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Pragmatic clinical trials - are they practical?

Making Education Easy 2018

In this review:

Abbreviations used in this review
CBT = cognitive behavioural therapy
CI = confidence interval
OR = odds ratio
RCT = randomised, controlled trial
RR = rate ratio

About the Reviewer

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Introduction

This review will highlight the key features of pragmatic or 'real-world' clinical trials and describe how they differ from traditional randomised, controlled (explanatory) clinical trials. It will discuss the advantages and disadvantages of both approaches, and give practical examples from the recent literature to illustrate the use of this type of study.

Background: why are pragmatic clinical trials needed?

Randomised controlled trials (RCTs) are often perceived to be poorly applicable to the real-world setting. Clinicians have detailed knowledge of the clinical setting, the relevance of inclusion and exclusion criteria, and the often poor recruitment and retention of eligible participants in RCTs which may encourage this attitude. As a consequence new interventions that are effective may not be widely adopted until there is more general evidence of their effectiveness.[1] This need has led to more real-world (pragmatic) trials, which test effectiveness (does the treatment work in genuine clinical practice) of new interventions[2] rather than testing 'efficacy' (does the treatment work within the specific environment of an RCT).

Definitions

Pragmatic trials test 'effectiveness' i.e. does the treatment work in real-world clinical practice.
Explanatory trials (RCTs) test 'efficacy' i.e. does the treatment work within the specific environment of an RCT.

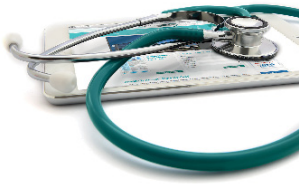
This distinction implies a clear dichotomy of trial design between those that are pragmatic and the more pure RCTs, which are designed to estimate comparative efficacy and to provide an understanding of the scientific processes of new interventions, often termed explanatory trials. However, Schwartz and Lelouch[3] who first recommended the use of pragmatic designs, acknowledge that trials usually contain both explanatory and pragmatic elements and that the degree of pragmatism is an attitude to trial design rather than a specific characteristic. There is therefore, a graduation from the explanatory to the pure pragmatic trial, with most RCTs containing elements of both designs. Notably the analysis of explanatory RCTs routinely includes both intention-to-treat and per-protocol populations for analysis, with the former considered closer to producing results applicable to the real-world setting.

Key features of pragmatic clincal trials

There are five key features of trial design which may differ between pragmatic and explanatory trials.[4] These are the five features identified by the PICOT approach to trial design: **P**atient population, **I**ntervention, **C**omparator, **O**utcomes, **T**iming.

Five key features of pragmatic vs explanatory clinical trials (PICOT approach)			
Feature		**Pragmatic trial (tests effectiveness)**	**Explanatory trial (tests efficacy)**
P	Patients	Real-life patient cohort	Homogenous patient group
I	Intervention	Flexible, changes possible	Tightly defined
C	Comparator	Active comparator	Clearly defined, often placebo
O	Outcomes	Clinically important outcomes	Objective/surrogate outcomes
T	Timing	Longer-term follow-up (e.g. 6 months)	Short-term follow-up (often weeks)

Table 1. Adapted from Williams et al. 2015[4]



Patient population

Pragmatic trials aim to recruit a pool of participants which reflect the full range of diversity in disease severity, comorbidities, age, sex, and social and ethnic groups for whom the intervention being tested will be ultimately applicable. There are limited participant inclusion and exclusion criteria and the setting for the trial will potentially extend beyond research centres and clinicians into general practice and into all other health care environments e.g. hospitals, specialist centres, and primary care relevant to the intervention. Pragmatic trials are also more likely to recruit from a larger, more varied, number of sites further improving the generalisability of the results. Explanatory trials are routinely conducted in established research centres which usually recruit from a specific patient pool and have rigid inclusion and exclusion criteria. These rigid criteria are usually deemed necessary for both safety and efficacy considerations. Safety perhaps on the basis that not enough is known about the new intervention so that potential interactions with concomittant medications and with comorbidities are avoided. Efficacy so that the recruited participants are a homogenous group who are potentially more likely to uniformly respond to the intervention.

Intervention

Pragmatic trials tend to be less prescriptive in defining the form of the intervention. Real world influences associated with the delivery of the intervention (beyond training effects) e.g. the treatment is not completed for any reason or the patient does not attend at the defined time for the intervention, are all considered part of the application of the intervention into usual practice, rather than protocol deviations or violations. These trials may therefore, identify unanticipated operational challenges associated with the intervention. The explanatory trial protocol on the other hand usually includes very explicit instruction on how and when the intervention is to be delivered.

Choice of comparator

Pragmatic trials tend to include 'treatment as usual' or current practice as the comparator group for comparison with the a new intervention, ostensibly identifying whether a change to the new treatment will improve effectiveness. Explanatory trials are more likely to test the specific attribute(s) of the new intervention to determine whether this impacts on efficacy. To this end, the comparison between the new intervention and the comparator will involve only this attribute differing between the trialled treatments. For example, an explanatory trial testing a sensitising agent prior to radiotherapy as described below, would include a placebo agent so that the pure effect of the new agent, rather than the complete effect of the intervention, can be quantified. It is crucial to address this more explanatory question as part of developing a more effective, cost-effective and safe intervention, but it does not specifically test the real-world consequences of changing practice in these regards.

Pragmatic trials are frequently used to compare test 'strategies' or complex treatment options or policies involving many individual components, and it is the totality of the intervention that is being trialled. Such interventions are often associated with population and health services research and cannot be tested within the more rigid explanatory trial environment.

This type of pragmatic trial is also likely to be very flexible with regards to the control or current practice comparator. Existing strategies are likely to vary between sites, therefore the specifics of the comparator are not dictated by the study protocol, but are allowed to continue as in current practice. While this may mean that the effect of the new strategy is likely to vary across different sites, this of itself reflects how the sites will respond to this strategy. Consequently the results will be more generalisable to the real-world setting if the strategy were universally adopted.

This increased variation in effectiveness across sites, and the tendency for participants within a site to have more similar outcomes when compared with those from other sites, has further important repercussions for the trial design. Such trials are likely to randomly allocate sites or possibly clinicians (rather than individuals) to the strategy, an approach which is necessitated by the form of the strategy when it can only apply at a site, not at an individual participant level.[5] When a strategy is testing site- or clinician-based changes then these need to be the unit of randomisation. If participants are not the unit of randomisation, then a form of cluster randomisation (e.g. randomising sites or clinicians) is required. Additionally, the tendency for participants within a site to have more similar outcomes when compared with those from other sites, quantified by the intra-class correlation coefficient (ICC), will mean that the numbers of participants and the numbers of sites will need to be considered in the sample size calculation. The required sample size will need to be inflated to adjust for the magnitude of the ICC. An example of a study that utilised cluster randomisation, tested the effectiveness of a modular approach to therapy in child and adolescent mental health services.[6] This study involved a two-stage randomisation which included random allocation of clinicians (the cluster) to the intervention or usual care arms.

Schwartz and Lelouch[3] provide a clear example which discriminates the pragmatic from the explanatory trial, specifically in terms of the choice of the comparator arm. The hypothesised trial was to compare the effects of a sensitising agent on the results of radiotherapy for cancer patients. For the pragmatic trial the comparator might be a procedure which goes directly to radiotherapy without additional intervention. The explanatory trial would involve administration of a placebo agent prior to radiotherapy. The latter option would enable any effects associated with delivery of the agent and the delay in radiotherapy to be removed from the comparison, but would certainly not mimic usual care without a sensitising agent.

Outcomes

The outcomes from pragmatic trials often need to reflect outcomes relevant to participants, funders, communities, and healthcare professionals. Such outcomes extend beyond the pure efficacy of the intervention, as typically measured in an explanatory trial.

Explanatory trials may include such measures as a blood pressure change, a change in a depression rating scale or a change in tumour size, all of which are directly and importantly related to the process and efficacy of the intervention. However, depending on the magnitude of these changes, and the totality of the effects of the intervention, including adverse events, cost, logistics of individual treatment and general implementation, these outcomes of themselves do not capture the full effectiveness of the intervention.

Pragmatic trials will routinely involve participant quality of life measures, cost-effectiveness outcomes and clinically relevant measures of effectiveness. Measures of effectiveness are more likely to be dichotomous forms of the efficacy measures, reflecting a clinically relevant improvement. For example, recovery from depression rather than change in a depression rating scale, or a defined complete tumour response rather than change in tumour size. While pragmatic trials frequently focus on a key primary outcome, the true measure of the relative effect of the intervention will consider all relevant outcomes in determining overall effectiveness.

Timing

Pragmatic trials are more likely to assess outcomes over a longer period than explanatory trials in order that the real-world consequences of the intervention can be measured. Explanatory trials may involve a short-term assessment of a surrogate measure, which then requires extrapolation for the potential effectiveness of the intervention to be assessed in terms of potentially more relevant clincial outcomes. For example, a pragmatic trial is more likely to include overall survival rather than tumour size, stroke incidence rather than total cholesterol levels, or sustained response rather than 6-week depression rating scale scores as primary clinical outcome measures. These types of outcomes routinely require longer follow-up times. Health service research trials are also likely to require longer follow-up times e.g. cancer screening trials need to consider cancer morbidity and mortality as the key outcomes and therefore require extended follow-up.

Potential disadvantages of pragmatic clinical trials

Pragmatic trials offer an attractive means by which the full utility of interventions can be evaluated, but inevitably they have inherent pitfalls.

Real-world, but not real-world

Pragmatic research trials are by their very nature not real-world. Participants or clinicians involved in a trial will not necessarily behave as they would in the genuine clinical setting (the Hawthorne effect). Additionally, the trial burdens of consent and randomisation, and of quantifying process and outcome measures (the observer effect) may influence the results of the intervention.

Lack of blinding

Blinding of participants, observers and clinicians is an integral component of phase III trials, ensuring good internal validity but this is frequently not possible in pragmatic trials. As a consequence the internal validity of pragmatic trials may be compromised.

Poor implementation of process measures

There is a tendency to perceive the pragmatic trial as the final stage in the evaluation of an intervention. As a consequence, key elements of phase III studies may not be considered, or may be downplayed in the design. These include screening and follow-up logs detailing uptake and retention of participants, and protocol deviations evaluating the extent to which the intervention is adopted by clinicians and participants. These process measures are essential to any pragmatic trial design as they allow useful scientific scrutiny and discussion particularly if the intervention does not produce the anticipated results.

Ethical considerations

Pragmatic trials frequently involve large-scale, innovative community interventions, often involving healthy participants, e.g. screening/prevention programmes. In these circumstances, and in the general context of health services research, the role of ethics committees as advocates for participants is uncertain. There is perhaps a tendency for ethics committees to insist on individual informed consent before particpants are approached or randomised for such trials. This process creates a signficant trial burden and may have substantial consequences in terms of the generalisability of the pragmatic trial. It may, of itself, reduce uptake and adherence to the trial protocol, which are core elements of any trial and could therefore profoundly impair an evaluation that seeks to reflect real-world applicability. This maybe particularly frustrating for researchers who are endeavouring to trial an intervention which in all likelihood will be adopted, possibly without the requisite robust evaluation of real-world costs and benefits. Without robust evalautions, ineffective or harmfull interventions may be adopted. The interplay between participants' interests, and accurate evaluations of interventions by pragmatic trials, needs further informed discussion.

EXAMPLES OF PRAGAMATIC CLINICAL TRIALS ILLUSTRATING THEIR KEY FEATURES

Incidence of fires and related injuries after giving out free smoke alarms: cluster randomised controlled trial[7]

Authors: DiGuiseppi C et al.

Summary: This cluster randomised trial evaluated the the impact of providing free smoke alarms to deprived, multiethnic, urban households on the rate of fire-related injuries. Households, located within forty of the most deprived electoral wards of two inner-city London boroughs, were pair-matched by Jarman score (a measure of material deprivation), with one of each pair randomly allocated to intervention or control. The intervention aimed to provide alarms to 25% of intervention households, thereby increasing local alarm ownership from 47% to the national average of 72%. Alarms, batteries and fittings were provided, along with fire safety brochures in multiple languages and an offer of free installation. The control group received no intervention. The primary outcome measure was the number of fires, and the number of injuries related to fire resulting in attendance at an emergency department, hospitalisation or death during the two years following the intervention. Intervention did not improve outcomes vs controls. The rate ratio (RR) for fires attended by the fire brigade was 1.1 (95% CI; 0.96, 1.3). Injuries related to fire had a RR of 1.3 (0.9, 1.9) and the RR for hospital admission and deaths was 1.3 (0.7, 2.3). Additonally, the two groups did not differ in terms of elements related to the intervention including proportion of households with alarms installed (OR 0.9; 0.5, 1.7) and alarms working (OR 0.9; 0.4, 1.8). The authors concluded that '*giving out free smoke alarms in a multiethnic poor urban population did not reduce injuries related to fire or fires, mostly because few alarms had been installed or were maintained.*'

Comment: This was a large, cluster randomised trial testing a pragmatic intervention, which at face value has considerable merit. The study assessed appropriate objective outcomes over a sufficient timeframe, and the nature of the trial itself involved little 'burden' to particpants and is likely to have effectively evaluated the genuine consequences of introducing the defined intervention. By determining the process measures related to the intervention, the installation of fire alarms, the study provides clues as to why the intervention was not effective.

Reference: BMJ. 2002;325(7371):995

Abstract

Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial[8]

Authors: Woodcock A et al., on behalf of the Salford Lung Study investigators

Summary: This open-label, randomised, controlled trial enrolled 4,233 adults with symptomatic asthma on maintenance inhaler therapy from 74 UK general practice clinics. The participants were randomised to initiate treatment with a once-daily inhaled combination of fluticasone furoate (100 or 200 µg) plus vilanterol 25 µg (n = 2,114) or to receive optimised usual care (n = 2,119). Follow-up was for 12 months. The primary endpoint was response, defined as patients with a baseline ACT score of < 20 who achieved a score of ≥ 20 points or an increase from baseline of ≥ 3 points at 24 weeks. An intent-to-treat analysis revealed that patients initiated on treatment with fluticasone furoate and vilanterol were significantly more likely than those receiving usual care to be classified as responders; 71% vs. 56%; OR 2.00 (95% CI; 1.70, 2.34). At week 24, the adjusted mean ACT score was increased from baseline by 4.4 points with fluticasone furoate and vilanterol, compared with 2.8 points with usual care ($p < 0.0001$); this outcome remained unchanged at 12 months. Pneumonia was uncommon, with no between-group difference in time to first on-treatment pneumonia; HR 1·45 (95% CI; 0·77, 2·74, p = 0·255). Similarly, other serious adverse events did not differ significantly between the groups. The authors concluded '*In patients with a general practitioner's diagnosis of symptomatic asthma and on maintenance inhaler therapy, initiation of a once-daily treatment regimen of combined fluticasone furoate and vilanterol improved asthma control without increasing the risk of serious adverse events when compared with optimised usual care.*'

Comment: This large multi-centre study was undertaken in a real-world setting, 74 general practice clinics in Manchester, UK and compared the initiation of the intervention with usual care in particpants with GP diagnosed asthma. The protocol did not dictate participant treatment beyond the initiation of the intervention except that the usual care group could not switch to the intervention treatment. The primary outcome and related effectiveness and safety outcomes are directly clinically relevant and captured over an extended timeframe. This trial clearly sits at the pragmatic end of the explanatory to pragmatic spectrum of trial designs for the above reasons and has produced results and conclusions which are likely to be broadly generalisable.

Reference: Lancet. 2017;390(10109):2247-55

Abstract

Classroom based cognitive behavioural therapy in reducing symptoms of depression in high risk adolescents: pragmatic cluster randomised controlled trial[9]

Authors: Stallard P et al.

Summary: This randomised, three-arm, cluster-randomised trial tested the effectiveness of classroom-based CBT as an intervention for adolescents at high risk of depression. All teens aged 12 to 16 years in school years 8 to11 attending eight non-denominational schools in the UK were eligible, 5,030 consented to participate and 1,064 were classified as being at high risk of depression. Participants were randomised 1:1:1 to the CBT intervention or one of two controls groups; an attention control intervention or usual school provision of personal, social and health eduction. The primary outcome measure was symptoms of depression (self-assessed by the short mood and feelings questionairre) amongst those at high risk of depression at baseline. Negative thinking, self worth, and anxiety were amongst the secondary outcomes assessed. *A-priori* the analysis was planned to independently compare CBT with both other treatments. At 1 years there was no difference in adjusted mean score on the short mood and feelings questionnaire between the CBT group and the attention control group; −0.63 (95% CI; −1.85, 0.58; P = 0.41), or for CBT vs usual school provision; 0.97 (−0.20, 2.15; P = 0.12). The authors concluded that '*In adolescents with depressive symptoms, outcomes were similar for attention control, usual school provision, and cognitive behavioural therapy. Classroom based cognitive behavioural therapy programmes may result in increased self awareness and reporting of depressive symptoms but should not be undertaken without further evaluation and research.*'

Comment: This was a moderate sized, real-world trial comparing three treatments for adolescents at high risk of depression with the treatments delivered within the school environment. The primary outcome was an accepted measure of depression symptoms in this group and was measured over an appropriate timeframe. The form of the primary comparison utilised the actual questionnaire score rather than a dichotomised measure as responder or non-responder. Of note, 66 schools were approached to participate and only eight consented, which casts doubts on the generalisability of the results as the participant population may not represent the target population. The study included measures of aderence to the proposed interventions and these usefully assist interpretation of the results. This pragmatic trial did not show any advantage of CBT over the two comparators. Of the 22 statistical comparisons of the primary and secondary outcomes (11 outcomes x 2 comparisons for each), only one reached statistical signficance. None of the non-significant differences appeared to represent clinically relevant differences in the outcomes, therefore the non-signficant results do not represent an under-powered study. This study explicitly claims status as a pragmatic trial, however elements of the design and conduct of the trial suggest that the results may not be as generalisable as suggested, and these issues are not raised in the limitations of the study.

Reference: BMJ 2012;345:e6058
Abstract

CONCLUSIONS

Pragmatic clinical trials are now an important part of the medical research landscape. The pure pragmatic trial captures the full effect of an intervention in the real world. This entails the comparison of randomised groups of patients that represent the target group in the real-world setting, and the use of comparators and outcome measures that are relevant in normal clinical practice.The components integral to such trials have been incorporated into a specific set of CONSORT (Consolidated Standards of Reporting Trials) guidelines[10] highlighting the reporting and reviewing of these components. These trials sit between phase III studies and what are often termed post-marketing or phase IV studies in the traditional spectrum of clinical trial design. These trials are not observational, they are randomised, controlled studies that attempt to retain the high internal validity of traditonal phase III studies while improving the external validity (generalisability) of the results so that they quantify the real-world effects of introducing the intervention. A pragmatic trial is essential for an evaluation of some interventions, notably health service and screening innovations, but will enhance the understanding and potential outcomes for any proposed intervention.

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