested, and the other (the comparison group or control) receiving an alternative conventional treatment (see figure). The two groups are then followed up to see if there are any differences between them in outcome (events).



The key idea of a clinical trial is that we wish to compare groups of patients who differ only with respect to their treatment. If the groups differ in some other way, then the comparison of treatment is *biased*. If we can identify a bias, then it may be possible to allow for its effect in the analysis, but unknown biases cannot be dealt with. The methods of design described in this article are aimed at the elimination of this bias.

The need for a comparison group.

It is natural to begin investigation by trying a new treatment on some patients to see what happens. This type of study is **uncontrolled**, so that any benefits or harmful effects seen in the patients will naturally be ascribed solely to the treatment. Such studies are usually **open**, where the clinician and the patients know what treatment each patient is getting. The investigator's natural enthusiasm for the new treatment may well influence his judgment of the patients' progress, and may also be transmitted to the patients and affect their well-being, especially for conditions where symptoms are subjective, such as degree of pain. Many early studies of this type have suggested that new treatments were highly effective, only for this apparent benefit to disappear on more careful examination. Therefore, it is important to have a comparison group acting as a control. The control group usually receives the standard therapy at the time of research or no treatment (if no standard treatment is available).

Selection of subjects

This part of the trial design is crucial because poor patient selection will undermine the generalisability of the study outcome or, even worse, reduce its validity if patient selection bias is introduced. The task begins with deciding what kind of subjects to study and how to go about recruiting them. It is important to set inclusion criteria that define clearly the subjects that are appropriate to the trial hypothesis.

For the findings of the study to be generalisable to the population as a whole, the sample must be representative of the whole population from which it is drawn. The best design is **consecutive sampling** from the accessible population (taking every patient who meets the selection criteria over a specified time period).

Patient exclusion criteria need to be defined and will include such subjects who have conditions which may contraindicate the intervention to be tested, subjects who will have difficulty complying with the required regimens, those who cannot provide informed consent, etc.

Sample size calculation

Clinical trial sample size calculation will be covered in the next issue of the EJS

Random allocation

A vital issue in design in a clinical trial is to ensure that the allocation of treatments to patients is independent of the characteristics of the patients – on other words, it is carried out in an *unbiased* way. The most widely used method of unbiased treatment allocation is to use **random allocation** to determine which treatment each patient gets. Random allocation gives all subjects the same chance of receiving either treatment, and is thus unbiased by definition.

Simple randomization

It is not always appreciated that **random** does not mean the same as **haphazard**. By random allocation we mean that each patient has a known chance, usually an equal chance, of being given each treatment, but the treatment to be given cannot be predicted.

The simplest method of random allocation is tossing a coin - heads is treatment A, tails is treatment B. An equivalent method is to use a table of random numbers (see table). In these tables each number occurs equally often, and the ordering is random, and so completely unpredictable. Another option is to use **a random number generator** on a computer.

Random numbers*

03	47	43	73	86	36	96	47	36	61	46	98	63	71	62	33	26	16	80	45	60	11	14	10	95
97	74	24	67	62	42	81	14	57	20	42	53	32	37	32	27	07	36	07	51	24	51	79	89	73
56	12	19	20	52	81	30	74	93	02	67	41	50	27	31	05	03	72	93	15	57	47	54	14	10
16	56	85	99	26	96	96	68	27	31	05	03	72	93	15	57	12	10	14	21	88	26	49	81	76
55	59	56	35	64	38	54	82	46	22	31	62	43	09	90	06	18	44	32	53	23	83	01	30	30

* This is an extract from a random numbers table

The first step is to decide the relation between the random numbers and the different experimental groups. For example, if we wish to allocate two treatments to subjects using a random table, we could take odd numbers to indicate one treatment, and even numbers to indicate the other. We must then choose a place to start, and this can be any where on the table. Second, we choose the direction in which to read the table.

Suppose that the first two digit numbers in the table from our starting place are:

12 19 20 52 81 30 74 93 02 67 41 50, etc.

If we take odd numbers for treatment A, and even numbers for treatment B, then these numbers indicate the following sequence for the first 12 subjects:

BABBABBABAAB

Alternatively, we could take each digit on its own, to give the following sequence for the first 24 subjects:

ABAABBABBAABABAABBBABAAB

A third approach would be to take numbers 00 to 49 for A and 50 to 99 for B, and there are countless other possible strategies. It makes no difference, which is used. We can easily generalize this last approach to situations with more than two treatments or experimental conditions. For example, we could use the following scheme for three groups:

01 to 33 : treatment A
34 to 66 : treatment B
67 to 99 : treatment C
00 : ignored

Notice that at any point in the sequence, the numbers of patients allocated to each treatment may differ.

Block randomization

Block randomization is used to keep the numbers of subjects in the different groups closely balanced at all times. For example, if we consider subjects in blocks of four at a time, there are six ways in which we can allocate treatments so that two subjects get A and another two get B:

1 AABB
2 ABAB
3 ABBA
4 BBAA
5 BABA
6 BAAB

If we use combinations of only these six ways of allocating treatments, then the numbers in the two groups at any time can never differ by more than two, and they will usually be the same or one part. We choose blocks at random to create the allocation sequence. Using the previous random sequence beginning:

121920528130749302674150

we can omit those numbers outside the range 1 to 6 to get:

12122134326415

from which we can construct the block allocation sequence and so on:

AABB ABAB AABB ABAB ABAB AABB ABBA BBAA ABBA

Randomized blocks can be of any size, but using a multiple of the number of treatments is more logical. Large blocks are best avoided as they control balance less well.

Stratified randomization

While simple randomization removes bias from all allocation procedure, it does not guarantee, for example, that the subjects in each group have similar age distributions. Indeed, in small studies it is highly likely that some chance imbalance will occur, which might complicate the interpretation of results. Even in studies with over 100 subjects, there may be some substantial variations by chance, especially for characteristics that are quite rare. In many clinical studies it is known beforehand that subgroups of patients are expected to respond differently to treatment. Here, it is advisable to ensure that the subjects receiving each treatment have similar characteristics.

We can use **stratified randomization** to achieve approximate balance of important characteristics without sacrificing the advantages of randomization. The method is to produce a separate block randomization list for each subgroup (stratum). For example, in a study to compare two alternative treatments for breast cancer, it would be important to stratify by menopausal status. Two separate lists of random numbers should be obtained, from which two separate piles of sealed envelopes can be prepared, for premenopausal and postmenopausal women. It is essential that stratified treatment allocation is based on block randomization within each stratum rather than simple randomization; otherwise there will be no control of balance of treatments within strata, and so the object of stratification will be defeated.

Stratified randomization can be extended to two or more stratifying variables. For example, we might wish to extend the stratification in the breast cancer trial to tumour size and number of positive nodes.

Some thought should be given to which variables are used for stratification. It is wise to restrict the choice to variables known to be prognostically important. Many trials stratify using age and sex. While age is frequently known to be prognostic, sex is often not prognostic and need not be used for stratification.

In a multicentre study, the patients within each centre will need to be randomized separately, unless there is a central coordinated randomizing service. Thus, 'centre' is a stratifying variable, and there may be other stratifying variables as well.

Blindness

The key to a successful clinical trial is to avoid any biases in the comparison of groups. Randomization deals with possible bias at the treatment allocation, but bias can also creep in while the study is being run. Both the patient and the doctor may be affected in the way they respectively respond and observe by knowledge of which treatment was given. For this reason, it is desirable that neither the patient, nor the person evaluating the patient knows which treatment was given. Such a trial is called

double-blind. If only the patient is unaware, as is sometimes the case, the trial is called **single-blind**. In several fields, such as in surgery, it is often impossible for a study to be double-blind. Clinical trials should use the maximum degree of blindness that is possible.

Placebos

When we wish to evaluate a new treatment for a condition there is the problem of what treatment to give to the control group. If (and only if) there is no existing standard beneficial treatment, then it is reasonable not to give the control group any active treatment. However, there are two reasons why it is desirable to give the control group patients an inert dummy or **placebo** treatment, rather than nothing. Firstly, the act of taking some treatment may itself have some benefit to the patient, so that if we give nothing at all to the control group, then part of any benefit observed in the treated group could be due to the knowledge or belief that they had taken a treatment. This is known as the **placebo effect**. Secondly, in order for a study to be double-blind, it is necessary for the two treatments to be indistinguishable. Placebo tablets should therefore be identical in appearance and taste to the active treatment, but pharmacologically inactive.

Placebos in surgery

Placebos can sometimes be used in non-drug trials, too. Some surgical trials have reported the use of placebo surgery. However, there may be ethical problems associated with such invasive placebos.

Ethical issues

A clinical trial is an experiment on human beings, so it is not surprising that there are several important ethical issues relating to clinical trials. One concern is the amount of information given to the patient. In general, the patient should be invited to be in the trial, and should be told what the alternative treatments are (although they will usually not know which they will get). They can decline to be in the trial, in which case they will be treated normally. If they agree to participate, they will often have to sign a form stating that they understand the trial.

This **informed consent** is controversial, because it is likely that many patients do not really understand what they are told, and that they are not always told as much as they should be. There are some cases where it is not possible to get informed consent, for example when the patients are very young, very old, or unconscious.

In many countries there are a large number of ethics committees set up to consider proposals to carry out clinical trials (and, indeed, any research involving human subjects). Ethics committees are mainly concerned with the welfare of the patient, and usually do not consider the scientific nor the statistical issues of the trial. However, any trial that uses suboptimal methodology or substandard statistical methods, especially in design or analysis, may be deemed unethical for three reasons:

1. the misuse of patients by exposing them to unjustified risk and inconvenience;
2. the misuse of resources, including the researchers' time, which could be better employed on more valuable activities; and
3. the consequences of publishing misleading results, which may include the carrying out of unnecessary further work.

Outcome measures

In most clinical trials information about the effect of treatment is gathered in relation to many variables, sometimes on more than one occasion. There is the temptation to analyse each of the variables and look to see which differences between treatment groups are significant. This approach leads to misleading results, because multiple testing will invalidate the results of hypothesis test. In particular, presenting only the most significant results, as if these were the only analyses performed, is fraudulent.

A preferable approach is to decide *in advance* of the analysis, which outcome measure is of major interest, and focus attention on this variable when analysing the data. Other data can, and should be, analysed too, but these variables should be considered to be of secondary importance. Any interesting findings among the secondary variables should be interpreted

rather cautiously, more as ideas for further research than as definitive results. Side effects of treatment should be treated in this way.

Sometimes, there really will be more than one major outcome measure. If there are two, then no great harm will come from analysing them both, perhaps taking a stricter cut-off for statistical significance. Sometimes it is possible to combine two variables into one, in particular when the variables of interest are alternative events, such as death or heart attack.

IN CONCLUSION

A well-designed and methodologically sound clinical trial evaluating an intervention provides strong evidence of a cause-effect relation, if one exists. It is therefore powerful in changing practice to improve patient outcome, this being the ultimate goal of research on therapeutic effectiveness. Conversely, poorly designed studies are dangerous because of their potential to influence practice on flawed methodology.