Pragmatic trials

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HSRU is funded by the Chief Scientist Office of the Scottish Government Health Directorates. The author accepts full responsibility for this talk.
Trials Change Lives

“Clinical trials are the backbone of primary research that informs clinical practice in the NHS in the UK”

Prof Hywel Williams, Director, Health Technology Assessment Programme (NIHR)

Clinical Trials for the NHS

www.methodologyhubs.mrc.ac.uk/trials-change-lives/
What are we trying to do with our trial?

- Who am I designing my trial for?
- What do they need?
What are we trying to do with our trial?

- Who am I designing my trial for?
- What do they need?
Now let’s think about design..

Work
Now let’s think about design..
Now let’s think about design..
Now let’s think about design..

What you have produced is irrelevant
Do we think enough about design?

‘...most therapeutic trials are inadequately formulated, and this from the earliest stages of their conception. Their inadequacy is basic..

Choosing the right design

RESEARCH

Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection

Céline Habre research fellow\textsuperscript{1}, Martin R Tramèr professor in anaesthesia\textsuperscript{2,3}, Daniel M Pöpping anaesthetist\textsuperscript{4}, Nadia Elia public health epidemiologist\textsuperscript{2,5}

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Abstract

Objectives To examine whether, according to the conclusions of a 2000 systematic review with meta-analysis on interventions to prevent pain of the new trials were considered clinically relevant since they used the most efficacious intervention as comparator or included a paediatric population.
Choosing the right design

Number of clinically irrelevant trials:
87 of 136 (64%)

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Abstract

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ORIGINAL ARTICLE

A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe,⁎, Merrick Zwarenstein⁎, Andrew D. Oxman, Shaun Treweek, Curt D. Furberg, Douglas G. Altman, Sean Tunis, Eduardo Bergel, Ian Harvey, David J. Magid, Kalipso Chalkidou

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‖‖‖Faculty of Health, University of East Anglia, Norwich, UK
‖‖‖‖Institute for Health Research, Kaiser Permanente Colorado; Departments of Preventive Medicine and Biometrics and Emergency Medicine, University of Colorado Health Sciences Center, Denver, CO, USA
‖‖‖‖‖National Institute for Health and Clinical Excellence, London, UK

Accepted 13 December 2008

Abstract

Objective: To propose a tool to assist trialists in making design decisions that are consistent with their trial’s stated purpose.

Study Design and Setting: Randomized trials have been broadly categorized as either having a pragmatic or explanatory attitude. Pragmatic trials seek to answer the question, “Does this intervention work under usual conditions?”, whereas explanatory trials are focused on the question, “Can this intervention work under ideal conditions?” Design decisions make a trial more (or less) pragmatic or explanatory, but no tool currently exists to help researchers make the best decisions possible in accordance with their trial’s primary goal. During the course of two international meetings, participants with experience in clinical care, research commissioning, health care financing, trial methodology, and reporting defined and refined aspects of trial design that distinguish pragmatic attitudes from explanatory.

Results: We have developed a tool (called PRECIS) with 10 key domains and which identifies criteria to help researchers determine how pragmatic or explanatory their trial is. The assessment is summarized graphically.

Conclusion: We believe that PRECIS is a useful first step toward a tool that can help trialists to ensure that their design decisions are consistent with the stated purpose of the trial. © 2009 The Authors. Published by Elsevier Inc. All rights reserved.
A pragmatic—explanatory approach to trial design

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cDepartment of Health Policy,管理Intervention, Reproductive Health & Population Sciences, Division of Clinical & Population Sciences, and Division of Public Health Sciences, Department of Medicine, and Division of Health Policy, University of Toronto, Toronto, Ont., Canada
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bCentre for Health Services Sciences, Sunnybrook Research Institute, Toronto, Ont., Canada
cDepartment of Health Policy, Management Intervention, Reproductive Health & Population Sciences, Division of Clinical & Population Sciences, and Division of Public Health Sciences, Department of Medicine, and Division of Health Policy, University of Toronto, Toronto, Canada

Abstract

Objective: To propose a tool to assist trialists in thinking through their decision-making.

Study Design and Setting: Randomized trials seek to answer the question, “Can this intervention work?” but no tool currently exists to help researchers determine how pragmatic or explanatory their trial is.

Results: We believe that PRECIS is consistent with the stated purpose of the trial.

Conclusion: We believe that PRECIS is consistent with the stated purpose of the trial.
Who am I designing my trial for and what have I done to make sure they don’t have to dismiss my trial as irrelevant?

Who are your users and what do they want?

Kirsty Loudon,
University of Edinburgh

ORGANISATION -
What expertise and resources are needed to deliver the intervention?

ELIGIBILITY -
Who is selected to participate in the trial?

RECRUITMENT -
How are participants recruited into the trial?

SETTING -
Where is the trial being done?

FLEXIBILITY:
DELIVERY -
How should the intervention be delivered?

FLEXIBILITY:
ADHERENCE -
What measures are in place to make sure participants adhere to the intervention?

FOLLOW-UP -
How closely are participants followed-up?

PRIMARY OUTCOME -
How relevant is it to participants?

PRIMARY ANALYSIS -
To what extent are all data included?
What expertise and resources are needed to deliver the intervention?

Who is selected to participate in the trial?

How are participants recruited into the trial?

Where is the trial being done?

What expertise and resources are needed to deliver the intervention?

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What measures are in place to make sure participants adhere to the intervention?

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How relevant is it to participants?

To what extent are all data included?

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ORGANISATION - What expertise and resources are needed to deliver the intervention?

ELIGIBILITY - Who is selected to participate in the trial?

RECRUITMENT - How are participants recruited into the trial?

SETTING - Where is the trial being done?

FLEXIBILITY: DELIVERY - How should the intervention be delivered?

FLEXIBILITY: ADHERENCE - What measures are in place to make sure participants adhere to the intervention?

FOLLOW-UP - How closely are participants followed-up?

PRIMARY OUTCOME - How relevant is it to participants?

PRIMARY ANALYSIS - To what extent are all data included?
Designing clinical trials is challenging. PRECIS – PRagmatic Explanatory Continuum Indicator Summary – is a clever acronym for a tool to help trialists designing clinical trials consider where they would like their trial to be on the pragmatic/explanatory continuum.

The PRECIS-2 website has two functions

1. a training resource;
2. a database of trials that have been scored using PRECIS-2

Trialists working on their own trial can apply for a password so that their team can score their trial while developing the trial design and protocol. This trial design information will only be visible to trialists using a password until they decide to make this information publicly available. We advise one...
Section II: PRCIS-2 Framework

Pragmatic-Explanatory Continuum Indicator Summary

Key Points

- No study is completely pragmatic, nor is it completely explanatory.
- PRCIS provides a reliable, helpful way to assess how pragmatic a project is on multiple dimensions.
- The PRCIS summary 'wheel' figure is an efficient, visual way to display study design features.
- The PRCIS system has recently been revised; PRCIS-2 contains 9 domains related to pragmatic trials that will be used throughout.

The "PRCIS wheel" figure has proven to be a very convenient summary of study design features. After a little experience, a user can quickly understand the overall extent to which and the dimensions along which a study is pragmatic vs. explanatory from glancing at the size and shape of the figure that results from connecting individual PRCIS scores.

The University of Dundee Health Informatics Centre, 2015: https://crs.dundee.ac.uk/prcisi/
So, how does PRECIS-2 help?

Who am I designing my trial for and what have I done to make sure they don’t have to dismiss my trial as irrelevant?
So, how does PRECIS-2 help?

Who am I designing my trial for and what have I done to make sure they don’t have to dismiss my trial as irrelevant?
#1— PRECIS-2: before and after
#1— PRECIS-2: before and after
#2– 23 included trials in a Cochrane review

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Total mortality</th>
<th>Blood pressure</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter [4]</td>
<td>pragmatic</td>
<td>0.58 (0.33-1.01)</td>
<td>Unclear</td>
<td>Thiazide, 76%, Methylidopa (0.75-2 g), bethanidine or debrisoquine. Stroke, mortality, CHD, CHF</td>
</tr>
<tr>
<td>Dutch TIA [5] Beta blocker</td>
<td>pragmatic</td>
<td>1.12 (0.79-1.57)</td>
<td>Low</td>
<td>Atenolol 50 mg daily identical placebo tablet Mortality, CHD, stroke, total CV events,</td>
</tr>
<tr>
<td>EWPHBPE [6, 7]</td>
<td>explanatory</td>
<td>0.92 (0.76-1.12)</td>
<td>Low</td>
<td>HCTZ/triamterene, 25/50 mg, 1 to 2 tabs, methylidopa 0.5-2 g. Mortality, stroke, CHD, CHF, systolic BP and diastolic BP</td>
</tr>
<tr>
<td>HOPE HYP [8] ACE inhibitors</td>
<td>explanatory</td>
<td>0.79 (0.67-0.93)</td>
<td>Low</td>
<td>Ramipril 2.5 mg titrating up to 10 mg or placebo. Other factor was Vitamin E 400 IU/day. Primary: composite of myocardial infarction, stroke, or cardiovascular death (total CV events), Total mortality, total stroke, total CHD.</td>
</tr>
<tr>
<td>HSCSG [9]</td>
<td>explanatory</td>
<td>1.01 (0.6-1.72)</td>
<td>Low</td>
<td>Deserpidine 1 mg plus methyldopa 10 mg. Mortality, stroke, CHD, CHF, systolic BP and diastolic BP</td>
</tr>
<tr>
<td>HYVET [10]</td>
<td>explanatory</td>
<td>0.82 (0.69-0.99)</td>
<td>Low</td>
<td>Indacaride 1.5 mg daily. Step 2 Captopril 2 mg daily. Step 3 captopril 4 mg. Total stroke, total coronary artery disease, total mortality, total cardiovascular events (including CHF), Total cardiovascular events (including CHF)</td>
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</tbody>
</table>
#2– 23 included trials in a Cochrane review
#3– Internal vs external validity

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<th>Risk of bias</th>
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<tr>
<td></td>
<td>High risk</td>
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<tr>
<td>Explanatory trials</td>
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<tr>
<td>n = 19</td>
<td></td>
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<tr>
<td>Pragmatic trials</td>
<td></td>
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<tr>
<td>n = 22</td>
<td></td>
</tr>
<tr>
<td>Neither one nor the other</td>
<td></td>
</tr>
<tr>
<td>n = 8</td>
<td></td>
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</table>
## #3— Internal vs external validity

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<tbody>
<tr>
<td></td>
<td>High risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Explanatory trials</td>
<td>1 (5%)</td>
<td>10 (53%)</td>
<td>8 (42%)</td>
<td></td>
</tr>
<tr>
<td>n = 19</td>
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<tr>
<td>Pragmatic trials</td>
<td>2 (9%)</td>
<td>13 (59%)</td>
<td>7 (32%)</td>
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</tr>
<tr>
<td>n = 22</td>
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<tr>
<td>Neither one nor the other</td>
<td>2 (25%)</td>
<td>4 (50%)</td>
<td>2 (25%)</td>
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<tr>
<td>n = 8</td>
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• All trial designers need to think about who the user is.

• For pragmatic trials this is likely to be a health professionals, patients and policymakers.

• For pragmatic trials we need to remember that the driver for the trial is improving patient care, not teasing out neat bits of science.

• Have a look at www.PRECIS-2.org
Thank you!

Twitter: @Trial_Forge

http://trialforge.org