Pills, People, and Preferences: Evaluating Real-Life Practice in Pragmatic Trials

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KEY POINTS . . .

There is a well-recognised spectrum of trial design from the tightly controlled, exploratory randomized controlled trial with high internal validity which establishes efficacy to the pragmatic, randomized trial with broader inclusion criteria and more room for clinical leeway, which can establish generalisability.

Moving beyond the explanatory-pragmatic spectrum, there are implementation studies where an intervention is offered as a clinical service that will be adapted to diverse clinical settings, and in which outcomes are reported for whole eligible populations at service level.

Each of these trial designs has different functions, but they all contribute to the evidence-base that informs guidelines on which clinical practice is based.

Introduction

Can we make experimental studies more like the real world?

There is a spectrum of trial design ranging from explanatory efficacy trials to pragmatic effectiveness trials to implementation studies. This schema was published in Lancet Respiratory last year (Fig. 1) [1]. On the y-axis, we have a spectrum ranging from the highly selected group of people eligible for efficacy trials with pure disease, no confounders, typically relatively young, to the population of people with a diagnosis including all ages, broad range of severities and many with comorbidities, i.e., a very diverse group of people. On the x-axis, we have the design of the trial, which moves from the highly controlled efficacy trial to the more flexible pragmatic trial and then to the real world implementation study.

Taking blood pressure control as an exemplar, the efficacy trial might aim to establish if a new drug reduces blood pressure in a compliant highly selected population. Longer term, we might want to measure the incidence of complications such as stroke. Pragmatic trials would be interested in whether the medication is effective when used in a more typical population including all ages, and people with co-morbidities – though still in people willing to be recruited to and randomized in a trial. Ultimately, however, we are interested in what happens when we use the drug in routine clinical practice, where the choices of professionals and preferences of patients will affect outcomes. Previous speakers have described the role of observational studies: I am going to focus on interventional implementation 'Phase IV' studies.

Explanatory – Pragmatic Spectrum

Let us look first at the explanatory-pragmatic (efficacy-effectiveness) spectrum. PRECIS is a tool designed to try and help researchers understand where their study fits on this spectrum [2].

An efficacy randomized controlled trial is designed to answer the question, "Can this intervention (e.g. taking a medicine) work under ideal conditions?" At the other end of this spectrum is the effectiveness

Figure 1. Framework for Considering Spectrum of Trial Design [1].
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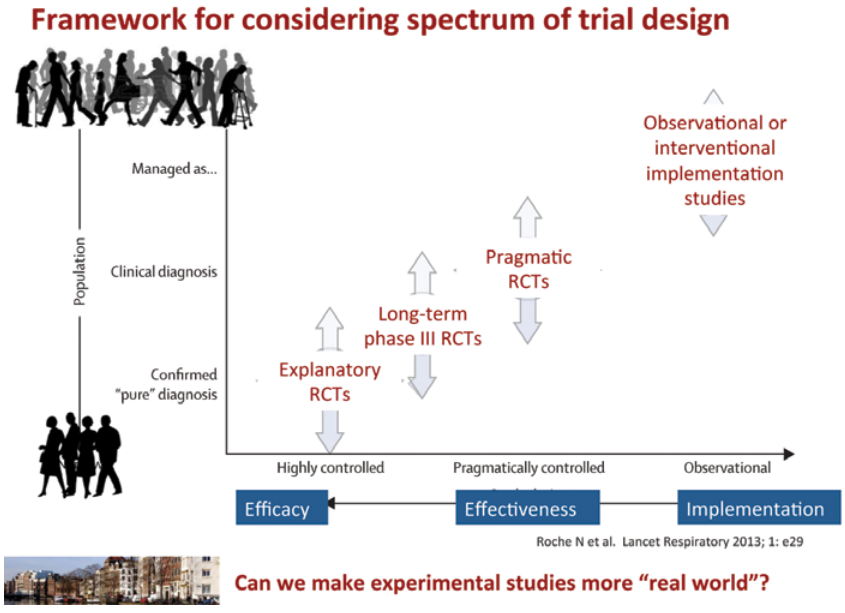

PRECIS: Explanatory-Pragmatic Spectrum [2]

Pragmatic (measures effectiveness)
Explanatory (measures efficacy)
Continuum
Indicator
Summary

pragmatic trial which answers the question "Does the intervention (e.g. the medicine) work when used in typical populations under routine conditions?"

The PRECIS tool invites us to consider this question under these headings.

Eligibility and Recruitment

In an efficacy trial, we choose a 'pure' population; ensure they do not have comorbidities, and that they are likely to comply with taking the treatment. For example, in an asthma trial we would often exclude everyone over the age of 50, and would almost certainly exclude smokers as we do not want the study population to include people who have Chronic Obstructive Pulmonary Disease (COPD). In contrast, trials at the pragmatic end of the spectrum will be inclusive and exclude as few people with the condition as possible.

Efficacy trials dominate our guidelines, and many recommendations are based exclusively on efficacy trials. For example, only 4% of people with asthma from the general population would satisfy the inclusion criteria for 17 of the largest randomized controlled trials that support the recommendations in the Global Initiative for Asthma (GINA) guidelines [3]. The trial evidence on which a general practitioner like me bases their decisions is thus derived from studies on only 4% of the population. It tells us very little about the remaining 96% who did not qualify for the study. Yet often these efficacy trials are the only evidence we have to inform prescribing decisions. This has important implications. Because smokers were excluded from the efficacy trials, it took almost 30 years from the launch of inhaled corticosteroids for us to realize that smokers do not get the same benefit from the medication as non-smokers.

Setting, Organization and Follow-Up

Explanatory trials are typically undertaken under controlled conditions, usually based in a clinical trials unit, with specialist expertise, and additional resources provided to do the trial. In contrast, a pragmatic trial normally take place within routine clinical care, perhaps in a primary care practice or a secondary care outpatient clinic using the usual resources available to health services.

Explanatory trials often involve intensive monitoring, which patients may appreciate as they feel well cared for, but frequent study visits will influence the outcomes. In a pragmatic trial, the follow-up will be according to clinical need with as few study visits as possible. Often data in pragmatic trials are only collected at baseline and endpoint – and they may even use routine data so that the patient is not involved in any study visits at all.

Fidelity and Adherence

Fidelity and adherence are two aspects of the same issue. Fidelity usually applies to what the researchers are doing and adherence to the patients' behavior. In an explanatory trial, the researchers will be provided with a detailed manual, which they are expected to follow to the letter, leaving little or no room for flexibility. There is a lot of oversight and monitoring to ensure that that is the case. From the patients' point of view, they will be excluded from an explanatory trial if they are poorly compliant and strategies may be used to improve and maintain their adherence.

Pragmatic trials also have a manual and instructions on what to do, however the protocol will usually allow some leeway for professionals to take clinical decisions depending on the clinical circumstances. Similarly, any strategies to encourage patients to adhere to medication regimes will reflect normal clinical practice.

Outcomes and Analysis

There are some differences in the selection of outcome measures. In the pragmatic context, our primary focus is on clinical measures and/or the patient-reported outcome measures, whereas an explanatory trial may use surrogate markers, physiological measures, or sometimes techniques that are unavailable in routine care. Of course, in a pragmatic trial, analysis is always on an 'intention to treat' basis including all participants in the group to which they were allocated regardless of whether they received or complied with the intervention. This is not necessarily the case in an explanatory trial.

There is a spectrum of trial design ranging from explanatory efficacy trials to pragmatic effectiveness trials to implementation studies.

The PRECIS Wheel

The PRECIS-2 wheel is a tool to enable researchers to determine where the trial they are designing is positioned on the explanatory/pragmatic spectrum [2]. Researchers consider their trial design in the nine categories indicated on the spider plot (Fig. 2). Explanatory trials generate low scores and the plot will be very small. Pragmatic trials produce points at the extremes of the axes. In reality few trials are at either extreme. The example below is from a trial we designed in the context of pulmonary rehabilitation for people with COPD and depression. Our aim was a pragmatic design, and we achieved that for some constructs, but ethical constraints (for example the need to obtain informed consent), and the decision to provide additional trained personnel meant that we could not achieve a 'perfect' pragmatic score.

Why Are Pragmatic Trials Important?

Let us consider an example of a clinical problem: a teenager who presents to me with uncontrolled asthma and who needs her treatment stepping up. The guidelines tell me that 'inhaled corticosteroids are the most effective preventive drug for achieving overall treatment goals' [4]. This seems pretty clear and is supported by evidence from a large randomized, controlled trial comparing fluticasone and montelukast in non-smokers, with proven reversible airway lung function [5]. The result clearly favors the inhaled corticosteroid which achieved a greater change in FEV-1 from baseline than the leukotriene antagonist. So, based on this and similar efficacy trials, the guideline is able to be dogmatic about the best treatment strategy for my patient: they need to take an inhaled corticosteroid.

However, when David Price asked a similar question in a pragmatic trial in which people with poorly controlled asthma were randomized to open label fluticasone or montelukast [6], he got a >

Figure 2. PRECIS-2 tool [2].
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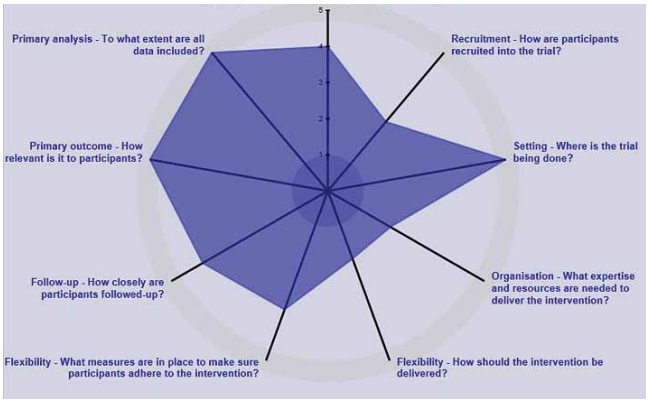

rather answer. In contrast to the efficacy trial in which the inhaled steroids were clearly more effective, there was no difference in the primary outcomes of asthma-related quality of life (miniAQLQ) or lung function between the two groups in the pragmatic trial.

There can be many reasons for this result. Some patients do not like taking inhaled corticosteroids so they may have chosen to stop the treatment. Inhaler devices can be difficult to use effectively – it is easier to swallow a pill. The protocol allowed clinicians to change the study medication after a month on the allocated treatment if they thought it was clinically appropriate (perhaps because the patient was no better, or they had side effects from the treatment). Patients in the montelukast group were slightly more likely to change to inhaled steroids: however, 20% of the inhaled corticosteroid group also swapped treatment. There is also the possibility that the patient may have taken up smoking during the two years study which we know makes inhaled steroids less effective.

In addition, we must recognize that people respond differently to therapy as indicated by a study [7], which used a crossover design, to compare children and adolescents taking fluticasone and montelukast. What they found was that about three-quarters responded better to the fluticasone (the inhaled corticosteroid), and about a quarter responded better to the montelukast.

So, the answer to my question about what is the best treatment strategy for my patient is not quite as clear-cut as it would seem from the efficacy studies and guideline recommendations . . .

Implementation

Returning to our spectrum of evidence (Fig. 1), and moving beyond the explanatory-pragmatic trials, the schema includes observational studies that use routine data to explore how treatments perform in real-life practice. There is, however, an alternative approach in which we implement a new strategy experimentally in a 'Phase IV' study. Implementation studies are often thought of in the context of complex health service interventions [8], but in reality even something as 'simple' as taking a pill has many elements which might impact on its effectiveness in real-life practice. Clinicians may know about the new drug, but they may (or may not) decide to prescribe it. The type of patients to whom they choose to give it will determine its effectiveness, and how positive they are when they suggest the new treatment will influence the patients' perceptions of whether it is likely to work. The patients' (and their families/friends) preconceived ideas will influence whether they decide to take the drug, and complex instructions about when and how to take the tablet will affect compliance. Media coverage may convince patients that a treatment is either a miracle cure or a dangerous drug.

Even a taking a tablet is thus a complex intervention and effectiveness will be affected by many variables when treatment is implemented in routine care.

Features of an Implementation Study

An implementation study must be based on Phase III randomized trial evidence or a guideline recommendation to support the intervention that is being implemented [9].

To give an example: at the University of Edinburgh we did a Phase III randomized trial comparing tele-monitoring or usual care for people with uncontrolled blood pressure [10]. We found that at the end of the trial people in the tele-monitoring group had better ambulatory blood pressure than people receiving usual care. This is a significant result, statistically and clinically, in terms of preventing future strokes.

Although we used a pragmatic design, the study was a trial in which patients were randomized. This is, by definition, not real world: we never randomize patients in clinical practice! In an implementation trial we would randomize at the practice level, allocating practices to offering their patients tele-monitoring or to managing hypertension in the usual way. All patients being managed for hypertension would be eligible, with no exclusion criteria, though physicians will select to whom they offer the new service and patients will choose whether or not they accept the offer. The eligible population is not static because people may leave or join the practice, there may be deaths, and new diagnoses will be made. Phase III trials report attrition: implementation studies describe 'turnover'. In an implementation study of providing telephone reviews for asthma we observed a 20% turnover in the study population [11].

In an implementation study the intervention is always resourced by and incorporated into routine clinical services with no extra funding from the research team. There may be some training so that professionals have necessary skills (as would be provided when a service is rolled out). The core components of the intervention are standardized, but how it is implemented will vary between study sites: indeed if there is no adaptation many would argue that the intervention is not really being adopted within the routines of the organization. In our example, it is likely that a very large practice in a semi-urban/rural area will use different strategies for implementing tele-monitoring for blood pressure than a small inner city practice.

Patients are offered, and may choose to accept or decline the new treatment or clinical service. Importantly, they do not have to participate in any form of research in order to access the intervention; it is available as a clinical service, and the uptake of that service/treatment, is an outcome.

Randomization will be at the level of the practice or clinical unit. The primary outcome is therefore at the practice level and may well use routine anonymous data on the whole practice population,

extracted from the electronic health record. Some patients may be recruited to a research process (for example: completing questionnaires) but they will be a subgroup of the study population and statistically need to be treated as such.

Summary

In summary, can we make experimental studies more real world? The answer is yes, we can. There is a spectrum of trial design from the tightly controlled, exploratory randomized controlled trial with high internal validity which establishes the efficacy of a drug, to the pragmatic, randomized trial with broader inclusion criteria and more room for clinical leeway, which can establish generalizability. Then, there are implementation studies where an intervention is offered as a clinical service, that will be adapted to diverse clinical settings, and where we reporting outcome from a whole population.

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Additional information:

The preceding article is based on a presentation given during the Third Plenary Session, "Health Care Evidence: Can We Get To the 'Real World?" at the ISPOR 17th Annual European Congress, 8-12 November 2014, Amsterdam, The Netherlands.

To view Dr. Pinnock's presentation, please visit the Released Presentations page for the 17th Annual European Congress at: http://www.ispor.org/Event/ReleasedPresentations/2014Amsterdam

The ISPOR Stated Preference Methods Special Interest Group (SIG) will hold an open meeting on Monday 9 November, 12:30-13:30, at the ISPOR 18th Annual European Congress in Milan, Italy. This meeting will provide an opportunity for participants to discuss issues and challenges within this field and develop projects to address them. All ISPOR 18th Annual European Congress registrants are welcome to attend. For more on the ISPOR Stated Preference Methods Special Interest Group, go to: http://www.ispor.org/sigs/Stated-Preference-Methods.asp.