Understanding controlled trials

What are pragmatic trials?

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Trials of healthcare interventions are often described as either explanatory or pragmatic. Explanatory trials generally measure efficacy—the benefit a treatment produces under ideal conditions, often using carefully defined subjects in a research clinic. Pragmatic trials measure effectiveness—the benefit the treatment produces in routine clinical practice.

An explanatory approach recruits as homogeneous a population as possible and aims primarily to further scientific knowledge. By contrast, the design of a pragmatic trial reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments. To ensure generalisability pragmatic trials should, so far as possible, represent the patients to whom the treatment will be applied. The need for purchasers and providers of health care to use evidence from trials in policy decisions has increased the focus on pragmatic trials.

While the intervention should be described precisely for both types of trial, in pragmatic trials this does not mean that the same treatment is offered to each patient. If, for example, two physiotherapy approaches are being evaluated for back pain the protocol may allow for the physiotherapist to apply different treatments to different patients: it is then the management protocol which is the subject of the investigation, not the individual treatments.

Randomisation deals with the main source of bias in clinical research—selection bias. However, several other sources of bias may affect the results. Biased assessment of outcome may occur when the researcher is aware of which treatment has been given: this is dealt with in both explanatory and pragmatic trials by having an independent assessor who is blind to treatment allocation. However, bias can also occur when patient or clinician is aware of the treatment being given; in explanatory trials this is dealt with by blinding both patient and clinician to the treatment.

While pragmatic trials may also be blinded, this is not always possible. Placebos are not generally used in pragmatic trials, as they aim to help clinicians decide between a new treatment and the best current treatment. Clinician and patient biases are not necessarily viewed as detrimental in a pragmatic trial but accepted as part of physicians' and patients' responses to treatment and included in the overall assessment. In pragmatic approaches, therefore, the treatment response is the total difference between two treatments, including both treatment and associated placebo effects, as this will best reflect the likely clinical response in practice.

Outcome measures differ between explanatory and pragmatic approaches. In explanatory trials intermediate outcomes are often used, which may relate to understanding the biological basis of the response to the treatment—for example, a reduction in blood pressure. In pragmatic trials they should represent the full range of health gains—for example, a reduction in stroke and improvement in quality of life.

In a pragmatic trial it is neither necessary nor always desirable for all subjects to complete the trial in the group to which they were allocated. However, patients are always analysed in the group to which they were initially randomised (intention to treat analysis), even if they drop out of the study or change groups.

The two approaches to trial design will sometimes arrive at different conclusions about the benefit of a treatment, either because a treatment which works in an ideal setting does not work in real life or because improvement in a biomedical endpoint does not produce the expected health gain—for example, sodium fluoride increases non-vertebral bone density in osteoporosis but increases fracture rates.[2] Clinicians need to understand these two approaches when reading trial reports, to judge the relevance of the findings to their own clinical practice.

1 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967;20:637-48.
2 Riggs BL, Hodgson SF, O'Fallon M, Chao EY, Wahner HW, Muhs JM, et al. Effect of fluoride treatment on the fracture rate in post-menopausal women with osteoporosis. *N Engl J Med* 1990;322:802-9.

This is the second of an occasional series on the methods of randomised controlled trials

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BMJ 1998;316:285

One hundred years ago

Pasteur's first patient

The shepherd Jupille, who was the first patient who underwent Pasteur's antirabic treatment, has been appointed concierge of the Pasteur Institute in Paris. At the age of 14 he went to the rescue of two children who had been attacked by a mad dog, and was himself badly bitten. He is now to be seen any day by visitors to the famous Institute of the Rue Dutot, a picture of health, wearing on the breast of his coat a silver medal awarded him for the courage which he displayed on that memorable occasion. He married some years ago, and is the father of two fine children. It may be worth mentioning for the edification of antivivisection fanatics that Jupille looks upon Pasteur as having saved his life. "Had it not been for him," he says, pointing to the group by Truffaut in front of the Institute, where he is represented struggling with the dog; "Had it not been for M Pasteur, that is all that would now remain of me." Jupille was first sent to Garches; then, as he grew up, he was employed in the antirabic laboratory in the Rue Dutot, and afterwards under M Roux. He is now 29, and is very proud of his office and of the neat little dwelling which M Duclaux has given him.
(*BMJ* 1898;i:1284)