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Pragmatic clinical trials

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Summary Both pragmatic and explanatory randomised controlled trials have a useful role to play in the evaluation of health care interventions. In this descriptive article, the key steps in conducting a pragmatic trial are described. The strengths and limitations of pragmatic trials are also discussed. The main strength of pragmatic trials is that they can evaluate a therapy as it is used in normal practice. Comparisons are made between pragmatic and explanatory trials, on the understanding that trials may have aspects to them that make the trial more of a hybrid. A case is made for the appropriate use and relevance of pragmatic trials in the evaluation of alternative and complementary medicine.

Introduction

Clinical trials can be designed to be either *pragmatic* or *explanatory*.[1] Pragmatic trials are designed to find out about how effective a treatment actually is in routine, everyday practice. Explanatory trials are designed to find out whether a treatment has any efficacy (usually compared with placebo) under ideal, experimental conditions. Both have a place in our repertoire of research methods. In this paper I will describe the key steps in undertaking a pragmatic trial, and describe some differences from an explanatory trial. My focus will be on the parallel-arm design, although the principles can be applied to other types of study. I will explore some of the strengths and weaknesses of pragmatic trials. I will then make some comparisons between archetypal pragmatic and explanatory trials, while acknowledging that some trials have hybrid designs. Finally I will make a case for the relevance of pragmatic trials in the clinical evaluation of complementary therapies.

Key steps in conducting a pragmatic trial

Appropriate research question

The study design should match the clearly defined research question: if you are interested in evaluating the benefits of a therapy in everyday practice, then you need to use a normal clinical setting and a pragmatic design. Pragmatic trials answer questions about the overall effectiveness of an intervention, and cannot study the contributions of its different components. You would use a pragmatic trial to test an overall 'package' of care, including the

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contribution of the therapeutic relationship, patients' expectations, and any specific therapy that is used. You would generally compare the effect of this package of care with another treatment, not with a placebo. In contrast, you would normally use an explanatory trial to establish whether a specific herb or acupuncture needle per se is better than a placebo. Pragmatic trials are used with the aim of providing the evidence that will help policy makers, practitioners or patients make choices between two interventions. They help define the best use of limited resources.

Defining the patient group

In pragmatic trials, the participating patients will need to be representative of the wider population, so that your results can be generalised. This means that you must set wide inclusion criteria, so that patients are not excluded if, for example, they have other medical conditions, or are taking medication. They must reflect everyday clinical practice. In the context of a trial of complementary medicine, bear in mind that not all patients will be interested, nor will all physicians in their role as gate-keepers be willing to refer patients. So you must identify an appropriate therapeutic niche for your therapy, depending for example on the condition itself, on current patterns of care and referral, on attitudes of patients to conventional care, on your complementary therapy and its particular strengths and weaknesses. For example, it would be sensible to choose a condition where conventional treatment is often unsatisfactory, like low back pain or irritable bowel syndrome, so that patients and their doctors are willing to consider an alternative approach. These are complex issues that need to be clarified during the design process, preferable with small pilot studies.

Identify a comparison group

After you have identified your patient group, it will be easier to identify the control group, i.e. the reference group against whom you will measure relative change. In a pragmatic trial, it is not usually appropriate to use a placebo control and blinding, as these are likely to have a detrimental effect on the trial's ecological validity. For example, the blinded practitioner would not know if the patient's lack of response was due to using the wrong treatment, or because the patient was in the placebo group. You need to model both arms of the trial on normal practice, since your aim is to produce the evidence to facilitate a real choice between treatment options. To ensure a level playing field, and for ethical reasons, both treatment options should be considered as having similar chance of success so that the trial is a fair comparison, not disadvantaging either intervention option. Ideally, choose a comparison treatment that is already credible in primary care, so that any differences you find can be easily interpreted.

Defining the treatment protocol

In pragmatic trials, it is easier to grant the practitioners the freedom to treat the patients normally, allowing them to use complex and individual approaches for different patients. This also allows the therapist make subtle variations in the treatment process from careful observation and questioning when the patient comes back for follow-up. Pragmatic trials are designed to model everyday clinical practice, so you will want to harness the skill of reasonably experienced practitioners. You should define what variations in treatment are permitted in the formal treatment protocol. There is a range of options here, from a very open protocol that allows wide flexibility within a defined framework, through to a tightly specified protocol that has been determined by consensus with experts.[2] With complex interventions, you may need firstly to compose a handbook or manual that defines the parameters for treatment.[3] Your aim here is to make sure the study protocol can be replicated, but at the same time is generalisable so that it is a reasonable match for routine practice.

Ensuring adequate sample size

You are likely to need a larger sample for a pragmatic trial than an explanatory trial, because you may well be recruiting from the wider population with a more heterogeneous mix of patients. Your treatment may not be maximally effective in patients who are taking medication, for example. This variability between patients dilutes the treatment effect but does not undermine the credibility of a pragmatic trial. In addition if you are interested in long-term follow-up (another feature of pragmatic studies, see below), then a larger sample size would also be needed to cover losses through patients dropping out. In an explanatory trial, you would normally select a homogeneous group of patients in whom the treatment is likely to work best, and to control for all extraneous variables, so reducing the trial to a straight relationship between a single intervention and a single outcome variable.

Referral, recruitment and randomisation

In a pragmatic trial, you will want to set up referral procedures that are practical and relevant to real life choices. Perhaps you are exploring a potential role for your therapy in primary care and plan to utilise referrals from general practitioners. In this case you will need a GP to help you make sure that your referral procedures are workable and meaningful. Some trials use a patient database to retrospectively identify patients with the condition you are interested in, but have been diagnosed in the past.[4] However, we do not yet know whether retrospective recruitment would reduce the generalisability of the trial. In other respects, recruitment and randomization are similar for pragmatic and explanatory trials.

Outcomes

In pragmatic studies, you should choose a primary outcome that is relevant to everyday life, particularly one that measures the patient's function or quality of life. This is less relevant for explanatory studies where, for example, you might choose to measure a change in the range of movement of a joint, if that is the most marked effect of your therapy. Moreover, a pragmatic study is more likely to include long-term follow-up, since patients and policy makers will be very concerned about whether any benefits are sustained. This has an additional advantage in studies of complementary medicine since patients' have reported that some changes takes place over a considerable period of time.[5] Also changes resulting from complementary medicine are often broader than just to the primary condition.[6] Hence there may be a need to monitor outcomes across a wider spectrum, including changes to outlook, attitude and behaviour.

Analysis

The analysis of a pragmatic trial needs to be on an "intention-to-treat" basis, i.e. the groups are compared as randomized. This reflects the importance of the randomization process in ensuring that both groups are as near as identical as possible at baseline. However, in pragmatic studies, which allow patients to change their treatments as they would in real life, there is a considerable risk that there will be a dilution the treatment effect. For example, in comparing osteopathy with standard care, patients who are in the standard care group may choose to pay for osteopathy themselves, and some in the osteopathy group may choose to have other different treatments too. This will dilute the difference between arms, but not compromise the integrity of the trial provided you compare patients in the groups to which they were randomised. After all, your study is designed to reflect what happens in the real world. The point is to record and report these variations rather than try to distort what would happen naturally by artificially restricting treatment options. Not only does this have ecological validity but also it respects patients' decisions to make changes to their treatment, something that makes obvious sense when there is a longer term follow-up.

Reporting and dissemination

The reporting of clinical trials in general is improved by adhering to the CONSORT guidelines[7] as well as guidelines for specific therapies, such as the STRICTA guidelines for acupuncture.[8] There is an additional reporting challenge for pragmatic trials in that the full intervention may be more complex than in an explanatory trial. What needs to be reported are all aspects of the treatment so that the intervention can be replicated. In disseminating the results, you will need to make it clear that your pragmatic design is appropriate to your research question, whilst acknowledging any inherent limitations.

Strengths and limitations

Limitations

The pragmatic trial design cannot be used to determine precisely what components within the treatment process might have caused any benefits, since it is a package of care that is being evaluated. For example, acupuncture is not being tested against a sham or "placebo" intervention, so pragmatic trials will not help isolate the effect of the needling per se. Therefore, the extent that the therapeutic relationship contributes to any overall benefit remains unknown after a pragmatic trial. Using several therapists for the study will reduce the influence on the outcome of any individual therapist. A potential problem with pragmatic trials is the increased resources, including costs that are needed for the larger sample sizes, as discussed above. Pragmatic trials can be criticized for their lack of blinding. Explanatory trials use blinding to reduce bias, i.e. to maximise internal validity. However, as explained, blinding reduces the ecological validity of the study, and anyway is not always practical or appropriate

for complementary therapies. Therefore, although pragmatic trials will have reduced internal validity because of the lack of blinding, there is likely to be a trade-off: they will be more likely to have higher external validity, that is, they will generalise better to normal clinic settings.

Strengths

The greatest strength of pragmatic trials is that they can deliver evidence of effectiveness in everyday clinical contexts.[9] Such trials make obvious sense for complex interventions. They are especially useful where the use of a placebo control to separate specific from non-specific effects is problematic, for example where you would expect a positive synergy between acupuncture needling and the therapeutic relationship, or alternatively a reduced overall effect because practitioners in an trial of individualised homeopathy lose confidence when their patient does not respond because of their uncertainty as to whether the lack of response is due either to an incorrect or to a placebo remedy.[10]

The evaluation of the economic impact fits well with the pragmatic type of trial design. The evidence pragmatic trials can generate should be of value to health care purchasers, providers or patients who are making choices about treatment, whether on behalf of others or for themselves. The results can help us understand more about the acceptability of the intervention to patients, and have potentially greater impact on decision-making, referral patterns and clinical guidelines, as happened for example for chiropractors after their successful pragmatic trial comparing chiropractic care with hospital out-patient care for treating back pain.[11] Because practitioners can have some flexibility in how they treat patients, they are more likely to be willing to be involved in a pragmatic trial. Likewise, patients are more likely to volunteer since they will not be asked to agree to the possibility of being offered a "placebo" treatment.

Comparing pragmatic and explanatory designs

Some features of explanatory and pragmatic trials can be presented archetypically as polar opposites (see Table 1). However, many randomised controlled trials lie somewhere along the spectrum between these two designs. For example, if a pragmatic trial has a more tightly specified treatment protocol than allowing practitioners a free hand to treat normally, then the design is no longer fully pragmatic. Nevertheless Table 1 is intended to highlight the key differences that inform the two types of design.

For drug trials, the explanatory approach is advocated on the basis that new medication must be tested for efficacy prior to being available for general release. However, this argument does not hold for complementary medicine, which now is in widespread use. For example an estimated 50,000 complementary practitioners are currently working in the UK providing treatment to around 5 million patients a year.[12] As the House of Lords identified,[13] this has now become a public health issue in that we do not really know much about the putative benefits of the therapies. This leads to the argument that our research effort should now be focused on the development of meaningful evidence about routine care. Only after it has been estab-

Table 1 Explanatory vs. pragmatic trials: archetypal features.

Explanatory trials	Pragmatic trials
Experimental setting	Routine care setting
Evaluate efficacy	Compare effectiveness
More suitable for acute conditions	More suitable for chronic conditions
Placebo controlled	Not placebo controlled
Patients blinded to minimise bias	Patients unblinded to maximise synergy
Aim to equalise non-specific effects	Aim to optimise non-specific effects
Standardised treatment, simple interventions	Routine treatment, complex interventions
Practitioner skilled for standard protocol	Practitioner skilled in routine care
Usually short-term follow-up	Often long-term follow-up
High internal validity, lower external	High external validity, lower internal
Low relevance/impact on practice	High relevance/impact on practice
Homogenous group of patients	Heterogeneous
May manage with smaller sample sizes	May need larger sample sizes
More commonly used	Less commonly used

lished whether there is a beneficial effect overall should we then start to unpack the "black box" and determine the effect of the individual components of treatment. This shift towards evaluating practice in a pragmatic way is reflected in two large scale trials of acupuncture, one for back pain and one for migraine, that have been funded by the UK government.[14,15]

Conclusion

Both explanatory and pragmatic trials have an important place in the evaluation of health care interventions, but they answer different research questions. Pragmatic trials are useful in answering questions about how effective a therapy is when compared to some standard or accepted treatment. They also overcome some specific difficulties that can be encountered with explanatory trials of complementary therapies, for example when evaluating complex packages of care. Pragmatic trial results can be generalised to wider clinical settings where they can provide evidence of how well therapies might perform as alternatives or adjuncts to conventional interventions. They also can help facilitate decision-making about whether therapies should be utilised more widely.

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