Randomisation in clinical trials

“There is an ethical imperative to ascertain that the treatments doctors provide are effective” (1)

Summary
Randomised controlled trials are accepted as the gold standard for testing the efficacy of a medical intervention. Patients included in a trial should have an equal chance of being assigned to any treatment group, ensuring that there is no systematic difference in the composition of the groups. This is achieved by randomisation. The process may be based on computer-generated random numbers or a random number table. The person assessing the eligibility of subjects must not know which group they will be allocated to. Ethically, if a study ought to be randomised then it must be. Randomisation should be mentioned in the title or abstract of the report and full details should be included in the text.

Key words
Medical ethics, Methodology of clinical trials, Randomisation.

Introduction
Acupuncturists have plenty of opportunity to observe that patients improve after acupuncture treatment. This provides them with the justification for continuing to practise an unorthodox therapy. But observations may be misleading, and sceptics require more evidence than simply the percentage of grateful patients. A higher level of evidence is provided by a randomised controlled trial (RCT) which has been carefully designed to avoid the three ogres of bad research: bias, chance variation and confounding. A trial is controlled when a control group is recruited to provide a standard for reference; there is no better way of doing this than by randomisation.

The first medical use of randomisation was by Sir Austin Bradford Hill in a trial of streptomycin for tuberculosis in 1946. The principle of an RCT is straightforward: the researcher compares the outcomes in two groups of patients who are comparable in all respects except their treatments. If there is a difference in the outcomes, and the study is well designed and performed, the researcher may conclude that the difference must be due to the difference in treatments. Thus it is fundamentally important that the groups are comparable in their prognostic factors, i.e. that there is no selection bias.

The best way of avoiding systematic differences between the groups is to recruit a sample from the population and assign each individual to a group by randomisation. This means that chance alone decides which group each patient is allocated to, so that there is no reason for the two groups to have a different prognosis - either from known or unknown factors. A second reason to assign patients at random is that the statistical methods which will be used to analyse the data have been based on an understanding of how random samples behave (2).

It is worth noting at this point that an RCT means just that: RCTs do not have to be placebo-controlled or double-blind. It all depends on the question that is being addressed. For example, acupuncture could be compared with physiotherapy in the treatment of headache, or it could be compared with placebo acupuncture. In both cases an RCT is needed. Placebo-control is necessary to examine whether patients have improved because of the specific effect of needling or the non-specific effects of acupuncture treatment (such as the Eastern mystery of the technique).

Ethics of randomisation
It is ethical for a clinician to randomise a patient to one of two groups only when there is substantial uncertainty about the correct treatment for that individual patient and, furthermore, when there is no certain evidence that one of the treatments to be offered is more effective than the other (1). Thus, a trial comparing acupuncture with placebo for the treatment of headache would be ethical, since there is no definite evidence to say that acupuncture has a clinical effect on headache, and the patient is not being denied another effective therapy. However, in treating nausea, for which acupuncture has been proven effective, it would probably be unethical to compare acupuncture with sham acupuncture since some patients would be denied a helpful therapy (3). Therefore an RCT would have to compare acupuncture with another effective treatment such as medication. Similarly, a patient’s strong preference for one of the interventions must be respected. The other side of the ethical coin is that if a study ought to be randomised then it must be randomised. Additionally, the Declaration of
Helsinki states that research "must conform to generally accepted scientific principles and should be based on ... a thorough knowledge of the scientific literature" (4).

Methods of randomisation
Altman has emphasised that allocation by randomisation is more than just a haphazard process (2). Each patient must have an equal chance of receiving acupuncture or control and neither the patient nor the doctor must be able to predict the result beforehand. There are different methods of assigning subjects, but not all are acceptable. The toss of a coin is truly random but has the drawback that the result cannot be verified later if a problem arises.

The most common method is to use a series of random numbers either generated by computer or provided directly in tables. The numbers are then converted into a group allocation in a systematic way, such as all even numbers representing the active treatment. This can of course lead to the unequal distribution of patients between groups. To prevent this, a system of block randomisation is often used in which the numbers in each group are equal when each block has been finished. Table 1 gives an example in which computer-generated random numbers have been used to construct a table of allocation into 2 groups in blocks of 4. If this table were to be used as it stands, the last letter in each block of 4 can be predicted from the first 3; to avoid this, the allocation must start at a number that is not 01, 05 or 4n + 1.

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Computer-generated numbers are converted to codes for allocating subjects to 2 groups in blocks of 4. Allocation should not commence with 01, 05 etc., in order to maintain concealment.

It may be the case that one baseline characteristic is a strong prognostic factor; for example, headaches that have been present for less than 6 months may respond better to acupuncture than long-standing headaches. In this case it is important to stratify patients into two groups by duration of headache, and then to randomise the groups separately. This ensures that one group does not have a preponderance of one prognostic factor.

Minimisation
The only acceptable alternative to randomisation is the process of minimisation. Prognostic baseline characteristics are obtained from each patient, who is then allocated by a procedure that will minimise the differences between the groups. This method has rarely been used in acupuncture trials, but produces well-matched groups and is especially useful for smaller studies. It has the drawback that unknown prognostic factors cannot be taken into account, and thus cannot influence the assignment. Details of the method are described by Altman (2).

Non-random allocation
Non-random methods of allocating patients are often used out of ignorance, and are sometimes called pseudo-randomisation, which is misleading since they involve no randomisation process: the subjects are not given an equal chance of being in either group. Examples include allocation by alternation, date of birth, day of the week or hospital number. Another problem with such methods is that they do not exclude selection bias. The researcher is open to the subsequent accusation that patients with a poor prognosis were more likely to be excluded if they were to receive acupuncture than the control therapy. However subconsciously this happens, and however scrupulous the investigator might believe himself to be, the sceptic will regard this as a possible source of error.

Concealment of randomisation
The clinician who is assessing the eligibility of a patient for the trial must not know in advance which group that patient will be allocated to. This is critically important. Schulz et al. (5) studied the methodology of 250 clinical trials to find out what difference it made to the outcome when randomisation was or was not concealed. The odds ratio for a positive result was exaggerated by a massive 41% in those studies where the randomisation was not concealed from the clinician at the time of enrolment.

The best method of concealing the allocation is to arrange for the decision on eligibility and the process of randomisation to be performed by different people in different places. For example, it might be arranged for the clinician to telephone a central office after each new patient is enrolled, a process referred to as central randomisation. Another commonly used and acceptable method is to arrange for someone unconnected with the clinical arm of the study to place the allocation codes in sequentially numbered, sealed, opaque envelopes. There have been some ingenious inventions of other methods of random allocation and concealment, but not all are advised. For example, in a controlled trial of acupuncture, Chate (6)
asked patients to choose one of two points (one of them a sham point) marked on the arm for treatment. This method is not ideal since it is possible that factors other than chance could influence the decision, e.g. previous injury to the arm.

**Reporting of randomisation**
Studies are indexed as randomised controlled trials by Medline and the Cochrane Database of Systematic Reviews only when the word random or some equivalent is used explicitly in the report. Randomisation should be mentioned in the title or abstract so that it is not easily missed by the indexer, and a full description should appear in the text of the report. If the study does not appear to be randomised, it will be classified as a controlled clinical trial. When it comes to performing systematic reviews on RCTs researchers need to know the details of the randomisation procedure in order to allocate a quality score. The report should ideally include three important aspects: how the random list was prepared, what mechanisms were used to allocate treatments and how the allocation was concealed before the inclusion of the patients. Jadad et al. (7) describe one frequently used scoring system.

Authors should provide a table of baseline prognostic characteristics of the groups in order to demonstrate that they are comparable. Important differences can of course occur by chance: randomisation guarantees that there is no systematic difference between the groups, but it does not guarantee that there is no difference at all between them. If, unfortunately, a difference might have an effect on the outcome, all is not lost, since particular forms of analysis can give an indication of the proportion of the difference between the groups that is due to the intervention, and the proportion which is due to baseline differences.

**Conclusion**
Randomisation is the best known method to eliminate selection bias from controlled clinical trials. Reliable techniques exist to allocate subjects into groups on a random basis, and to conceal the allocation until after enrolment. Such techniques should be applied assiduously and reported carefully in all RCTs of acupuncture. A clinical trial might be considered unethical if randomisation was not applied when it should have been, since the reliability of results is seriously affected by its lack.

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**References**
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