

Position paper: Designing clinical trials

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One of the principal objectives of HealthWatch is to promote the testing of treatments and the conduct of clinical trials. There are three false arguments used to claim trials are unnecessary for certain types of treatment.

1. If patients feel better after the treatment, nothing else matters.
2. Trials of truly holistic treatment are impossible: there can never be a control patient with whom the result can be compared because each patient is different and the treatment is tailored to the individual.
3. Clinical trials cost huge sums of money that small independent practitioners cannot afford.

We believe that due to a lack of proper testing, patients are offered treatments that are less effective, less safe and more expensive than they need to be, both in conventional and alternative medicine.

If a patient feels better after a treatment, it is very satisfactory but does not mean the treatment is effective. The patient might have improved without any treatment, or there might have been even more improvement with a simpler, cheaper or safer treatment. The best way to find out, almost always, is to do a suitable clinical trial.

Every good practitioner, whether conventional or alternative, should practise *holistic* medicine; treatments should always be chosen to suit the whole patient in their particular circumstances and environment, and not simply the pain or lump that they may have. Similar pains or lumps may be treated differently in different patients. Despite this, it is still possible to do valid clinical trials using the guidelines set out below.

The onus of providing evidence of efficacy is on those who promote a treatment and not, as is sometimes stated, on the scientific community in general. It is true that large scale multi-centre drug trials can be very costly, but most of the expense is in administration and in the biochemical tests that are not an essential part of the comparison, but are to check for any unexpected harmful effects of the treatment.

Some minimum conditions for a proper trial to compare two treatments:

Protection of research subjects:

It is illegal to conduct any research involving human subjects without the prior approval of a *Research Ethics Committee*. It is the duty of these committees to check that the research is properly designed, and that previous research on the topic to be studied has been adequately considered. Any conflict of interest (e.g., the research is sponsored by an organisation with a commercial interest in treatment being tested or the researchers have a financial interest such as company shares) must be declared. Any possible harm to trial participants must be as little as possible, and volunteers must be given a clear description of what the trial involves and what other treatments might be, so they are able to give fully *informed consent* that they are willing to

participate. They need to be told that they are free to opt out of the trial at any time, without giving any reason and without suffering any detriment.

Choice of treatments:

If there is no treatment that is known to be safe and effective for the condition under study, then a new treatment may be compared with a *placebo* treatment. If, on the basis of existing evidence, two (or more) treatments are equally appropriate and it is not known which is better, they should be compared, using a group of patients for each treatment. If the new treatment is to be compared with one of several already established treatments, the best should be selected as the comparator treatment. Each treatment should be clearly described, including its formulation, dose, route and frequency of administration, full product characterisation and details of manufacturer.

Aims and objectives of the trial:

These must be adequately described, e.g., to compare the effectiveness of two treatments for a specific medical condition, over a given period of time, in a specific group of patients. The measurements of the desired treatment effects (*outcome measures*) must be appropriate, precisely defined and, where possible, objective and reproducible.

Patient allocation:

To be as sure as possible that the groups are otherwise similar, and to avoid the researchers choosing which patient is given which treatment (avoidance of *selection bias*), allocation of patients to treatment groups must be random. Assigning patients by alternation or by dates of birth is not acceptable. Ideally, true randomisation is best achieved with the aid of a third person not directly involved in the trial (often contacted by phone) who, after having checked that the patient meets the entry criteria, allocates the randomly selected treatment group for that patient.

Registration of Clinical Trials:

The trial should be on a register. This ensures other researchers working in the same field are aware of its existence and means the results will be available for review even if the outcome is unfavourable to the procedure or product. Registration reduces the trend for positive trials to be published and hence available to reviewers, while negative trials are not, thus avoiding *publication bias*. The register held by the European Medicines Evaluation Agency (EMA) of the European Union could form a part of such a register, but must be freely available to researchers and not maintained 'Commercial in Confidence' as it currently is.

Methods:

This should include a clear description of the types and characteristics of patients eligible to take part (*entry criteria*), their previous treatments or medication(s), details of who will administer the treatments and how, and how the treatment effects will be recorded. For example, in a trial comparing methods of pain relief, one needs to devise a method of scoring the intensity of pain, which can then be compared with the intensity of pain before treatment and between treatments. Ideally, to prevent any possible bias, neither the patient nor the person who assesses the effects of treatment should know which treatment is being used (known as *blinding*), though this is not always possible. Other factors that could influence the effects of the treatment being

tested, such as diet, exercise and other medications, need to be recorded, as do side effects and reasons for dropping out of the trial.

Data analysis:

Patients who fail to complete treatment for any reason should not be excluded from the final analysis, as comparisons should usually be on an *intention to treat* (ITT) basis. In some trials it is necessary to report results both based on ITT analysis and also using only completers. It is always necessary to report how many patients refused consent, how many patients met the entry criteria, how many were randomised to each of the two (or more) comparison groups, and how many dropped out from each of the treatment groups and their reasons for doing so, if known. Any apparent differences in results must be analysed to determine the probability of their arising by chance. A probability of less than one in twenty is often regarded as a reasonable indication of a real difference. For this reason, the more patients who enter a trial, the smaller the differences that can be detected. Small numbers can reliably detect only big differences, and make it more likely that the two groups are not properly comparable in important respects other than the treatment.

This is a very simple summary of essential features of a well-designed clinical trial. HealthWatch is very willing to give advice to anyone seeking to evaluate the efficacy of any method of treatment and or type of benefit or side effect.

Further reading about trial design

From trial outcomes to clinical practice. Drug & Therapeutics Bulletin. **34**:38-40. (1996)

Randomised controlled trials in single patients. Drug & Therapeutics Bulletin **36**:40 (1998)

Excellent advice on the *reporting* of clinical trials is on www.consort-statement.org

This position paper was revised by John Garrow and Walli Bounds and endorsed by the executive committee of HealthWatch on 12 January 2005.