What Is a Pragmatic Clinical Trial?

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INTRODUCTION

This article summarizes the scientific concepts underlying pragmatic clinical trials as a research technique that is worthy of wider use in dermatology.

PRAGMATIC TRIALS

Pragmatic clinical trials seek to determine the *effectiveness* of an intervention in a real-world setting to inform clinical decision making (Roland and Torgerson, 1998). Researchers designing pragmatic trials take particular care to ensure that the study population is as similar as possible to the population on which the intervention is meant to be used (external validity), reflecting the normal range of diversity in disease severity, comorbidities, age, sex, and social and ethnic groups seen in everyday clinical practice. Pragmatic trials also ensure that the sorts of interventions tested can be plausibly rolled out in clinical practice and that the outcomes used to assess effectiveness are valid and easily understood by a range of users, including clinicians, patients, *policy* makers, and health commissioners. Pragmatic clinical trial patients may also be used to test "strategies" or treatment policies rather than one specific drug at a time. For example, the BLISTER (Bullous Pemphigoid Steroids and Tetracyclines Study) randomized controlled trial tests the *policy* of starting treatment for bullous pemphigoid patients with either doxycycline or prednisolone (Chalmers *et al.*, 2015). The policy evaluates the trade-off between the short-term smaller benefit for blister control, as might be anticipated for doxycycline, and the long-term safety concerns that may disadvantage patients randomized to prednisolone. It does not matter whether the dose of prednisolone is altered during the study as would normally occur in clinical practice, nor does it matter if some of the patients initially randomized to the strategy of starting with doxycycline are switched subsequently to prednisolone—what matters is a *comparison of the two strategies* to which the participants were originally randomized. Cost-effectiveness analysis is usually a key component of pragmatic trials to enable care providers to make informed decisions on value for money (Thomas *et al.*, 2006).

Table 1. PICOT comparison—a comparison of pragmatic versus explanatory trials in dermatology in terms of their five main components: patients, intervention, comparison, outcome, and time of assessment

Pragmatic trial: tests effectiveness	Explanatory trial: test's efficacy
Real-life patients	Homogeneous patients
Flexible intervention with changes	Tightly defined intervention
Active comparator instead of placebo	Clearly defined control group, often placebo
Clinically important outcomes	Objective/surrogate outcomes
Longer-term follow-up times (e.g., 6 months)	Short-term follow-up time (e.g., 6 weeks)

WHAT PRAGMATIC CLINICAL TRIALS DO

- Pragmatic clinical trials seek to answer important questions that are applicable to everyday clinical practice.
- The design of pragmatic trials aims to test an intervention in a study environment that is closer to real life in terms of study population, intervention, comparator, and outcomes.
- Pragmatic trials must still adhere to the stringent trial methods for minimizing selection, performance, information, attrition, selective outcome reporting, and publication bias.
- Pragmatic trials must be prospectively registered and reported fully according to the pragmatic trials extension of the CONSORT statement.
- The PRECIS tool is one method for assessing where on the pragmatic–explanatory continuum a trial resides and which aspects are more pragmatic or explanatory.
- More pragmatic trials should be considered in dermatology so that they better inform patient care.

LIMITATIONS

- Pragmatic clinical trials can cost more than explanatory trials, and may require a more complex study design.
- The majority of clinical trials are neither entirely pragmatic nor entirely explanatory—they are part of a continuum.
- Pragmatic trials are not suitable for early trials that seek to explore whether a new experimental intervention shows any biological effect.

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EXPLANATORY TRIALS

Explanatory clinical trials, on the other hand, seek to determine the *efficacy* of an intervention under ideal conditions. Participants are often a highly selected and homogenous group exhibiting good compliance, and are usually recruited in secondary or tertiary care (Treweek and Zwarenstein, 2009). Participants are more likely to remain in the study, typically have only the target condition, and are subject to strict dosing schedules and monitoring. Explanatory trials are deliberately designed to give the maximum chance of showing an effect, if one is present. Outcomes may include cellular markers that explore disease mechanisms (Papp *et al*., 2012), as well as composite clinical scales for assessing clinical efficacy. Per protocol analysis tends to be carried out and cost-effectiveness analyses are unusual. Explanatory trials thus typically answer the question "can this treatment work under ideal conditions?" They usually precede pragmatic trials which then ask "we now know it can work, but how well does it work in real world clinical practice?" Table 1 shows the contrasting features between a typical pragmatic and explanatory trial in terms of patients, intervention, comparison, outcome and time of assessment (PICOT framework).

THE PRAGMATIC/EXPLANATORY CONTINUUM AND THE PRECIS WHEEL

Having described the main differences between pragmatic and explanatory trials to aid understanding of their underlying concepts, it is important to recognize the limitations of such a dichotomous approach because most trials contain components of both approaches. This concept of a continuum has led to the development of a useful method to assess the degree of pragmatism when designing a clinical trial, called the Pragmatic–Explanatory Continuum Indicator Summary (PRECIS) tool (Thorpe *et al*., 2009). Figure 1 shows how investigators of the BLISTER trial (www.blistertrial.co.uk) rated the degree of pragmatism for 10 features on the PRECIS tool (Bratton *et al*., 2012). For example, flexibility of the experimental intervention that permitted investigators to alter the dose of oral corticosteroids for bullous pemphigoid patients in a way that reflected normal clinical practice resulted in a mean score toward the outer pragmatic boundary of the PRECIS wheel, whereas the domain of "eligibility criteria" scored somewhere between the pragmatic outer boundary and the explanatory center of the wheel—probably as a result of exclusion of patients with dementia. The resultant diagrams, which resemble spiderwebs, provide an immediate visual guide as to how pragmatic a study is overall and where the most pragmatic elements reside. Highly explanatory trials show a "web" that is closely tucked into the center, whereas pragmatic trials are dispersed toward the periphery. The PRECIS wheel can be used both at the design stage and when trying to assess the degree of pragmatism in an ongoing or published study (Bratton *et al*., 2012).

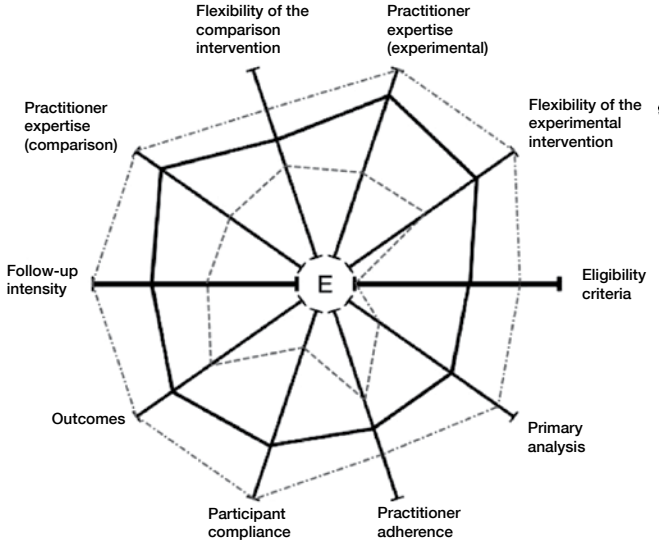

Figure 1. PRECIS wheel showing the mean of the scores given by BLISTER trial management group members (solid line). Also presented are the most explanatory scores (inner line) and most pragmatic scores (outer line) given in each domain. Scores were plotted on the wheel using a simple picture-editing program (Bratton *et al*., 2012).

LIMITATIONS OF THE TECHNIQUE

There is a perception that pragmatic trials are equivalent to saying that "anything goes." Although this is true for some aspects, such as allowing flexible dosing for reasons of safety and to mimic how the intervention might be delivered in clinical practice, all critical aspects to reduce bias—e.g., randomization, blinding, treating both groups equally, and analyzing all those originally randomized—must be adhered to (Williams and Gilchrest, 2015). Sometimes blinding of the intervention (as in surgical procedures) is simply not possible, yet it is almost always possible to ensure a blinded evaluation of outcome. Pragmatic clinical trials are usually more expensive to conduct than explanatory trials because they are typically larger in order to identify minimally clinically important differences in real-life settings. They often require longer follow-up and additional cost-effectiveness analyses, which can add to study complexity and cost. Feasibility work or explanatory trials are often needed before embarking on such studies. Like all study designs, there are good and bad pragmatic studies, and like all clinical trials published in the *JID* and elsewhere, they must be fully registered and reported fully using the pragmatic-trials extension of the Consolidated Standards of Reporting Trials (CONSORT; http://www.consort-statement.org/extensions?ContentWidgetId=556) so that the reader can judge study quality.

WHICH IS BEST?

Despite the widespread publication and acceptance of pragmatic clinical trials as the cornerstone of primary research for health technology assessment in the top general medical journals (Thomas *et al*., 2013), they are still not widely understood or conducted in dermatology, where explanatory trials still appear to be the norm (Williams and Dellavalle, 2012). For example, a PubMed search (11 February 2015) using the terms "dermatology AND randomized AND pragmatic" found only 15 citations, of which only 5 were completed studies, compared with an estimated 5,000 randomized controlled clinical trials in dermatology as a whole. Perhaps the small yield of pragmatic studies in the above search is due to the fact that many such studies fail to mention the term "pragmatic" in the title or study text, a feature that can be righted easily by making the design

clear in the study title and description. The choice of an explanatory or pragmatic design clearly depends on the perspective of the question and where in the research cycle the technology being tested is positioned. New drugs or devices typically require explanatory trials when testing whether the intervention demonstrates clinical benefit against vehicle or placebo. Placebo-controlled explanatory trials rarely inform clinical practice because it is unusual to use placebos in clinical practice and because patients are not typically perfectly adherent to the prescribed treatment for various reasons. Those interventions that have shown efficacy against placebo should then be tested for effectiveness against active comparators using pragmatic designs. Pragmatic clinical trials are the cornerstone of the comparative effectiveness agenda (Agency for Healthcare Research and Quality), which has gained significant funds from the 2009 US Government American Recovery and Reinvestment Act (Sox and Greenfield, 2009). Most of the definitive national clinical trials funded by the UK National Institute of Health Research Health Technology Assessment Board are also pragmatic in nature (http://www.nets.nihr.ac.uk/programmes/hta).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

A PowerPoint slide presentation appropriate for journal club or other teaching exercises is available at http://dx.doi.org/10.1038/jid.2015.134.

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QUESTIONS

This article has been approved for 1 hour of Category 1 CME credit. To take the quiz, with or without CME credit, follow the link under the "CME ACCREDITATION" heading.

For each question, more than one answer may be correct.

1. What is NOT a typical component of a pragmatic trial?

A. Designed to assess clinical effectiveness.
B. Highly selected patients with no comorbidities.
C. Includes study population similar to real-life population.
D. Cost-effectiveness analysis.

2. What is the main aim of an explanatory trial?

A. To compare strategies of treatment.
B. To evaluate how the intervention will work in everyday clinical practice.
C. To determine efficacy.
D. To assess rare adverse effects.

3. Most trials in clinical dermatology can be considered

A. Pragmatic.
B. Explanatory.
C. Neither A nor B.
D. A continuum of A and B.

4. Which statement regarding the PRECIS tool is correct?

A. The acronym stands for Pragmatic-Explanatory Continuum Indicator Summary tool.
B. It provides a numerical rating of pragmatism.
C. It contains eight assessment features.
D. Explanatory trials show a "web" towards the periphery.

5. Which statement is true regarding a pragmatic trial?

A. They are typically more costly due to trial size and cost-effectiveness analysis.
B. They often require background feasibility or explanatory work beforehand.
C. They are the cornerstone of the comparative effectiveness agenda.
D. All of the above.

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