How to show that an ineffective therapy works

'…the aim of clinical trials is not to prove that therapy X works, but to test whether or not it works.'

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Greenhalgh recently described 'Ten ways of cheating with statistics' [1]. Here are a few tips on how to 'cheat' with the design of a clinical trial. 'Cheat' is actually the wrong word – what is really meant is the clever design of a study to increase its chances of yielding 'positive' results (i.e. results that apparently demonstrate the effectiveness of the treatment under scrutiny).

The simplest approach is to conduct a study without a control group. Most conditions improve over time and regression towards the mean will also help to normalize parameters that were abnormal at an initial reading. Thus, with repeated measurements of clinical endpoints, one will almost invariably find an apparent overall improvement. This apparent improvement can be entirely unrelated to the therapeutic intervention applied. The trick is to ignore this well-known fact and conclude that the treatment was effective.

Controlled clinical trials lacking design features that minimize bias are more prone to generate a positive result than studies that incorporate design features such as placebo controls, blinding and randomization [2]. Failure to blind subjects, therapists, those assessing outcome measures and those analysing the data can all lead to biased results and interpretation. Randomization is used to prevent the experimenter from allocating subjects to treatment groups in a biased way, and to achieve groups that are balanced for important prognostic factors. The success of randomization in terms of balance is, however, a judgement call. One way to obscure differences between groups that favor the experimental group is to apply a statistical test of significant difference. Such tests are conservative because they are designed to err towards finding no difference. They can yield no statistically significant difference, even if there are clinically relevant differences in important prognostic factors. The inappropriate use of tests of significant difference to establish baseline comparability between groups is widespread and often remains unrecognised.

There are other subtle methods that can be used to demonstrate that ineffective therapies work, including equivalence or non-inferiority trials. For example, one could conduct an under-powered equivalence trial comparing an experimental therapy with a 'gold standard' therapy; because of the small sample size the trial would fail to show a difference. Consequently, one could conclude (falsely) that the experimental therapy was as effective as the gold standard. Alternatively, one could carry out an adequately powered equivalence trial and use an ineffective comparator treatment. This would actually show that both treatments are ineffective, but the trick is to convince the reader that this evidence demonstrates the effectiveness of the treatments.

Perhaps the most reliable way to fool people with clinical trials is to use a comparator therapy that causes a deterioration of your primary clinical outcome measure. In a typical parallel group design this will create an inter-group difference favoring the experimental, ineffective treatment. Consequently, you need only to convince the reader that this was due to the effectiveness of your therapy, and at the same time omit the fact that the comparator intervention led to a deterioration of the control group.

Experienced, critical professionals will find these techniques far too obvious, therefore we need to consider even more refined ways of producing false-positive results. A report recently published by Paterson *et al.* [3] provides a subtle example of this concept. Consider a group of patients who, at entry to a trial, are asked whether they prefer acupuncture (treatment A) or homeopathy (treatment B) for their condition. Those who prefer treatment A are allocated to treatment arm A and those who prefer treatment B go to arm B. Both groups are then randomized to receive either the preferred therapy or standard GP care. Patients

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are subsequently treated with A or B and the therapeutic success is evaluated according to protocol, as with most other controlled clinical trials. If you think that this is a smart design that accounts for patients' preferences, think again. Patients who have expressed a preference for a given therapy and only receive standard care are likely to be disappointed; conversely, those who receive their chosen treatment will be delighted. This disappointment (and delight) will almost certainly be reflected in the clinical outcome, particularly in conditions that have a psychological element to them (and which condition has not?). What we have here is an example of an elegant, covert way of producing false-positive results with a trial design that is likely to impress people because of the attempt to account for patients' preferences.

In conclusion, there are many ways of demonstrating that an ineffective therapy apparently works. Some are obvious, others are not. Researchers should take adequate steps to prevent such misleading research, and readers of clinical trials must be made aware of the often subtle pitfalls that will probably produce positive findings. All parties involved should remember that the aim of clinical trials is not to prove that therapy X works, but to test whether or not it works.

References

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3 Paterson, C. *et al*. (2003) Treating dyspepsia with acupuncture and homeopathy: reflections on a pilot study by researchers, practitioners and participants. *Complement. Ther. Med.* 11, 78–84

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